2002 Consensus Conference on Management of Obesity

Introduction

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During Digestive Disease Week, The Society for Surgery of the Alimentary Tract (SSAT), in collaboration with the American Society for Bariatric Surgery (ASBS), hosted a conference on the management of obesity. Participants in the panel included five speakers: June Stevens, Ph.D., School of Public Health, University of North Carolina; Lee M. Kaplan, M.D., Ph.D., Massachusetts General Hospital; Thomas A. Wadden, Ph.D., University of Pennsylvania; Samuel Klein, M.D., Washington University in St. Louis; and Philip R. Schauer, M.D., University of Pittsburgh. Other participants included two discussants: Xavier Pi-Sunyer, M.D., Columbia University, New York, NY; and Harvey A. Sugerman, M.D., Medical College of Virginia; and members of the SSAT Education and Research Committee: Carlos Fernandez-del Castillo, M.D., Massachusetts General Hospital; W. Scott Helton, M.D., University of Illinois; Walter Koltun, M.D., Penn State University; and W. Wiley Souba, M.D., Penn State University.

The speakers were asked to address the following questions and to suggest topics for future research that would facilitate answering these questions:

1. How is obesity best defined and what is its prevalence? Of what importance are age, sex, and ethnicity? Are better definitions needed?
2. What are the physiologic mechanisms by which weight and body fat stores are regulated? How are these mechanisms perturbed in severe obesity? What complications are associated with obesity and what are the pathogenic factors responsible for their development?
3. What are the behavioral aspects of obesity? What lifestyle modifications are best utilized in obesity management and with what efficacy?
4. What medical regimens are used in treating obesity and with what efficacy? What are the mechanisms through which they operate? What modalities are being developed for future testing or application?
5. What surgical regimens are used in treating obesity and with what efficacy? What are the mechanisms by which they effect weight loss? What modalities are being developed for future testing or application?

The evidence presented by the speakers was used to draft a statement reporting on the workshop. The participants extensively discussed this draft and made modifications when agreeable to all. Final revision of the document was made utilizing comments offered by members of the audience and the SSAT Education and Research Committee.

GENERAL SUMMARY

1. From a clinical perspective, obesity is usually defined as a body mass index (BMI) $\geq$30 kg/m^2. This affliction contributes to more than 300,000 deaths per year and costs our nation more than $100 billion annually. Recent national surveys suggest that more than 25% of the population is obese. There is little evidence to support the concepts that recommended body weight should vary with

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age or that the risk of elevated BMI is influenced by gender. Some evidence suggests different BMI thresholds for obesity in persons of African and Asian descent.

2. Complications of obesity are numerous and include hypertension, heart disease, type II diabetes, osteoarthritis, vertebral disc disease, venous stasis disease, gastroesophageal reflux disease, and sleep apnea, among others. Progression of these complications can also contribute to further weight gain.
3. The central controller of body energy metabolism and storage resides within the hypothalamus. This weight regulatory system appears to defend an energy "set point," which loosely correlates with body fat and BMI. What causes "defense" of an abnormally high body weight in obese individuals is unknown, although genetic predisposition and environmental triggers appear to be important factors.
4. The major goal of obesity therapy is to induce negative energy balance in order to consume endogenous triglyceride stores as fuel. Even modest weight loss ($\leq$10% of initial body weight) is associated with significant improvement in comorbid conditions. Lifestyle modification (dietary intervention, physical activity, and behavioral therapy) is integral to all weight loss programs. Unfortunately, achievement of *long-lasting* weight loss of significant magnitude (>10% of initial body weight) has proved difficult with lifestyle modification alone.
5. Dietary interventions remain the cornerstone of weight reduction efforts, typically focusing on alterations in caloric content or macronutrient balance. Reducing diets are categorized as very low calorie (<800 kcal/day) or low calorie (800 to 1500 kcal/day). The lower the calorie intake, the greater the resultant short-term weight loss. Most individuals regain one third of the weight lost within 1 year.
6. Exercise alone produces minimal weight loss without concurrent caloric restriction. However, regular exercise facilitates maintenance of weight loss and improves overall health. Exercise regimens typically focus on programmed and/or lifestyle activities. Ideally, such regimens should result in energy expenditures of 1500 to 2500 kcal/wk. Improved fitness resulting from regular physical exercise is associated with reduced risk of cardiovascular disease, regardless of body weight.
7. Behavioral therapy focuses on identification of "triggers" associated with overeating or inactivity. Goal setting and self-monitoring are integral to this process, which is most effective when continued long term.
8. Weight loss drugs are currently approved for persons with a BMI $\geq$30 kg/m^2, or with a BMI $\geq$27 kg/m^2 if associated with an obesity-related medical complication. With the exception of orlistat, which inhibits intestinal fat digestion and absorption, all currently approved medications act as anorexiants, which alter cerebral monoamine metabolism. Because short-term drug use is usually followed by weight regain when the drug is discontinued, long-term use is more appropriate. Only orlistat and sibutramine are approved for long-term use, and typically produce loss of 5% to 10% of initial weight at 1 year. Combining pharmacotherapy with a comprehensive weight management program (including lifestyle modification) is more effective than either alone.
9. Obesity (bariatric) surgery is currently recommended for persons with a BMI $\geq$40 kg/m^2, or $\geq$35 kg/m^2 if associated with an obesity-related medical complication. Bariatric surgery appears to influence physiologic weight regulatory mechanisms and is much more effective than either lifestyle modification or medical therapy.
10. Loss of approximately 50% of excess weight (approximately 25% to 30% of initial weight) is maintained long term after Roux-en-Y gastric bypass. In addition, surgically induced weight loss is associated with a marked reduction in life-threatening comorbid conditions and an improved quality of life. Long-term follow-up demonstrates that a small proportion of patients experience significant weight regain.
11. Bariatric surgical procedures are typically based on restrictive or malabsorptive strategies. Although learning curves are steep, most bariatric operations can now be performed laparoscopically. Experienced surgeons report mortality rates of 1% or less and major morbidity rates of 10% after Roux-en-Y gastric bypass. Compared to open procedures, the less invasive laparoscopic approaches produce equivalent weight loss, as well as comparable improvement in obesity-related comorbid conditions and quality of life, while decreasing postoperative complications and hastening recovery.
12. Despite documented efficacy, health care coverage for weight reduction therapy remains inadequate. Well-designed long-term studies

are needed to address the individual (health status, quality of life) and societal (cost:benefit) consequences of weight loss. Appropriate funding for such studies is vitally needed.

DIAGNOSIS AND EPIDEMIOLOGY

Obesity is the spectrum of disorders characterized by excess body fat stores. From a clinical perspective, it is usually defined as a BMI $\geq$30 kg/m^2. Various national surveys document a striking increase in the prevalence of obesity, with some estimates suggesting that the prevalence exceeds 30% of the population. The National Health Interview Survey suggested that the prevalence continues to increase annually. Similar trends have been noted outside the United States.

Recommendations for "desirable" or "optimal" weight are based on studies of the relationship between height-standardized weight and mortality. Although numerous studies have addressed the effect of age on this association, there is no convincing data to suggest that this relationship changes with increasing age. Similar conclusions appear appropriate with regard to proposed differences in the range of BMI associated with the lowest mortality rate in men as opposed to women. In contrast, studies addressing the BMI cutoff for obesity suggest that alternative levels may be appropriate for people of African and Asian descent.

PATHOPHYSIOLOGY AND COMPLICATIONS

Body weight is exquisitely and tightly regulated—within a tolerance of 0.15%. Most of the body's energy stores are in the form of fat. Over time, small mismatches (e.g., 1% to 2%) between energy ingested and expended can lead to large amounts of fat accumulation and obesity. In our current environment, which is the first in which there is an abundant supply of food available at all times (without significant energy cost), the majority of the population appears predisposed to some degree of excess fat storage.

Using numerous neuronal pathways and multiple neurotransmitters, the hypothalamus functions as the central controller of body energy metabolism and storage. This structure receives multiple inputs regarding existing energy stores, recent food intake, and ongoing metabolic activity, and interacts with other key regulatory systems within the central nervous system including the solitary tract nucleus ("satiety" center), circadian rhythm generators, central dopaminergic reward systems, and serotonergic pathways.

The weight regulatory system defends an "energy set point," which loosely correlates with body fat and BMI. Deviation from this baseline stimulates compensatory mechanisms. What causes "defense" of an abnormally high body weight in obese individuals is unknown, although genetic predisposition and environmental triggers appear to be important factors.

Complications of obesity are numerous and include hypertension, heart disease, type II diabetes, osteoarthritis, disc disease, and sleep apnea, among others. Progression of these complications can also contribute to further weight gain. These complications lead to shortened lifespan and decreased quality of life.

BEHAVIORAL ASPECTS AND THERAPEUTIC OPTIONS

The major goal of obesity therapy is to ingest fewer calories than are expended in order to consume endogenous triglyceride stores as fuel. Lifestyle modification (dietary intervention, physical activity, and behavioral therapy) is integral to all weight loss programs and can achieve beneficial but modest weight loss ($\leq$10% of initial body weight) in the short term. Achievement of *long-lasting* weight loss of greater magnitude has proved difficult with lifestyle modification.

Dietary interventions remain the cornerstone of weight reduction efforts, typically focusing on alterations in caloric content and/or macronutrient balance. Once an individual is in negative caloric balance, the relative proportion of carbohydrate and fat has little impact on weight loss. Reducing diets are categorized as very low calorie ($<$800 kcal/day) or low calorie (800 to 1500 kcal/day). The lower the calorie intake, the greater the resultant weight loss. Compensatory changes in energy metabolism ultimately limit the effectiveness of dietary restriction. Low-calorie diets (usually supplemented with behavioral therapy) produce losses of approximately 8% initial body weight within 16 to 26 weeks. The more expensive and more dangerous very-low-calorie diets are reserved for patients with BMI $\geq$30 kg/m^2. These diets are associated with increased risk of gallstone formation, which appears to be mitigated with concurrent ursodeoxycholic acid or aspirin therapy. Although initial weight loss is greater with very-low-calorie diets, subsequent weight regain after cessation of the diet is also greater.

Although increased physical activity is recommended as part of all weight reduction programs, exercise alone produces minimal weight loss without

concurrent caloric restriction. Regular exercise does facilitate maintenance of weight loss and improves overall health. In hopes of improving exercise adherence, both programmed activities and altered lifestyle activities have been explored. Ideally, such regimens should result in energy expenditures of 1500 to 2500 kcal/wk. Regular physical exercise has positive behavioral and physiologic benefits, the most beneficial being the reduced risk of cardiovascular disease, which occurs regardless of body weight.

Assuming that obese individuals can benefit from adopting healthier lifestyle habits, behavioral therapy focuses on identification of "triggers" associated with overeating or inactivity. Goal setting is critical to this process by which individuals set very specific goals with measurable outcomes. Self-monitoring is integral to this process and is most effective when continued long term.

MEDICAL MANAGEMENT

With the exception of orlistat, which inhibits intestinal fat digestion and absorption, all currently approved medications act as anorexiants. The anorexiant agents either increase satiation (decreasing the amount of food eaten) or satiety (decreasing the frequency of eating) via alterations in monoamine metabolism in the hypothalamus and other regions of the brain. Weight loss drugs are currently approved for persons with BMI $\geq$30 kg/m^2, or with a BMI $\geq$27 kg/m$\geq$ if associated with an obesity-related medical complication. Because short-term drug use is usually followed by weight regain when the drug is discontinued, long-term use (approximately 1 year) is more appropriate. Only orlistat and sibutramine are approved for long-term use, and typically produce loss of 5% to 10% of initial weight at 1 year. Better results are achieved when pharmacotherapy is administered within a comprehensive weight management program including lifestyle modification (see above).

Orlistat binds to endoluminally secreted pancreatic lipases. At a therapeutic dose of 120 mg three times a day, up to 30% of ingested triglycerides are not absorbed and are excreted. Approximately one third of patients treated with orlistat will lose up to 10% of initial body weight; best results are seen in patients consuming relatively high-fat diets. Side effects are predominantly gastrointestinal and can be minimized by concomitant psyllium mucilloid therapy. Substituting carbohydrate calories for fat calories to avoid complications diminishes the drug's effectiveness.

Sibutramine alters cerebral reuptake of monoamines, increasing satiation. The usual starting dose is 10 mg/day, which can be decreased or increased to 5 or 15 mg/day as needed; continuous or intermittent therapy can be used. Resultant weight loss may be somewhat less than that seen with orlistat therapy. Side effects may include dry mouth, headache, insomnia, constipation, and hypertension.

Potential new agents being considered for treating obesity include centrally acting appetite suppressants, thermogenic agents, gastrointestinal hormones, novel lipase inhibitors, adipocyte differentiation modulators, and other metabolic agents.

SURGICAL MANAGEMENT

Obesity surgery appears to influence physiologic weight regulatory mechanisms, including mechanoreceptors and gut peptide release in the stomach and proximal jejunum and chemoreceptors in the proximal jejunum. The resultant weight loss is much greater than that resulting from either lifestyle modification or medical therapy: Thus, after Roux-en-Y bypass, loss of approximately 50% of excess weight is maintained long term (>10 years). Further, postsurgical weight loss appears to be fundamentally different from other methods. Most patients experience a sharp decrease in appetite, increase in satiety, and decrease in stress sensation. These changes appear to be the opposite of what usually occurs with diet and behavioral approaches. These and other observations suggest that gastric surgery alters the body's set point control mechanisms; if so, the resulting weight loss would be in response to these physiologic changes, rather than to a conscious resistance to the internal control mechanisms.

Bariatric surgical procedures are typically based on restrictive (gastroplasty, gastric banding) or malabsorptive (biliopancreatic diversion, duodenal switch, and distal long-limbed gastric bypass) strategies or a combination of the two (standard Roux-en-Y gastric bypass). Restrictive operations cause early and prolonged satiety by creating a small gastric reservoir with a restricted outlet. Although restrictive procedures are technically simpler, significant dietary compliance is necessary postoperatively because patients can still consume high-calorie liquids and soft foods. The more complex malabsorptive operations bypass various lengths of the absorptive surface in the small bowel, resulting in greater sustained weight losses, which are less dependent on dietary compliance.

Although learning curves are steep and operating times long, most bariatric operations can now be performed laparoscopically. Experienced surgeons report mortality rates of 1% and major morbidity rates of 10% following laparoscopic Roux-en-Y gastric bypass. Compared to open procedures, the less

invasive laparoscopic approaches produce equivalent weight loss as well as comparable improvement in obesity-related comorbid conditions and quality of life, while decreasing postoperative complications (pulmonary and wound) and hastening recovery.

AREAS FOR FUTURE INVESTIGATION

1. What are the molecular mechanisms responsible for regulating energy balance?

   Based on the preceding research, can novel pharmacologic agents be developed for obesity management that decrease energy intake or increase energy expenditure? If they can, such agents will need to be tested in long-term trials, either alone on in combination with other therapeutic modalities.
2. What are the cellular and physiologic factors responsible for the link between excess adiposity and the various obesity-related complications (e.g., diabetes, hypertension, arthritis, and so forth)?

   Can agents be developed to minimize these risks?
3. What role might ethnicity play in current definitions and therapies of obesity?
4. How can nonsurgical modalities such as macronutrient manipulation, meal replacement, specific exercise or activity programs, or innovative technologic approaches (e.g., Internet) be implemented on a wider basis to improve obesity management?
5. Randomized prospective and case-control trials are needed to better define optimal strategies for the surgical treatment of obesity. These trials should focus on both obesity and its associated complications
6. In the long term, what are the individual and societal consequences of intentional weight loss?
7. Are the currently recommended indications for institution of weight loss therapy appropriate?
8. Can effective programs or interventions be developed to *prevent* obesity?

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Epidemiology and Consequences of Obesity

June Stevens, M.S., Ph.D., Kimberly P. Truesdale, Ph.D.

In 1994, a report from the National Health and Nutrition Examination Survey (NHANES III)[1] focused the attention of the nation on the rising prevalence of obesity. Although previous national surveys conducted since 1960 had shown very modest changes in body weight, between the NHANES II (1982 to 1984) and the NHANES III (1988 to 1994) surveys there was a startling increase. The prevalence of obesity (defined as a body mass index [BMI] $\geq$30 kg/m^2) increased from 16.5% to almost 25% in women and from 12% to 20% in men.[2] There is currently no evidence that increases in the prevalence of obesity have subsided since 1994. In fact, data from the National Health Interview Survey indicate that the prevalence of obesity in the United States continues to increase annually.

Increases in the prevalence of obesity are being seen not only in the United States but also around the world in developed and developing countries. The prevalence of obesity in European countries in adults 40 to 60 years of age ranges from 15% to 44% in women and from 10% to 18% in men.[3] In the Western Pacific countries, the prevalence of obesity varies drastically, with less than 3% in China and Japan, 10% to 15% in New Zealand and Australia, and 41% to 70% in Micronesia and Polynesia.[4] Martorell et al.,[5] in 2000, reported the obesity prevalence for women aged 15 to 49 years in developing countries. They concluded that obesity is a problem in several developing countries and that there is an association in the poorest countries between obesity and income.

The prevalence of obesity is a function of the measure and the cutoff point used for defining the condition. Currently BMI (weight in kg/height in m^2) is a very popular metric to assess obesity, and associations with mortality have traditionally formed the basis of recommendations for "desirable" or "optimal" body weight.[6,7] It has been questioned whether the same weight standard should be used for everyone when assessing mortality or disease risk or if there should be different standards depending on age, sex, or ethnicity. This report will focus on whether the BMI associated with the lowest mortality rate differs by age, sex, or ethnicity.

CONSEQUENCES OF OBESITY AMONG DIFFERENT AGE GROUPS

Although there has been little, if any, controversy over the fact that weight tends to increase as individuals progress from early to late adulthood, the issue of whether the association between weight and mortality changes with age has been the subject of intense debate.[8–14] This debate had been fueled by methodologic details of study design, analysis, and interpretation. In 1987 Manson et al.[15] brought attention to several of these methodologic issues in a review of 50 studies on the relationship between obesity and mortality. They noted that studies have shown no association, a positive association, a J- or U-shaped association, and even an inverse association between weight and total mortality. Reasons for discrepant results in the field cited by these investigators and others included lack of control for cigarette smoking, inappropriate adjustments for biological effects of obesity, failure to control for patients who had experienced disease-induced weight loss, and inadequate statistical power.

Since that time several investigators have studied the effects of age on the association between obesity and mortality using techniques to reduce or avoid these methodologic problems. Among these, two of the most informative studies were conducted using data from Cancer Prevention Studies (CPS) I and II.[16,17] The baseline data from the CPS-I study were collected in 1960, whereas those from the CPS-II study were collected in 1982. Both studies examined more than one million Americans in a variety of urban and rural locations across the United States, and thus had excellent statistical power as well as good generalizability to the American population. The investigators excluded subjects who smoked and those who had formerly smoked from the analyses in order to avoid confounding by smoking. Persons who were ill or in poor health were excluded from the analyses using several exclusion criteria so that patients who had experienced disease-induced weight loss could be avoided. In addition, these studies did not adjust for biological variables that are likely mediators of the effect of obesity on mortality.

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Despite differences of more than 30 years in the timing of the baseline data collections, the results of these studies were quite similar. Both studies showed that in a follow-up period of more than 10 years, a baseline BMI between 18.5 and 25 was associated with the lowest mortality rate. In addition, there was no evidence from these studies that the BMI associated with the lowest mortality rate was higher with increasing age. Figs. 1 and 2 show the association between BMI and mortality in four age groups examined in the CPS-I study.[16] In general, regardless of age at baseline, subjects with a BMI between 19 and 21.9 had the lowest mortality rate. However, the mortality rate among those with a BMI of 22 to 24.9 was generally not significantly increased above the reference rate (19.0 to 21.9).

One difference in the findings between CPS-I and CPS-II was the results seen in subjects 75 years of age and older. In CPS-I there were no significant associations between BMI and mortality in participants who were 75 years of age or older at baseline. In CPS-II the mortality rate was increased at elevated BMI levels in this age group, and the increase was statistically significant from the reference (BMI 23.0 to 24.9) in the 28.0 to 29.9 category in both men and women.

Both CPS-I and CPS-II support the notion that the BMI associated with the lowest mortality is between 18.5 and 24.9 over a span of ages ranging from 30 to 74 years. The more current analysis (CPS-II) indicated that even after 75 years of age, a BMI at the high end of this range may be associated with the lowest mortality. Thus there appears to be little support for the notion that the range of recommended body weight should vary with age.

CONSEQUENCES OF OBESITY AMONG MEN VS. WOMEN

Women have less lean body mass and more adipose tissue than men, and the normal adiposity level in women is approximately 27%, whereas in men this level is approximately 15%. This difference could lead to the hypothesis that, at the same height, a heavier weight would be more appropriate for men than for women because, on average, less weight would be in the form of adipose tissue. However, there are surprisingly few data to support this hypothesis.

Fig. 3 shows the rate ratios for mortality among 30- to 70-year-old men and women in the CPS-I cohort.[18] The rate ratios for mortality associated with

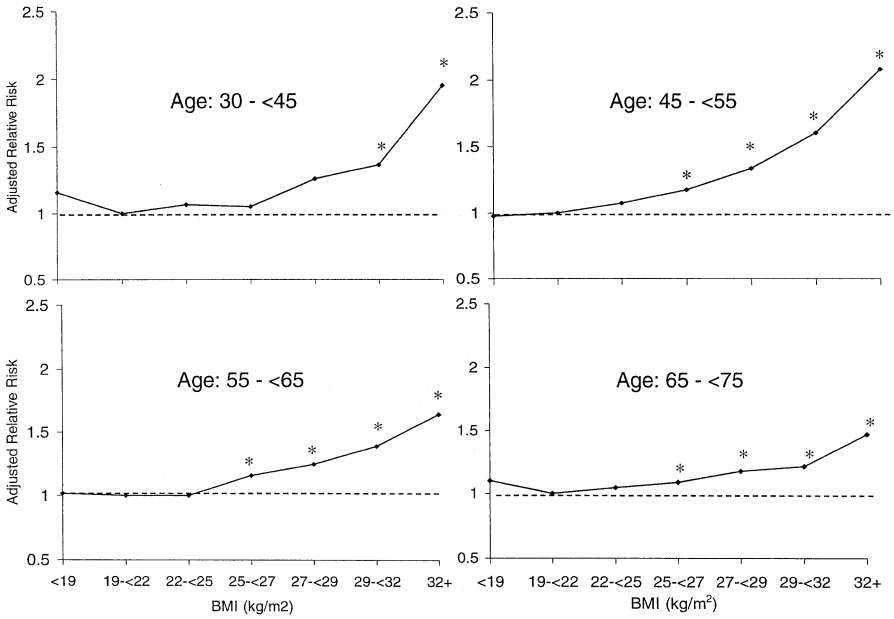

Fig. 1. Relative risk of all-cause mortality in women. Data were from the CPS-I cohort, and analysis was restricted to white women who had never smoked cigarettes, had no history of heart disease, stroke, cancer (other than skin) at baseline in 1959–60, and no history of recent unintentional weight loss (n = 255,682). The relative risks were calculated using proportional hazards regression. Analyses were adjusted for age, education, alcohol consumption, and physical activity. The 19.0 to 21.9 BMI category was the referent. *BMI categories that were significantly ($P < 0.05$) different from the reference category. (Adapted from Stevens J, Cai J, Pamuk E, Williamson D, Thun M, Wood J. The effect of age on the association between body-mass index and mortality. N Engl J Med 1998;338:1–7.)

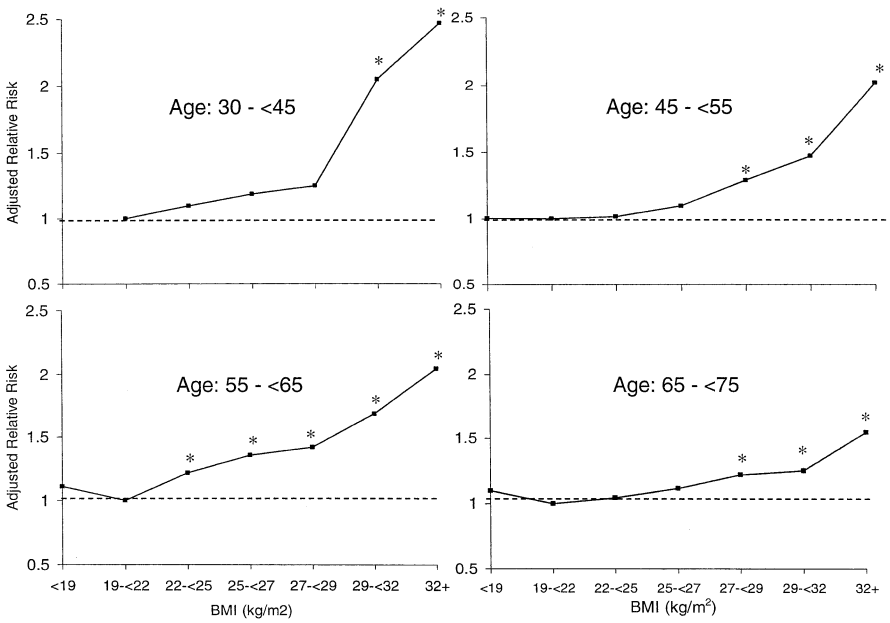

Fig. 2. Relative risk of all-cause mortality in men. Data were from the CPS-I cohort, and analysis was restricted to white men who had never smoked cigarettes, had no history of heart disease, stroke, cancer (other than skin) at baseline in 1959–60, and no history of recent unintentional weight loss (n = 60,217). Relative risks were calculated using proportional hazards regression. Analyses were adjusted for age, education, alcohol consumption, and physical activity. The 19.0 to 21.9 BMI category was the referent. *BMI categories that were significantly ($P < 0.05$) different from the reference category. (Adapted from Stevens J, Cai J, Pamuk E, Williamson D, Thun M, Wood J. The effect of age on the association between body-mass index and mortality. N Engl J Med 1998;338:1–7.)

moderately increased BMI (25.0 to 29.9) were very similar (1.19 in men and 1.17 in women). At higher levels of BMI, differences in risk between men and women were not statistically significant, but the risk within BMI categories tended to be higher in men than in women—exactly the opposite of what might have been predicted from the known differences in body composition. Similarly, in the CPS-II cohort,[17] the lowest BMI above the reference level at which a significant increase in mortality risk was observed was the same in men and women (25.0 to 26.6 for ages 30 to 64 years). Finally, the BMI associated with the lowest mortality in the NHANES I Epidemiologic Follow-up Study (NHEFS) was not statistically different by sex at 24.8 (95% confidence interval [CI]: 23.8 to 25.9) in men and 24.3 (95% CI: 23.3 to 25.4) in women.[19] Thus it does not appear that there are differences in the range of BMI associated with the lowest mortality in men as opposed to women.

CONSEQUENCES OF OBESITY AMONG DIFFERENT ETHNIC GROUPS

In February 2000 a report was issued jointly by the Regional Office for the Western Pacific World Health Organization, the International Association for the Study of Obesity, and the International Obesity Task Force, which addressed the definitions of overweight and obesity in Asian populations.[20] The report states that, "In Pacific Island populations, e.g., Samoa, the recommended BMI standards should be higher than those recommended by WHO…, whereas in certain other Asian populations, such as Chinese and Japanese, it is likely that they should be lower." There are many studies showing that the risk associated with obesity may differ from that seen in Caucasians in other ethnic groups. This review will be limited to data from African-Americans.

There have been a limited number of studies of the BMI-mortality association in African-Americans, and most of those studies are from small cohorts formed more than three decades ago. Given the secular changes that have occurred in all-cause and cause-specific mortality rates over this period,[21,22] and the social changes that have occurred among African-Americans since 1960, it is likely that associations with obesity have also changed. Stevens et al.[23] recently reviewed several studies on associations of obesity with all-cause mortality in African-Americans. In general, these studies found that the relative

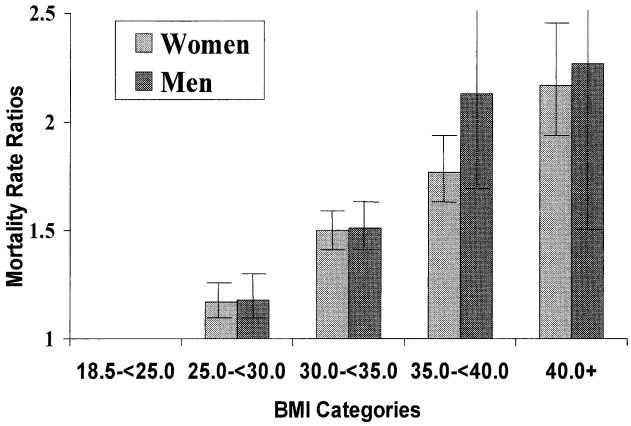

Fig. 3. Rate ratios for mortality among 30- to 70-year-old white men and women. Data were from the CPS-I cohort, and analysis was restricted to 30- to 70-year-old healthy white men (n = 57,073) and white women (n = 240,158) who had never smoked. Rate ratios were calculated using proportional hazards regression. Values were adjusted for age, education, and physical activity. All values were significantly different from the normal range ($P < 0.001$). (Adapted from Stevens J, Cai J, Juhaeri Thun M, Wood J. Evaluation of the WHO and the NHANES II standards for overweight using mortality rates. J Am Diet Assoc 2000;100:825-827.)

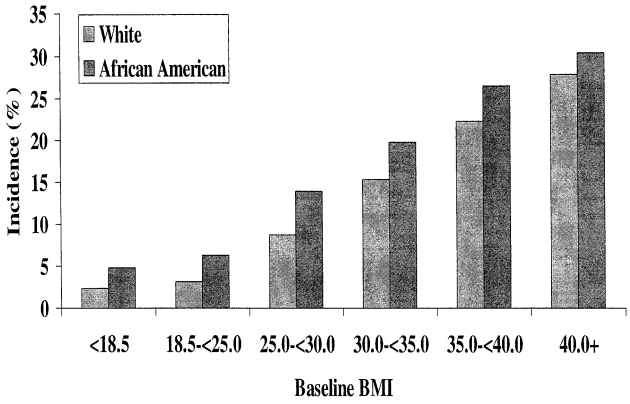

Fig. 4. Nine-year incidence of diabetes (%) in white and African-American women. Data were from the ARIC study, and analysis was restricted to white (n = 5552) and African-American (n = 2078) women who did not have diabetes at baseline. Participants were classified as having diabetes on the basis of the following criteria: (1) self-report that a physician had told them they had diabetes; (2) self-reported use of diabetes medication; (3) fasting serum glucose level ≥126 mg/dl; or (4) nonfasting serum glucose level ≥200 mg/dl. Incidence rates are unadjusted.

risk associated with BMI was smaller in African-Americans compared to Caucasians, and indeed was often not statistically significant.[17,19,24–30]

If the available studies on the association between BMI and mortality were to form the basis of a decision regarding the need for the ethnic-specific BMI cutpoint for obesity, there appears to be ample evidence to support a higher cutpoint for African-Americans than for Caucasians. However, more studies are needed in modern cohorts of African-Americans. In addition, mortality may not be the appropriate outcome or the only outcome that should be considered in assigning risk associated with BMI. Obesity is associated with several health conditions such as hypertension, diabetes mellitus, insulin resistance, dyslipidemia, cardiovascular disease, gallbladder disease, and sleep apnea.

Fig. 4 shows the associations between BMI and the incidence of diabetes in African-American and Caucasian women from the Atherosclerosis Risk in Communities (ARIC) study. The incidence of diabetes was higher within every BMI category in African-American women compared to Caucasian women. Nevertheless, the incidence increased steadily with increasing BMI in both African-American and Caucasian women.

We have demonstrated that a higher, a lower, or a similar BMI cutpoint for obesity could be recommended for African-American women relative to Caucasian women depending on the outcome and the measure of effect examined.[31] Some of the differences in BMI-associated risk noted here between African-Americans and Caucasians could be due to differences in body composition that are not captured by BMI.[32] In addition, cultural and environmental factors other than body weight may have powerful effects on these outcomes.

Several different diseases and health outcomes could be used to set BMI cutpoints; however, it is difficult to defend the use of any one disease or risk factor over others to set standards for obesity. A measure such as disability-adjusted life years offers one option that could be used as an outcome to set obesity standards.[33] Explicit statement of the measures of effect and the outcomes used to determine a BMI cutpoint for obesity would aid the quantitative evaluation of cutpoints for different ethnic groups. Current evidence indicates that the BMI associated with the lowest mortality rate in adults does not differ by age or by sex. More research is needed on obesity and its consequences in ethnically diverse populations.

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Body Weight Regulation and Obesity

Lee M. Kaplan, M.D., Ph.D.

Obesity can be defined as a state of excess body fat, or body energy stores in excess of physiologic needs. During the past 25 years, this disorder has increased dramatically throughout the world. In the United States the prevalence in adults has more than doubled to nearly 31%.[1] Rates of increase are even greater in children, suggesting that the prevalence of obesity will continue to rise for the foreseeable future.[2] Most disturbingly, the most severe form of obesity (class III or above by body mass index; see below) now affects 2.2% of the adult population in the United States, up from 0.78% as recently as 1990.[3] Because excess body fat is associated with a large number of debilitating and life-threatening medical complications, the medical consequences of obesity are increasing rapidly as well. In the late 1990s it was estimated that in the United States alone, approximately 300,000 premature deaths yearly resulted from complications of obesity.[4] This premature mortality rate is second only to tobacco use. Recent economic analysis suggests that the total medical costs associated with obesity exceed those associated with tobacco, likely because of the prolonged course of many of the serious medical complications of obesity.[4] The yearly medical costs of obesity are conservatively estimated at $123 billion in this country, with consumers spending nearly $50 billion more on products and services to induce weight loss.[5]

For clinical convenience, the degree of obesity is most frequently estimated by body mass index (BMI), which correlates reasonably well with total body fat. BMI is calculated as weight divided by the square of height and is reported in the metric units of kg/m^2. If measurements are made in pounds and inches, the following formula can be used to convert from English to metric units:

$$\text{BMI (in kg/m}^2) = \frac{\text{weight (lbs.)}}{[\text{height (in.)}]^2} \times 703$$

Table 1 lists the definitions of normal and disordered body weight by BMI criteria.

Morbidity from complicating disorders, as well as overall mortality, has been shown to be closely associated with the degree of obesity.[6–8] Depending on the particular medical complication examined, the risk may increase linearly (e.g., hypercholesterolemia, gallstones) or exponentially (e.g., diabetes, obstructive sleep apnea) with increasing BMI.

More than 40 distinct disorders are caused, exacerbated, or made substantially more likely by obesity. These medical complications (or "comorbidities") can be conveniently classified into five categories: metabolic, anatomic, degenerative, neoplastic, and psychological.[9] Table 2 lists the major disorders in each category. This list does not include specific disorders that can *cause* obesity (e.g., medications, hypothyroidism, Cushing's disease, and hypothalamic tumors or injury). Nonetheless, it is important to note that several of the *consequences* of obesity listed in Table 2 can, in turn, exacerbate the underlying obesity itself, leading to a vicious cycle. For example, arthritis and vertebral disc disease can interfere with physical exercise, increasing the propensity to additional weight gain. Several of the treatments for diabetes mellitus promote weight gain; these include insulin, sulfonylureas, and the thiazolidinediones (e.g., pioglitazone [Actos] and rosiglitazone [Avandia]).[10] Psychological complications, including depression and binge eating disorder, and several of the medications used to treat depression, may also exacerbate the underlying obesity[11,12] (Table 3).

The severe clinical effects of obesity, along with the increasing understanding of the biological mechanisms of normal and abnormal body weight regulation, have raised the awareness of obesity as a medical disorder and has accelerated the search for effective management strategies. The profound and durable effect of weight loss surgery, described elsewhere

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Table 1. Definitions of body weight disorders in adults by body mass index (BMI)*

BMI (kg/m^2)	Classification
<18 (women)	Underweight
<19 (men)	
18–25 (women)	Normal weight
19–25 (men)	
25–30	Overweight
>30	Obesity
30–35	Class I
35–40	Class II
>40	Class III
40–50	Class IIIr
50–60	Class IV (superobese)
>60	Class V (super-super obese)

*The World Health Organization and the United States Centers for Disease Control and Prevention define three classes of obesity, as listed in the table. The rapid increase in the prevalence of class III obesity, coupled with evidence that patients with BMI greater than 50 or 60 may benefit from different surgical approaches, suggests the utility of further subdividing class III obesity, listed in this table as class IIIr, class IV, and class V. In the surgical literature, people with class IV obesity have often been termed "superobese" and those with class V obesity "super-super obese."

Table 2. Medical complications of obesity

A. Metabolic
- Diabetes mellitus, type II
- Hypertriglyceridemia
- Hypercholesterolemia
- Hypertension
- Gallstones
- Fatty liver disease (NASH)
- Pancreatitis
- Central sleep apnea (obesity hypoventilation syndrome)
- Platelet dysfunction (hypercoagulability)
- Reproductive dysfunction

B. Anatomic/structural
- Obstructive sleep apnea
- Gastroesophageal reflux disease (GERD)
- GERD-associated asthma
- Stress incontinence
- Pseudotumor cerebri
- Venous stasis
- Stasis-associated cellulitis
- Deep venous thrombosis
- Pulmonary embolism
- Fungal skin infections (intertrigo)
- Decubitus ulcers
- Accidental injuries

C. Degenerative (require obesity over extended time)
- Atherosclerotic cardiovascular disease
- Complications of diabetes (neurologic, ophthalmologic, renal)
- Heart failure
- Degenerative joint disease
- Vertebral disc disease
- NASH-related cirrhosis

D. Neoplastic
- Breast carcinoma
- Ovarian carcinoma
- Endometrial carcinoma
- Prostate carcinoma
- Colorectal carcinoma
- Gallbladder carcinoma
- Pancreatic adenocarcinoma
- Esophageal adenocarcinoma
- Renal cell carcinoma
- Non-Hodgkin's lymphoma

E. Psychological
- Anxiety disorders
- Depression
- Binge eating disorder
- Reactive bulimia

in this issue, provides hope and opportunity for patients and physicians.[13,14] Moreover, examination of the mechanisms by which surgery induces weight loss will be a boon to investigators seeking to understand the biological basis of obesity itself. Despite the increasing awareness of the causes, complications, and effective treatments of obesity, persistent misconceptions about the nature of weight disorders fuel continued prejudice among health care professionals and the public at large. It is particularly unfortunate that, despite having an increased risk of several "preventable" diseases, persons with obesity undergo routine health screening procedures significantly less frequently and less consistently than others.[15–17]

OVERVIEW OF WEIGHT REGULATION

On the simplest level, maintaining a stable body weight requires balancing food intake and energy expenditure. Fat accounts for nearly all of the body's energy stores, and appropriate regulation of these energy stores (particularly the avoidance of energy depletion) is critical to normal growth and development. Under normal circumstances, body weight is very tightly regulated. Despite wide daily variations in food intake, overall energy expenditure is regulated to match energy input within a tolerance of less than 0.2%. Even a small mismatch (e.g., 1% to 2%) between energy intake and expenditure, applied over time, can lead to profound fat accumulation and severe obesity.[18,19]

Experiments in animals and humans have demonstrated the extraordinary effectiveness of body energy

Table 3. Medications commonly associated with weight gain

Corticosteroids
Estrogens
Hormone-replacement therapy
Olanzapine (Zyprexa)
Clozapine (Clozaril)
Valproic acid (Depakote and others)
Antidepressants (e.g., mirtazapine [Remeron], risperidone [Risperdal])
Serotonin-selective reuptake inhibitors (SSRIs; e.g., citalopram hydrobromide [Celexa], paroxetine [Paxil])
Insulin
Sulfonylureas (e.g., glyburide, glipizide)
Thiazolidinediones (rosiglitazone [Avandia], pioglitazone [Actos])

(and therefore weight) regulatory mechanisms. After a period of forced overfeeding and weight gain, mice and rats exhibit a profound decrease in food intake until their weight has returned to normal, at which time food intake increases to normal.[20] The reverse is true after a period of starvation. That similar mechanisms operate in humans has been demonstrated most dramatically in actors who must gain a large amount of weight for specific roles. They often need to consume vast quantities of food to overcome the natural resistance to acute weight gain; after filming is complete, they typically lose most of the excess weight rapidly and easily.

The apparent physiologic effects of acute weight change are shown in Fig. 1, which depicts patterns of energy intake and expenditure with varying BMI.[20]

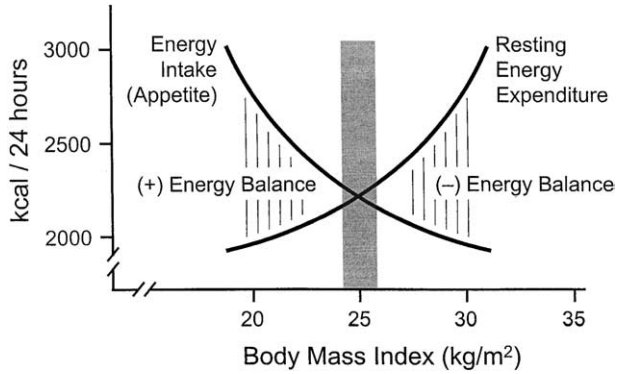

Fig. 1. Theoretical basis for a stable energy set point. According to this model, as energy stores (body weight) vary from the equilibrium set point, compensatory changes in energy intake (appetite and food ingestion) and total energy expenditure act to return energy stores to baseline. (Adapted from Weigle DS. Appetite and the regulation of body composition. FASEB J 1994;8:302–310.)

Under normal circumstances, energy intake equals energy expenditure. This situation is often termed the energy "set point," although the specific parameter that is "set" (e.g., total body fat, leptin level, and so forth) and how the set point is established are currently unknown. Acute deviation to a higher weight (e.g., by overfeeding) appears to cause an increase in resting energy expenditure and a decrease in food intake (through a diminished appetite). The reverse occurs with acute weight loss (e.g., after dieting). In that case compensatory mechanisms, including an increased appetite and decreased resting energy expenditure, foster a return to baseline conditions. It is unknown why some persons exhibit an elevated set point and appear to defend an inappropriately high body weight. Why, for many individuals, the set point appears to increase over time, is equally unclear. It is tempting to speculate that periods of acute weight loss (e.g., from diets) are interpreted as evidence of a scarce food supply and that compensatory mechanisms favor subsequent storage of excess fat as a protection against the possibility of future "famine."

The system of energy and body weight regulation reflects the influence of many millennia of mammalian and human evolution. The environmental conditions during most of evolutionary history likely included a relative scarcity of food and the high energy cost of hunting and gathering nutrients. As a result of this influence, genetically determined systems to regulate energy homeostasis are likely biased to prevent starvation and its metabolic consequences. Most people appear to have fewer protections against excess fat storage.[21] The current environment is likely the first in human history with an abundant supply of highly palatable, energy-dense food available at all times and without a significant energy cost. This environment appears to upset the normal energy balance, either by disrupting the regulatory mechanisms or simply overwhelming the body's ability to compensate metabolically for excessive food intake. Some people appear to be more predisposed to these environmental effects than others, likely as a result of different genetic determinants.

PHYSIOLOGIC MECHANISMS OF WEIGHT AND ENERGY BALANCE

Regulation of body weight appears to be coordinated primarily by the hypothalamus, which receives afferent input from a variety of sources.[22] Circulating leptin levels provide information about body energy stores.[21,23] Signals from the pancreatic islets (especially insulin) and the liver (via vagal afferents) indicate metabolic activity, energy demands, and nutrient

availability for metabolic needs. Recent food intake is signaled by the gastrointestinal tract, and cortical input provides information about nutrient availability (e.g., sight and smell of food).[22] The hypothalamus then orchestrates the physiologic response, including regulation of food intake and energy expenditure. Systems for this coordinated response are complex and appear to include regulation of appetite and satiety, interest in food, food-seeking behavior (via cortical pathways), nutrient transport and metabolism, resting energy expenditure in muscle and fat (via the sympathetic nervous system), and physical activity (Fig. 2).[22–24]

The Role of Leptin

Leptin, a hormone secreted by adipocytes, was discovered in 1994 by Zhang et al.[25] in a naturally occurring mutant, the *obese* mouse. They discovered that this mouse has a mutation in the gene encoding leptin so that it is unable to make any of this protein. The hypothalamus misinterprets the complete absence of circulating leptin as a profound deficiency of energy stores. As a result, these animals are stimulated to excessive food intake and profound energy conservation, leading to severe obesity (body weights up to five times normal). Treatment of these animals with leptin completely reverses these effects and returns the animals to a normal, healthy weight.[21]

Overall body fat stores are reflected in circulating concentrations of leptin.[21] Increases or decreases in total body fat mass are associated with parallel changes in blood leptin levels. Two classes of hypothalamic neurons bearing leptin receptors are able to sense leptin levels and coordinate an appropriate physiologic response.[22,23] Activation of one group of neurons stimulates food intake and energy conservation. These neurons typically secrete melanocortins (e.g., α-melanocyte–stimulating hormone) and cocaine- and amphetamine-related transcript protein. The other group of neurons, which secretes neuropeptide Y and agouti-related peptide, exerts the opposite effects. Under conditions of starvation and decreased fat stores, low blood leptin levels *activate* neurons in the first group and *inhibit* neurons in the second group, in both cases stimulating an increase in net body energy storage.

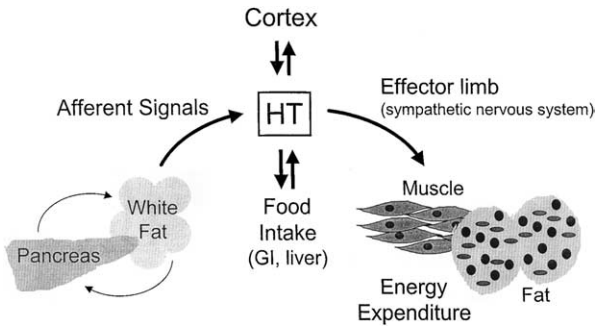

Fig. 2. Regulation of body energy stores. The hypothalamus (HT) is the central coordinator of body energy stores. It receives input from the pancreatic islets, white fat, gastrointestinal tract, liver, and cerebral cortex and coordinates energy homeostasis by influencing behavior, food intake, and energy expenditure.

The Role of the Gastrointestinal Tract

Information about recent food intake and digestion, communicated from the gastrointestinal tract and liver to several areas of the brain, appears to have a strong influence over ingestive behavior and overall energy homeostasis.[26,27] Several peptides synthesized and secreted within the gastrointestinal tract are known to regulate eating behavior. Ghrelin, galanin, and protein YY (PYY) stimulate food intake,[28–30] whereas cholecystokinin (CCK), gastric inhibitory peptide, glucagon-like peptide-1 (GLP-1), urocortin, and a circulating fragment of PYY ($PYY_{3–36}$) have the opposite effect.[26,29,31,32] Many of these peptides circulate in the blood and have direct access to parts of the hypothalamus and the area postrema, brain regions involved in the regulation of food intake. In addition, locally secreted peptides within the gut appear to influence the activity of neurons, especially vagal afferents that project from the gastrointestinal tract to the brain.[22]

The current working model suggests that food ingestion stimulates both mechanical (stretch or pressure) and chemical receptors within the stomach that activate vagal fibers projecting to the nucleus of the solitary tract.[22,26,33] These signals act to decrease appetite and promote satiety, presumably via connections from the nucleus of the solitary tract to the hypothalamus and other regions involved in the regulation of body weight and energy balance. Additional signals emanate from the small intestine, where chemoreceptors, and possibly additional mechanical receptors, sense the presence of nutrients. These mechanisms likely regulate the size of meals and prevent potentially dangerous overeating when food becomes available after a prolonged period of fasting.

Despite the powerful influences of gut peptides on ingestive behavior, the role of the gastrointestinal tract in the overall regulation of energy balance has been unclear. For example, while administration of CCK or GLP-1 leads to immediate cessation of eating, chronic administration of these peptides leads

to an increased number of smaller meals, without changing total food intake or body weight.[26]

Three recent observations suggest a greater physiologic role of the gastrointestinal tract in regulation of body weight. The first relates to ghrelin, a peptide synthesized primarily in the stomach that strongly stimulates food intake. In animals and people, circulating ghrelin levels vary widely depending on the recent history of food intake. They rise with fasting and fall rapidly after each meal is eaten, suggesting that ghrelin may be a major determinant of hunger and satiety.[28] In addition, acute weight loss (e.g., from dieting) is associated with an increase in circulating ghrelin in both fed and fasting states, suggesting that ghrelin may contribute to the mechanisms by which the body attempts to counteract acute weight loss.

A second recent observation is that administration of $PYY_{3–36}$, a fragment of PYY with unique biological properties, inhibits both food intake and short-term body weight gain.[29] Thus $PYY_{3–36}$ exhibits at least the potential of exerting long-term influences on body weight and energy balance. The degree to which these peptides, or the many other gastrointestinal proteins that affect food intake, contribute to the overall regulation of energy homeostasis remains unknown.

The third, and possibly most compelling, line of evidence for gastrointestinal regulation of body weight comes from studies of gastric and intestinal surgery. As described elsewhere in this issue, Roux-en-Y gastric bypass, gastroplasty, and gastric banding induce profound and sustained weight loss in persons with severe obesity.[13,14,34–37] These "restrictive" procedures have long been thought to work by limiting the amount of food that can be ingested at any one time and provide strong negative feedback overeating (e.g., from nausea, vomiting, and substernal pain) to that induces behavioral change.[14,38] More recent observations, however, suggest that many of the observed effects of these operations result from alterations in physiologic mechanisms regulating appetite, satiety, and energy expenditure.[39,40] Patients undergoing gastric weight loss surgery report dramatic reductions in hunger, accelerated satiety, decreased overall interest in food, decreased food cravings, and altered food preferences, all of which suggest modification of the basic appetite control mechanisms (Baker CW, Kaplan LM, 2002, unpublished observations). In addition, one small study suggests that resting energy expenditure, which normally decreases dramatically in response to acute weight loss, is preserved after gastric bypass or gastroplasty.[41] The latter observation, in particular, suggests that these anatomic manipulations of the upper gastrointestinal tract work through mechanisms other than simple restriction of food intake. Further supporting this notion are recent observations by Cummings et al.[28] who found that circulating ghrelin levels fall dramatically late after gastric bypass surgery. The decrease in ghrelin after weight loss surgery contrasts sharply with the increase in circulating levels after other forms of weight loss. Lower ghrelin levels may contribute to the diminished appetite and increased satiety experienced by patients undergoing gastric bypass. Moreover, these data provide additional evidence that surgery works through mechanisms other than "forced" dietary restriction.

WHAT CAUSES OBESITY?

Despite the rapid increase in knowledge about the physiologic mechanisms regulating body weight and energy balance, the causes of human obesity remain poorly understood. Worldwide, a few dozen persons have been identified as having a genetic deficiency of leptin or its receptor,[21] and a few others with profound obesity have been found to have other mutations in known weight-regulating genes.[31]

Human obesity appears to result from a combination of genetic, developmental, environmental, and psychological influences.[42] Clinical observation suggests that obesity represents the common outcome of a spectrum of different disorders, evident by the differing ages of onset, distribution of body fat, eating behaviors, associated diseases, and heritability. These phenotypic variations are likely to reflect distinct defects (or groups of defects) in the cortical (including psychological), hypothalamic, gastrointestinal, endocrine, and metabolic components of the weight regulatory system, although no specific information is yet available to distinguish them. It is nonetheless intriguing to consider whether such variations might predict prognosis or response to specific therapies.

Genetic Factors

Several lines of epidemiologic evidence suggest that genetic factors account for up to 80% of a person's predisposition to develop obesity.[42] The discovery during the past several years of specific genetic defects that lead to or provide protection against obesity in animals and humans has increased our understanding of the important role of genes in this disorder. Evidence for a strong genetic contribution to human obesity comes from a variety of sources including twin and family studies. Several such studies have calculated the correlation between the BMI of related pairs of individuals. For genetically unrelated spouses, the BMI correlation is approximately 10%. For first cousins it is approximately 15%. For

parent-child pairs and siblings, the correlation is approximately 25%, and for monozygotic twins it is between 80% and 90%.[42]

Other support for the genetic basis of obesity comes from animal studies.[31] There are several naturally occurring models of weight dysregulation in mice and rats, including single-gene defects that lead inexorably to obesity and polygenic traits that affect the susceptibility to diet-induced obesity. As described earlier, the defect in one of these strains, the *obese* (*ob/ob*) mouse, was shown by Zhang et al.[25] to reside in the gene encoding leptin, a circulating hormone secreted by fat cells that signals the level of energy reserves (body fat) to the hypothalamus. Identification of the defects in other strains of genetically obese mice and rats has revealed several additional components of the normal weight regulatory system. Similar studies have also identified the mechanisms underlying the resistance to obesity exhibited by other naturally occurring and genetically engineered strains of mice.

Although a few individuals with severe obesity have been shown to lack leptin, nearly all obese individuals exhibit an excess of circulating leptin in direct proportion to their BMI.[21] Thus human obesity appears to result from functional resistance to the effects of leptin, much as type II diabetes results, in part, from resistance to the physiologic effects of insulin. Not surprisingly, therefore, early clinical trials have shown little effect of leptin in substantially decreasing body weight in most obese individuals. The precise mechanisms of leptin resistance in human obesity are currently unknown.[19,23]

Recent genetic discoveries have illuminated the biological mechanisms and metabolic pathways whose disruption underlies obesity. These discoveries have provided several new targets for intervention and drug discovery.[10,31,43] They have led to accelerated activity within the biotechnology and pharmaceutical industries and have generated great enthusiasm within the scientific community. At present, there are more than 150 new drugs undergoing evaluation for obesity treatment, with about a dozen in early clinical development.

Environmental Contributors

Although genetic mechanisms strongly influence body weight regulation, recent history clearly demonstrates the important role of the environment. During the past generation, the prevalence of obesity has doubled in the adult population and more than doubled in children and adolescents. These dramatic changes underscore the influence of environmental factors on the regulation of body weight and their importance to the development of obesity. One way to reconcile the respective roles of genetics and environment in the development of obesity is to consider the population distribution as a function of BMI (Fig. 3). Where one sits on this distribution (lower end, middle, or upper end, for example) is likely determined by genetic factors. People who are at the heavier end of the distribution today would likely have been at the heavier end if they had lived earlier in history. The environmental factors determine the *breadth* of this curve, and recent changes in our environment have stretched the distribution far to the right. As a result, people who sit in the middle of the BMI distribution are now edging into the obesity range.

Several environmental factors have been proposed to explain the recent rise in the prevalence of obesity.[6,44] There is a decreased requirement for physical activity at school, home, or work, or for short-distance travel. Work and leisure time activities are less and less likely to require physical exertion. Remote controls, computers, escalators, and automobiles are integral parts of modern life that contribute to this phenomenon. Food has never been more abundant or accessible. Moreover, our appetite and weight regulatory mechanisms may be fooled by highly processed, homogeneous, and/or calorie-dense foods,

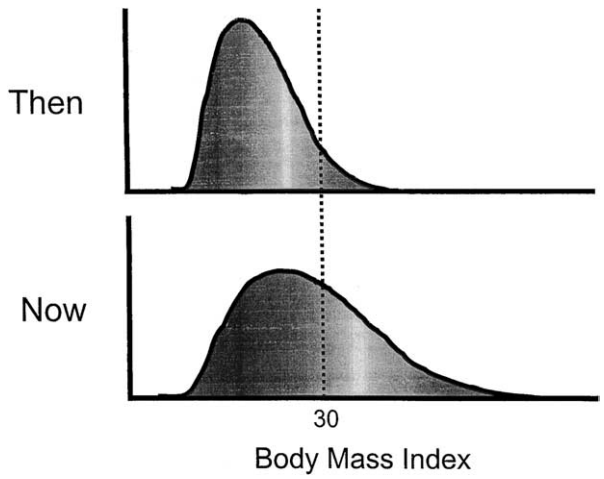

Fig. 3. Model of the interaction of genetic and environmental influences on obesity. Genetic influences likely determine a person's place in the BMI distribution (spectrum) of the population. Environmental factors determine the characteristics of the population as a whole. In recent years the BMI distribution has been skewed strongly to the right. Although a person's predisposition to obesity is partly determined by genetic factors, it is also affected by the overall prevalence of obesity in the population, which is strongly influenced by environmental factors.

leading to excess caloric intake. The marginal economic cost of additional calories has plummeted with the trend toward "supersizing" in fast food restaurants and outsized quantities of food available through wholesale outlets. There has been an average 200 to 250 kcal/person/day increase in food consumption by adults over the past 25 years, despite a decrease in the percentage of fat in the diet.[45,46] The consumption of carbohydrates, particularly simple sugars and starches, has risen profoundly during this time. Other potential environmental contributors are the chaotic patterns of food consumption, with rapid eating, snacking, "grazing," and steady consumption of high-calorie soft drinks the norm. These patterns have largely replaced the regular, slow-paced meals that remain in parts of the world where obesity is less prevalent. The increasing stress and pace of modern life, the lack of sleep, and disordered sleep patterns may also play a role, although their specific effect on the weight regulatory machinery is not known.

Other environmental factors act more immediately on food consumption. Certain situations, times of day, or emotional experiences may provoke eating. The sight, smell, and proximity to food contribute as well. The relative contributions of these various factors and how they interact with the endogenous weight regulatory machinery are not known. Which factors can be resisted with careful planning or sheer willpower, which are amenable to change, and which are immutable or intrinsic to modern society remain subjects of considerable debate. It appears that obesity is a heterogeneous series of disorders affecting different individuals differently. If so, the answers to these questions will vary for different people.

One unique type of environmental exposure results from treatment with medications that promote obesity. Drugs in several classes are associated with abnormal weight gain (Table 3), most notably steroids, insulin, and several classes of psychotropic agents.

Developmental Influences

Developmental effects include those environmental stimuli that exert changes that persist beyond the period of the stimulus. Such effects, often limited to susceptible periods of development, may be difficult to reverse or extinguish at later times. They are often described as "hard-wired," nongenetic events and may include patterns of speech, accents, memory for specific quotes, songs, or pieces learned on a musical instrument, physical skills, and habits.

Relatively little is known about developmental influences on obesity. An early suggestion of the importance of such influences, however, came from examination of children born soon after the Dutch famine of 1947. This famine was profound but short-lived, providing the opportunity to examine the role of maternal nourishment on fetal outcomes. As shown by Ravelli et al.,[47] offspring of mothers who were in the first half of pregnancy at the time of the famine had a significantly greater likelihood of developing obesity than those whose mothers were in the third trimester or those were newly born. Other factors have been postulated to exert a developmental influence on obesity, including eating patterns and food exposure during early childhood as well as use of food as a reward mechanism in time-pressed households. These factors, along with decreased physical activity in school and at play, may all conspire to set patterns that are impossible to reverse later in life. To the degree that environmental influences in early childhood promote obesity during adolescence and adulthood, preventive strategies applied early in life will be essential.

Psychological Factors

Many obese persons appear to increase their food intake in response to emotional stress. In some cases specific emotions provoke eating, such as anxiety, depression, boredom, or even happiness.[38,48] In others, the response is less specific. The conflict between cultural ideals and physical reality can lead to frustration, depression, and low self-esteem, which may exacerbate these tendencies. The intense societal focus on thinness, combined with pressures from the commercial weight loss industry, creates unrealistic expectations about desirable body weight. This environment is conducive to psychological sequelae including binge eating, emotional eating, bulimia, or body image distortion, any one of which can exacerbate or complicate the obesity itself. The degree to which psychological factors are the *primary* cause of obesity is less clear. Several studies have reported an association between previous psychological trauma (sexual, physical, and/or emotional) and the development of obesity. Others, however, suggest that persons with weight disorders are no more likely to have experienced such trauma than persons without excess weight or obesity.[49,50] They would conclude that the eating disorders associated with obesity reflect an innate genetic predisposition or a conditioned response to stressful experiences. Whatever their role in individual patients, it appears that psychological contributors to obesity, similar to the physiologic ones described earlier, reflect a combination of genetic, environmental, and developmental influences.

IMPLICATIONS FOR OBESITY THERAPY

Recent studies have revealed the strength and complexity of the body's weight and energy regulatory systems. A variety of endocrine, metabolic, gastrointestinal, neurobiological, and psychological mechanisms contribute to these control systems. The increasing knowledge of the molecular basis of weight regulation has led to the identification of a large number of potential targets for antiobesity drugs. As a result, dozens of new compounds have been developed and are undergoing preclinical and clinical testing.[10]

The dramatic and sustained effects induced by weight loss surgery provide a unique model for the study of obesity. Gastric surgery appears to induce profound effects on physiologic mechanisms that regulate body weight. The decreased appetite, altered behavioral response to food, and relative increase in energy expenditure suggest that surgery may alter the physiologic set point (see Fig. 4 for a potential model of this effect). If so, the resulting weight loss would represent a response to these physiologic changes rather than a conscious resistance to these control mechanisms. Identification of the precise mechanisms that account for weight loss after gastric and intestinal surgery will contribute substantially to our understanding of the regulation of food intake, energy metabolism, and body weight, especially the role of the gastrointestinal tract in these processes. Knowledge of the mechanisms of weight loss after surgery and the basis for variation in the clinical response may also reveal important clues to the molecular basis of obesity itself. Most important, better understanding of these mechanisms will facilitate the search for less invasive means of achieving the same result, whether through physical manipulation, medications, or a combination of the two.

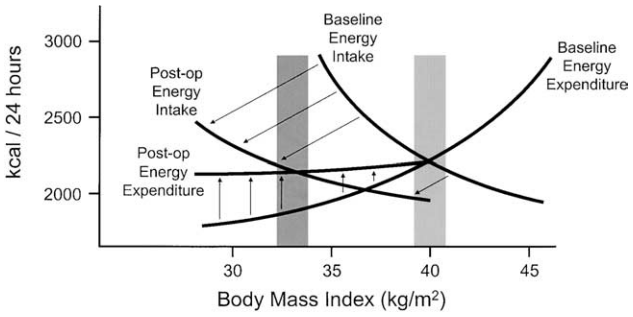

Fig. 4. Proposed model of the effect of gastric bypass surgery on the energy set point. Changes in neuroendocrine signals from the stomach and intestines after gastric bypass surgery alter the relationships among energy stores (represented here as *Body Mass Index*), energy intake (appetite), and total energy expenditure. Surgery appears to decrease energy intake at any given BMI by altering hunger and satiety. There is also evidence that surgery blunts the decrease in total energy expenditure associated with weight loss. If the equilibrium or "set point" is determined by the position at which energy intake equals energy expenditure, surgery would be predicted to cause a decrease in the set point as shown. This model predicts that the body would defend the new set point, with attempts at further weight loss met by normal compensatory responses in appetite and energy expenditure.

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Lifestyle Modification in the Management of Obesity

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America is experiencing an epidemic of obesity. The most recent data indicate that 34% of adults are overweight, defined by a body mass index (BMI) of 25.0 to 29.9 kg/m^2, and an additional 27% are obese, as judged by a BMI $\geq$30 kg/m^2.[1] Obesity is associated with an increased risk of heart disease, stroke, type II diabetes, hypertension, sleep apnea, and osteoarthritis, and contributes to approximately 300,000 deaths per year.[2] In 2000 this disorder cost our nation close to $117 billion.[3]

To address this growing public health problem, a joint committee of the National Heart, Lung, and Blood Institute (NHLBI) and the North American Association for the Study of Obesity (NAASO) recently issued guidelines for the assessment and treatment of obesity.[4] The committee recommended that obese individuals set an initial goal of losing 10% of their body weight. This goal was based on findings that "even moderate weight loss…can significantly decrease the severity of obesity-associated risk factors."[5]

The most compelling evidence, to date, of the health benefits of a modest weight loss was provided by the Diabetes Prevention Program.[6] This randomized controlled trial enrolled more than 3000 overweight or obese persons with impaired glucose tolerance (i.e., fasting blood glucose of 95 to 125 mg/dl). Participants who received an intensive program of diet and physical activity lost an average of 7 kg and reduced their risk of developing diabetes by 58% over a 3- to 4-year period, compared with individuals who received placebo. As shown in Fig. 1, the lifestyle intervention was also superior to treatment with metformin (i.e., 850 mg bid). The lifestyle intervention was effective in all persons, including minority members and older participants. In addition, lifestyle participants experienced marked reductions in the risk of developing diabetes despite regaining 2 to 3 kg after the first year of treatment. These data leave little doubt about the health benefits of modest weight loss.

The NHLBI/NAASO panel provided an algorithm to guide the selection of weight loss therapy, based on BMI and the presence of risk factors.[4] Persons with a BMI of 25.0 to 29.9 kg/m^2, who have one or no risk factors, are encouraged to prevent weight gain rather than trying to lose weight. Weight loss, however, is recommended for patients with a BMI of 25 to 29.9 kg/m^2 who have two or more risk factors, as it is for persons with a BMI $\geq$30 kg/m^2, regardless of their risk of health complications. As shown in Table 1, all of these individuals should receive a program of diet, physical activity, and behavior therapy. If this intervention is not sufficient to induce a 10% weight loss, additional therapy, including weight loss medications and bariatric surgery, may be provided to appropriate patients.

This article reviews the three major components of lifestyle modification for obesity: (1) diet; (2) exercise; and (3) behavior therapy. We note that behavior therapy refers to a set of principles and techniques for modifying diet and activity.[7,8] It teaches patients ways to achieve their eating and exercise goals.

DIETARY INTERVENTIONS FOR WEIGHT LOSS

Dietary intervention remains a cornerstone of weight reduction efforts.[9] This is because obese persons typically find it easier to reduce their food intake than to increase their physical activity (in order to induce negative energy balance). Dozens of diets are available, but they differ with regard to two principal dimensions—their calorie content and macronutrient balance. Of the two, calorie content is by far the more important for weight loss.[9] The lower the calorie intake, the greater the energy deficit and the resulting weight loss. If a person is in negative energy balance, the relative balance of carbohydrate and fat has little impact on weight loss.[10]

Reducing diets are frequently categorized on the basis of their calorie content, as noted in a report

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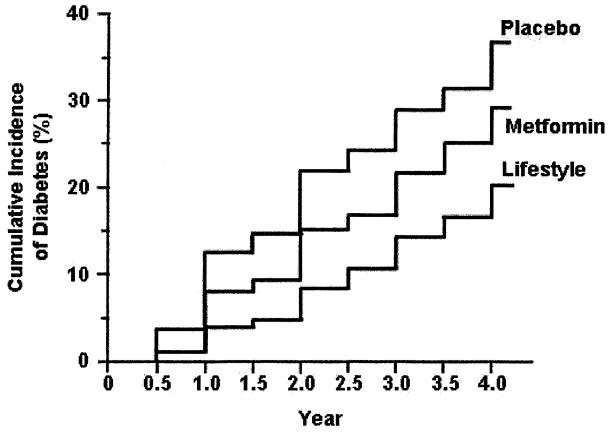

Fig. 1. Cumulative incidence of diabetes for participants in the Diabetes Prevention Program. Patients were randomly assigned to *placebo*, *metformin* (850 mg/day bid), or *lifestyle* modification. The incidence of diabetes differed significantly among the three groups ($P < 0.001$ for each comparison). (From Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.)

prepared by the NHLBI[5] that preceded the joint NHLBI/NAASO publication. Very-low-calorie diets are defined as those providing fewer than 800 kcal/day and low-calorie diets are those that contain 800 to 1500 kcal/day. The term "hypocaloric balanced-deficit diet" is sometimes used to describe diets that provide more than 1500 kcal/day of conventional foods, with an appropriate balance of macronutrients.[10]

The NHLBI/NAASO panel recommended that overweight persons (BMI of 25.0 to 29.9 kg/m^2) who have two or more cardiovascular risk factors consume a mildly hypocaloric balanced-deficit diet to achieve gradual weight loss and, thus, improvement of health complications.[4] A reduction of daily food intake by 300 to 500 kcal may be sufficient.[5] Alternatively, patients may consume a low-fat diet that allows ad libitum consumption of carbohydrates (as discussed later). Persons with a BMI $\geq$35 kg/m^2 often require a more aggressive caloric deficit of 500 to 1000 kcal/day, as induced by a low-calorie diet.[5] These individuals must lose more weight to reach a 10% loss, and greater caloric restriction helps them lose more rapidly. Those who are not successful with this approach may benefit from a portion-controlled low-calorie diet or from a very-low-calorie diet.

Low-Calorie Diets

Table 2, which is taken from the NHLBI/NAASO report,[5] provides an example of a low-calorie diet that would be appropriate for most obese individuals. It calls for a 500 to 1000 kcal/day reduction in energy intake, with approximately 15% of calories from protein, $\leq$30% from fat, and $\geq$55% of calories from carbohydrates. Other recommendations include 20 to 30 grams of fiber a day, as well as 1000 to 1500 mg/day of calcium.

More than 30 randomized trials have shown that low-calorie diets, providing 1000 to 1500 kcal/day, produce losses of approximately 8% of initial body weight in 16 to 26 weeks of treatment.[5] However, two points should be noted about these results. First, in most research trials, patients were given a predetermined calorie goal, rather than one calculated by subtracting 500 to 1000 kcal/day from their baseline energy requirements. For example, Wing[7] usually instructs women to eat 1000 kcal/day and men 1500 kcal/day. This practice is followed for reasons of simplicity and to ensure that all patients achieve a substantial caloric deficit. Second, patients in most studies received behavior therapy, which will be discussed later, in addition to the low-calorie diet. Patients kept diaries in which they recorded daily the foods and number of calories they consumed. Such record keeping is essential for losing weight on a low-calorie diet

Table 1. A guide to selecting treatment

Treatment	BMI category				
	25–26.9	27–29.9	30–35	35–39.9	>40
Diet, exercise, and behavior therapy	With comorbidity	With comorbidity	+	+	+
Pharmacotherapy		With comorbidity	+	+	+
Surgery				With comorbidity	+

Notes: Prevention of weight gain with lifestyle therapy is indicated in any patient with a BMI of 25 kg/m^2, even without comorbid conditions whereas weight loss is not necessarily recommended for those with a BMI of 25 to 29.9 kg/m^2 or a high waist circumference, unless they have two or more comorbid conditions. Combined therapy with a low-calorie diet, increased physical activity, and behavior therapy provide the most successful intervention for weight loss and weight maintenance. Consider pharmocotherapy only if a patient has not lost 1 pound per week after 6 months of combined lifestyle therapy. +=Use of indicated treatment regardless of comorbidity.

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Table 2. Low-calorie step 1 diet

Nutrient	Recommended intake
Calories*	Approximately 500 to 1000 kcal/day reduction from usual intake
Total fat†	30% or less of total calories
Saturated fatty acids‡	8% to 10% of total calories
Monosaturated fatty acids	Up to 15% of total calories
Polyunsaturated fatty acids	Up to 10% of total calories
Cholesterol‡	<300 mg/day
Protein§	Approximately 15% of total calories
Carbohydrate‖	55% or more of total calories
Sodium chloride	No more than 100 mmol/day (approximately 2.4 g of sodium or approximately 6 g of sodium chloride)
Calcium¶	1000 to 1500 mg
Fiber‖	20 to 30 g

*A reduction in calories of 500 to 1000 kcal/day will help achieve a weight loss of 1 to 2 pounds/wk.

†Fat-modified foods may provide a helpful strategy for lowering total fat intake but will only be effective if they are also low in calories and if there is no compensation by calories from other foods.

‡Patients with high blood cholesterol levels may need to use the step 2 diet to achieve further reductions in LDL cholesterol levels; in the step 2 diet saturated fats are reduced to less than 7% of total calories, and cholesterol levels to less than 200 mg/day. All of the other nutrients are the same as in step 1.

§Protein should be derived from plant sources and lean sources of animal protein.

‖Complex carbohydrates from different vegetables, fruits, and whole grains are good sources of vitamins, minerals, and fiber. A diet rich in soluble fiber, including oat bran, legumes, barley, and most fruits and vegetables, may be effective in reducing blood cholesterol levels.

¶During weight loss, attention should be given to maintaining an adequate intake of vitamins and minerals. Maintenance of the recommended calcium intake of 1000 to 1500 mg/day is especially important for women who may be at risk of osteoporosis.

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of conventional foods. Many patients also attended group weight-loss sessions or met individually with a dietitian. Most obese patients will require such care in order to lose 8% of initial weight.[7]

Portion-Controlled Servings and Meal Replacement Plans

Several studies have demonstrated the benefits of using low-calorie diets that provide portion-controlled servings of conventional foods, or of liquid-meal replacements.[7] Portion-controlled diets provide patients with a fixed amount of food with a known calorie content, an approach that facilitates adherence to the target calorie goal. By contrast, obese persons underestimate their caloric intake by 30% to 40% when instructed to consume a reducing diet of self-selected foods.[11] Jeffery et al.,[12] for example, showed that patients who were prescribed a conventional, balanced-deficit diet of 1000 kcal/day lost 7.7 kg in 6 months. Those who were prescribed the same number of calories, but who were also given the actual foods for their breakfast and dinner meals 5 days of each week, lost a significantly greater amount of weight (10.1 kg). The provision of food ensured that patients ate the appropriate portion sizes and number of calories.

Similarly favorable results were obtained with a popular liquid-meal replacement (i.e., Slim Fast). Dietschuneit et al.[13] showed that patients who replaced two meals a day with a liquid supplement lost 8% of their initial weight during the first 3 months, compared with a loss of only 1.5% for patients who were prescribed the same number of calories (i.e., 1200 to 1500 kcal) but consumed a self-selected diet of conventional foods. More impressive were findings that patients who continued to replace one meal and one snack a day with Slim Fast maintained a loss of 11% at 27 months and 8% at 51 months.[14] These findings suggest that long-term use of a meal replacement may significantly improve the maintenance of weight loss compared with treatment by a conventional balanced-deficit diet.[14] Meal replacements, which include frozen food entrees and prepackaged fresh foods, would appear to offer an excellent antidote to the supersized portions marketed to the public by fast-food restaurants and convenience stores.

Very-Low-Calorie Diets

Very-low-calorie diets are reserved for patients with a BMI $\geq$30 kg/m^2 in whom the greater risk of health complications may justify more aggressive (and expensive) interventions.[15,16] These diets provide 200 to 800 kcal/day and large amounts of dietary protein, approximately 70 to 100 g/day, to preserve lean body mass. A popular liquid diet provides 800 kcal/day, with 70 g of protein, 100 g of carbohydrate, and 15 g of fat. Alternatively, protein may be obtained from lean meat, fish, or fowl, an approach referred to as a protein-sparing modified fast. Both diets appear to be safe when supplemented with adequate vitamins and minerals and when provided to appropriately selected patients under careful medical supervision, as described elsewhere.[15,16] Very-low-calorie diets are, however, associated with an increased risk of gallstones, a complication that can be prevented by taking ursodeoxycholic acid or aspirin.[17]

Very-low-calorie diets produce reductions of approximately 15% to 20% of initial weight in 12 to 16 weeks of treatment—losses nearly double the size of those produced by a conventional low-calorie diet in a comparable period. At least seven randomized trials have compared the short- and long-term results of these two dietary approaches.[18–24] All but one study[18] found that patients treated by either approach regained weight within the year after treatment. Those treated by a very-low-calorie diet, however, regained substantially more weight so that at follow-up there were not any statistically significant differences between the two approaches. These findings raise questions concerning whether very-low-calorie diets are worth the greater expense (i.e., approximately $3000 for a 6-month program) compared with a traditional low-calorie diet.

Low-Fat and Low-Energy Density Diets

Both low-calorie diets and very-low-calorie diets focus principally on caloric restriction which, while effective in the short-term, may be associated over the long term with reports of hunger and deprivation, as well as with weight regain.[10] These findings have led several investigators to propose an alternative strategy that focuses on reducing fat intake while allowing ad libitum intake of carbohydrates.

Two principal findings have emerged from studies of ad libitum low-fat diets as a treatment for obesity. The first is that reducing fat intake alone produces smaller weight loss than restricting both fat and total calorie intake,[9] as would be expected. Schlundt et al.,[25] for example, found that patients who were instructed to eat 25 g/day of fat, with ad libitum intake of carbohydrate, lost 4.6 kg in 20 weeks, compared with a significantly greater loss of 8.8 kg for patients who were prescribed the same fat goal as part of a 1200 to 1500 kcal/day diet. The second finding, contrary to expectations, is that long-term weight losses have generally not been superior with ad libitum low-fat diets.[25,26] At 9 to 12 months' follow-up, patients in Schlundt's low-fat group maintained a loss of only 2.6 kg, compared with 5.6 kg for patients who consumed the low-calorie diet.[25] Jeffery et al.[26] found that patients who lost 4.5 kg on an ad libitum low-fat plan regained the weight and returned to their baseline weight within the year after treatment. More encouraging results were reported by Toubro and Astrup.[27] Two years after having lost an average of 13.6 kg, patients who were assigned to a low-fat ad libitum diet during the maintenance period regained only 5.4 kg, compared with a gain of 11.3 kg for patients prescribed a low-calorie diet.

Low-fat diets are typically low in energy density, the latter term referring to the energy (i.e., calories) in a given weight (grams) of food. Although replacing fat (9 kcal/g) with carbohydrate or protein (each 4 kcal/g) is the most common method of reducing energy density, there are other methods including adding fiber or water to the diet.[10] Water, in particular, increases the weight of food without increasing caloric content. This is potentially important in light of findings that food intake appears to be regulated, at least short term, by the weight of food ingested rather than by the energy content.[28] In laboratory studies, both lean and obese individuals ate a constant weight of food, even when the fat content and energy density of the diet were systematically manipulated. In one study,[28] for example, participants ate the same weight of food and reported comparable satiety, when they consumed a high-fat/high-energy density diet that provided 3000 kcal/day, compared with a low-fat/low-energy density diet that contained 1570 kcal/day.

For obese persons who report that they "never get enough to eat," Rolls and Bell[28] have shown that lowering the energy density of the diet will allow them to double the weight of food consumed. This can be achieved by increasing the intake of high-water content fruits, vegetables, and soups, as well as by limiting the intake of dry foods such as crackers and pretzels, which are high in energy density.

Ad libitum low-fat/low-energy density diets would appear to be an excellent option for overweight individuals (i.e., BMI of 25.0 to 29.9 kg/m^2), whether for inducing modest weight loss or preventing weight gain. With obese individuals, long-term studies are needed to determine whether patients gradually compensate for low-energy density by eating a greater weight of food (and thus more calories). Further studies, similar to that of Turbo and Astrup,[27] are also needed to determine whether this approach produces superior maintenance of weight loss, compared with a low-calorie diet.

PHYSICAL ACTIVITY FOR WEIGHT CONTROL

A joint report of the American College of Sports Medicine and the Centers for Disease Control and Prevention recommended that all adults exercise at a moderate intensity for at least 30 minutes a day, most days of the week.[29] This is the amount and intensity of activity believed to improve cardiovascular health. The NHLBI panel also strongly recommended that increased physical activity be incorporated into all weight-control efforts.[5] This section discusses methods of increasing physical activity in obese individuals, after first examining the effects of exercise on weight control.

Exercise and Short-Term Weight Loss

Exercise alone, in the absence of caloric restriction, produces minimal weight loss. For example, a program of walking four times a week for 45 to 60 minutes per bout usually induces a loss of only 2 to 3 kg during 16 to 52 weeks of training.[30] Similarly, as reviewed by the NHLBI panel, the addition of regular exercise to a low-calorie diet (1000 to 1500 kcal/day) only marginally increases weight loss (by 2 to 3 kg) during a 16- to 26-week behavioral program.[5,30] Patients who consume a very-low-calorie diet or a portion-controlled low-calorie diet may observe no increase in weight loss with the addition of exercise.[31] This is because the energy deficit of 1500 to 2500 kcal a day, induced by a very-low-calorie diet, swamps the deficit of only 1000 kcal a week, produced by the walking program described above. These findings indicate that the weight-reducing benefits of exercise should not be overstated, lest patients grow disappointed by the results. The true benefits of exercise are for facilitating the maintenance of weight loss and for improving health.[32–34]

Exercise and Long-Term Weight Control

For obese individuals improved maintenance of weight loss is usually the most desired benefit of regular exercise.[33] This benefit has been demonstrated by three types of investigations, the first being case studies that identified individuals who, by their own reports (or as documented by medical records), had lost a substantial amount of weight and kept it off.[35,36] Almost invariably such individuals reported that they exercised regularly, as found, for example, by Kayman et al.[37] in members of a health maintenance organization and by Klem et al.[38] in participants in the National Weight Control Registry. These latter individuals reported expending approximately 2800 kcal/wk, the equivalent of walking more than 1 hour a day 7 days a week.

A second set of studies followed patients prospectively in clinical trials and examined differences between persons who later maintained their weight loss or regained the weight.[39,40] Again, participants who reported exercising regularly maintained their weight losses significantly better than self-identified sedentary individuals. Randomized clinical trials have provided the third type of evidence. Some, although not all, studies found that persons who were assigned to a regimen of diet plus exercise maintained substantially greater weight losses than those treated by diet alone.[30] This finding was obtained when exercise was combined with either low-calorie[41,42] or very-low-calorie diets.[43,44]

Programmed vs. Lifestyle Activity

Exercise is clearly "good" for people, whether they are lean or obese. The problem is that few Americans exercise regularly. Thus recent studies have investigated methods of improving exercise adherence. This has included exploring the benefits of programmed vs. lifestyle activity. Programmed activity consists of regularly scheduled bouts of running, swimming, cycling, and other aerobic activities, which are usually engaged in for a discrete period of time (i.e., 30 to 60 minutes) at a relatively high level of intensity (i.e., 60% to 80% of maximum heart rate). Lifestyle activity, by contrast, involves increasing energy expenditure during the course of the day by practices such as walking rather than riding, using stairs rather than escalators, and discarding energy-saving devices such as TV remote controls and extension telephones. The principal goal is to increase energy expenditure with no concern for the intensity of activity.

Programmed Activity. Two approaches may improve adherence to programmed activity. The first, for individuals who "can't find the time" to exercise, is to break programmed activity into several short (i.e., 10 minutes) bouts rather than one long one (i.e., 40 minutes). Two studies of average-weight volunteers found that three daily brief bouts of activity (jogging at 65% to 80% of maximum heart rate) were sufficient to significantly improve fitness, as assessed by maximal oxygen consumption.[45,46] In one study, however, the increase in VO_{2max} was significantly greater in persons who engaged in the long bouts of activity.[46] In a study of obese individuals, Jakicic et al.[47] found that weight losses and improvements in cardiovascular fitness were comparable in patients assigned to short vs. long bouts of activity. Participants in the two groups were prescribed the same number of minutes of activity (i.e., up to 40 minutes/day of walking 5 times a week), to be performed at the same intensity (i.e., 70% of heart rate reserve), but those in the short-bout group split their activity into multiple 10-minute bouts.

A second method of facilitating exercise adherence is to have patients exercise at home rather than at a health club or similar facility. Perri et al.[48] showed that adherence to a walking program and maintenance of weight loss were significantly better at 1 year and beyond in patients who were assigned to walk at home (at 60% to 70% of maximum heart rate), compared with those who participated in a supervised on-site program. Home exercise appears to be associated with fewer barriers including costs, travel, and time. Use of home exercise equipment, such as a treadmill, may also improve adherence and long-term weight loss.

Lifestyle Activity. The preceding studies improved adherence by incorporating short bouts of activity and by having participants exercise at home. Nevertheless, these investigations all required participants to exercise at a relatively high intensity (i.e., approximately 60% to 80% of maximum heart rate).[45–47] Lifestyle activity, by contrast, involves increasing physical activity throughout the day, without concern for the intensity of the activity.[49–51] As Epstein[50] has noted, "Life-style exercise involves a less structured exercise program that does not emphasize intensity. If the goal of the exercise is to produce weight loss, then the energy expenditure, and not the exercise intensity, is the important factor." From this perspective, small daily increases in physical activity could improve weight control without obese individuals ever breaking a sweat. Lifestyle activity has numerous potential advantages over structured exercise including reducing patients' negative attitudes and improving their self-efficacy concerning physical activity.[49,51] Recent studies also have shown that physical activity need not be as vigorous as once thought in order to improve fitness and reduce mortality. Moderately vigorous activity, requiring ≥4.5 metabolic equivalents (METS), may be sufficient to reduce mortality and can be achieved, for example, by brisk walking.[52]

Comparison of Programmed Exercise and Lifestyle Activity. In the first comparison of these two types of exercise, Epstein and Cluss[53] found that lifestyle activity was associated with significantly better maintenance of weight loss in obese children than was programmed exercise. The superiority of lifestyle activity was replicated in a follow-up study, again of obese children.[54] A recent study of obese women found that both lifestyle activity and programmed exercise, when combined with a 1200 kcal/day diet, produced a weight loss of approximately 8.5 kg during a 16-week behavioral program.[55] Equivalent improvements were observed in cardiorespiratory fitness, as well as in lipids and lipoproteins. As shown in Fig. 2, there was also a (nonsignificant) trend in this pilot study for lifestyle activity to be associated with better maintenance of weight loss 1 year after treatment. Thus lifestyle activity would appear to provide an excellent alternative for obese persons who report that they "hate to exercise."

Exercise Target for Maintaining Weight Loss

Recent studies indicate that, to maintain weight loss, patients should expend approximately 1500 to 2500 kcal/wk. (This is more than double the 700 to 1000 kcal/wk goal recommended in earlier weight loss studies.) The lower value of 1500 kcal/wk could be achieved by walking, at a brisk pace, approximately 200 to 250 minutes a week, as shown by Jakicic et al.[56] Patients will have to increase both their lifestyle and programmed activity to achieve the high rates of energy expenditure (i.e., 2800 kcal/wk) reported by participants in the National Weight Control Registry.[38] Pedometers provide a reliable and inexpensive method of tracking most forms of programmed and lifestyle activity. A reasonable goal is to increase the number of steps walked daily by 1000 per month, until the person walks at least 5000 steps above baseline (equal to approximately 2 additional miles/day).

Despite the desirability of these high-activity goals, it is important to note that any increase in physical activity is better than none. Obese persons must initially set modest activity goals that they can achieve

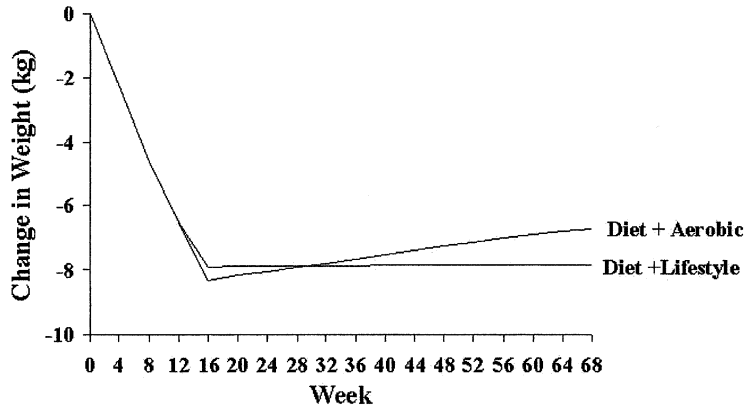

Fig. 2. Mean changes in body weight in participants assigned to diet plus lifestyle activity and diet plus programmed aerobic activity. The difference between groups at week 68 approached statistical significance ($P < 0.07$). (From Andersen RE, Wadden TA, Bartlett SJ, Zemel BS, Verde TJ, Franckowiak SC. Effects of lifestyle activity vs. structured aerobic exercise in obese women: A randomized trial. JAMA 1999;281:335–340.)

rather than such ambitious goals that they are destined to fail. Individuals of all weights should be encouraged to increase their physical activity to improve their physical health and emotional well-being, regardless of the effects on body weight.[57]

Benefits of Physical Activity

Increased physical activity clearly increases energy expenditure and thus may help patients remain in energy balance long term, despite occasional episodes of overeating. Exercise, however, may have additional behavioral or physiologic effects that facilitate the maintenance of weight loss. Grilo et al.,[34] for example, believe that regular exercise improves weight maintenance by enhancing self-esteem and mood, which in turn may improve adherence to a low-calorie, low-fat diet and the ability to cope with eating-related situations.

Physiologic Effects. Exercise may also have positive physiologic effects, which include minimizing losses of fat-free mass (FFM)[58] and, possibly, reductions in resting energy expenditure (REE),[59] which occur with dieting and weight loss. The most favorable effects of physical activity on both FFM and REE generally have been observed when exercise was combined with conventional reducing diets of 1200 to 1500 kcal/day[59,60] rather than with very-low-calorie diets providing ≤800 kcal/day.[31,61,62] It should be noted, however, that even when favorable effects were obtained, they were very modest. In two studies, for example, FFM increased by approximately 1 kg in obese participants who were treated by strength training.[63,64] This change, however, would be predicted to increase REE by only 30 kcal/day,[65] equal to 200 kcal a week. By contrast, participants could easily increase their energy expenditure by 200 kcal a day simply by walking one to two miles each morning. This is precisely what persons who maintain their weight loss report doing.[37]

Cardiovascular Effects. Perhaps the most important benefit of regular physical activity is improved fitness, which appears to be associated with a reduced risk of cardiovascular disease, regardless of body weight. Lee et al.[66] examined nearly 22,000 men whom they divided into lean, normal, and obese groups, based on body composition assessment by hydrostatic weighing and/or skin fold measurements. Men were further divided into fit and unfit groups on the basis of results of a maximal exercise test performed on a treadmill. As shown in Fig. 3, fitness was a far stronger predictor of cardiovascular disease and all-cause mortality than was fatness. Fat but fit men had a significantly lower risk of health complications than did lean men who were unfit.

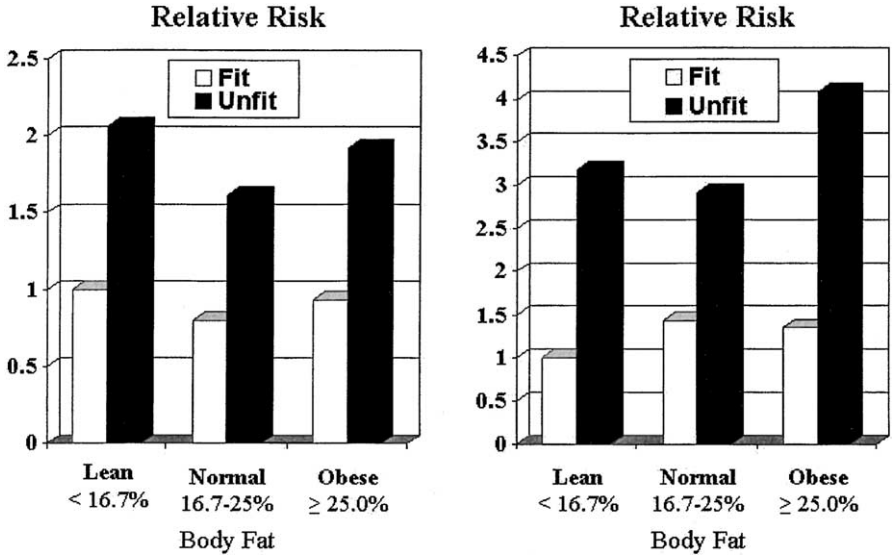

Fig. 3. Relative risks for all-cause mortality (*left panel*) and cardiovascular disease (*right panel*) and all-cause mortality by stratum of percentage of body fat and cardiorespiratory fitness level in 21, 925 men followed for 176,742 person-years of observation (428 deaths, 144 from cardiovascular disease). Relative risks are adjusted for age (single year), examination year, smoking status, alcohol intake, and parental history of coronary heart disease. Unfit men (*black bars*) were the least fit 20% in each age group, and all other men were classified as fit. (From Blair SN, Leermakers EA. Exercise and weight management. In: Wadden TA, Stunkard AJ, editors. Handbook of Obesity Treatment. New York: Guilford Press, 2002, pp 283–300.)

BEHAVIOR THERAPY FOR OBESITY

Behavioral therapy for obesity provides patients with a set of techniques for modifying eating patterns, activity levels, and thinking habits that contribute to excess weight. This approach recognizes that metabolic and genetic factors play a role in obesity for many persons,[67–69] but holds that they can still benefit from adopting healthier lifestyle habits. Once this understanding is established, treatment focuses on identifying "triggers" associated with overeating or inactivity. The former triggers may include times, places, emotions, or other events that are paired with eating. If the two items are linked often enough, the link becomes stronger and eventually the presence of one stimulus triggers the other. An example of this classical conditioning principle is eating popcorn while at the movies. If these two events are paired repeatedly, entering a theater will eventually trigger a craving for popcorn. Behavior therapy seeks to identify such links and extinguish their connection. This generally involves identifying several factors, or links, that lead to overeating and designing methods to break the chain.[70]

Goal setting is a critical component of behavior therapy. Participants are instructed to set very specific goals with measurable outcomes. For instance, goals to "exercise more" or "eat healthier" are vague and do not provide criteria to evaluate success. In contrast, goals such as "walking three evenings per week" or "eating two pieces of fruit per day" are clearly defined and allow for progress to be measured accurately. Patients develop specific plans (for reaching their goals) that are grounded in what they will do (e.g., walk) and when, where, and how frequently they will do it (e.g., "walk for 30 minutes on Monday, Wednesday, Friday, and Saturday evenings in the neighborhood park"). Patients are also taught problem-solving skills to surmount barriers they encounter in working toward their goals. This approach reinforces the notion that planning, not willpower, is the key to successful weight management. Finally, in choosing their goals, patients are encouraged to make small, manageable changes. Such changes are more easily adhered to and thus increase the likelihood of success. Frequent successful experiences serve as the foundation for further positive changes.

Treatment Components

Behavior therapy incorporates multiple components. These include self-monitoring, stimulus control, social support, cognitive restructuring, problem-solving skills, and relapse prevention. Detailed descriptions of these components are available elsewhere.[7,71] Thus the present description is limited to self-monitoring and cognitive restructuring.

Self-Monitoring. Self-monitoring is the cornerstone of behavior therapy[71,72] and involves keeping detailed records of food intake and physical activity. Patients record their usual eating and activity habits in order to discover patterns in their behavior and identify opportunities for change. They then reduce their calorie intake by approximately 500 kcal/day to achieve a weight loss of approximately 0.5 kg/wk. Records become more detailed as the program progresses to include information about times, places, and feelings (i.e., additional targets for intervention). Several studies have shown that self-monitoring correlates with successful long-term weight control.[32]

Cognitive Restructuring. Cognitive restructuring involves helping patients identify and correct negative thoughts that undermine their weight loss efforts.[70,71] This technique is most useful when dealing with setbacks and helping patients accept less-than-desired weight losses. Setbacks are discussed and defined objectively as temporary lapses from which recovery is possible. The lapses are examined to determine the events that contributed to them, and a plan is developed for handling similar situations in the future. Cognitive restructuring teaches patients to avoid extreme responses to setbacks, such as "catastrophizing": ("I've blown it") or denial ("It's nothing to worry about"). Similarly, cognitive intervention encourages patients to view less-than-desired weight losses in a more realistic light. Patients are taught to focus on the medical benefits of small weight losses and are encouraged to set more realistic weight-loss goals.[70] In doing so, feelings of failure, which lead to lapse and weight regain, can be avoided.

Treatment Delivery

Behavioral treatment can be offered on an individual or group basis and, in clinic settings, is provided by dietitians, exercise specialists, psychologists, health educators, or nurses. Treatment duration is typically 16 to 26 weeks, with predetermined starting and ending dates. Groups consist of 10 to 12 people, and the members remain constant throughout the treatment program.[70,71]

Commercial or self-help programs offer treatment to groups of 100 or more and are led by lay persons who have been successful in the programs.[73] These "open" groups do not have set beginning or ending points, with new members joining already established groups at any time. The treatment lasts indefinitely, with participants attending as many or as few sessions as they like. Clinical experience suggests that time-limited therapy, with definitive beginning and ending points, results in greater weight loss

and superior retention compared to open-ended treatment. Controlled trials, however, are needed to evaluate these different methods of treatment.

Results of Behavioral Treatment

Comprehensive group behavioral treatment produces a mean loss of 9% of initial weight in 20 to 26 weeks.[7,70,71] The amount of weight lost has more than doubled over the past 25 years as the duration of treatment has doubled from 3 to 6 months. Surprisingly, extending treatment beyond 26 weeks results in only marginally greater weight loss.[70] Current behavioral and pharmacologic treatments are inadequate to induce and sustain mean weight losses greater than 10% to 12% of initial weight, regardless of the duration of treatment. These findings suggest that there are limits to weight loss, which could result from compensatory biological responses to weight reduction (e.g., decreases in leptin or resting energy expenditure) or from behavioral fatigue.[70,71]

In the absence of follow-up care, patients typically regain 30% to 35% of their lost weight in the year following treatment.[74] After 5 years, more than half of patients will have regained all of their lost weight.[22] These results indicate the necessity for long-term continuous care, as required with other chronic conditions such as diabetes and hypertension.

Several studies have shown that long-term behavioral treatment, consisting of twice-monthly clinic visits or regular contact by telephone or mail, significantly improves the maintenance of weight loss.[21,23,48] Perri et al.,[48] for example, found that patients who attended every-other-week group maintenance sessions for the year after weight reduction maintained 13.0 kg of their 13.2 kg end-of-treatment weight loss, whereas those who did not receive such therapy maintained only 5.7 kg of a 10.8 kg loss. Maintenance sessions provide participants with the support and motivation necessary to continue using the behavioral techniques (including self-monitoring and reducing caloric intake) learned during treatment. The key behaviors that participants should practice include the following: (1) exercising more than 200 minutes a week; (2) continuing to consume a low-calorie, low-fat diet; and (3) monitoring weight regularly (i.e., at least once a week). These are the key behaviors practiced by persons in the National Weight Control Registry who have lost 29 kg and maintained this loss for 5.5 years.[38,75]

ROLE OF LIFESTYLE MODIFICATION FOR PATIENTS UNDERGOING BARIATRIC SURGERY

Bariatric surgery is increasingly used in the treatment of extremely obese individuals (BMI $\geq$40 kg/m^2 or $>$35 kg/m^2 with comorbid conditions). The most common procedures are the gastric bypass and vertical banded gastroplasty, both of which drastically reduce stomach capacity, thereby facilitating weight loss. The operations typically induce losses of 30% and 25% of initial weight, respectively.[76] These methods, although effective, are not foolproof; 10% to 15% of patients undergoing bariatric surgery fail to achieve an acceptable weight loss (losing less than 40% of excess weight).[77] These failures are often attributed to patients' constant nibbling on high-calorie foods and/or their lack of regular physical activity.[77] For instance, patients can circumvent the capacity limitations of their smaller stomachs by consuming high-calorie soft foods such as ice cream and milkshakes. In addition, patients' stomachs may begin to stretch over time, allowing them to consume larger portions of food at one time. Adjunct lifestyle counseling could provide these patients with the tools to facilitate optimal dietary and exercise adherence. Controlled trials are needed to test this hypothesis.

CHALLENGES WITH LIFESTYLE MODIFICATION

Lifestyle modification, as described above, clearly is efficacious in inducing weight loss and improving health, as demonstrated by the Diabetes Prevention Program.[6] A major limitation, however, is that this treatment is not widely available. It is provided principally in research and hospital settings by experienced multidisciplinary teams. A key challenge is to find effective methods of translating findings from clinical trials into primary care and community practice. In short, how can we make treatment available to the millions of overweight and obese Americans who need it? Primary care practitioners could play a major role if provided additional training and, equally important, appropriate reimbursement for treating obesity. There is a pressing need for initiatives in this area.

Self-help and commercial programs, such as Weight Watchers, could also play an important role in managing the obesity epidemic.[73] These organizations exist nationwide, and many provide a sensible program of diet and exercise at a reasonable price (i.e., $\leq$\$12 a week). Reimbursement of the cost of treatment could increase the use of such programs. The internet is also a potential vehicle for delivering lifestyle modification.[78] It is highly accessible, convenient, and could easily serve large numbers of people. Research is needed to determine if any of these alternatives could approximate the results obtained in research and hospital-based programs. Weight

losses as little as 2% to 5% of initial weight, in hundreds of thousands of people, could improve the nation's health.

Finally, far greater resources and effort must be devoted to the prevention of obesity if we are to halt this disorder, let alone reverse it. Our best hope for prevention may lie with children and adolescents. Efforts should be devoted to improving the meals and snacks served at schools, providing more opportunities for physical activity, and educating youth about the importance of diet, activity, and a healthy body weight.

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Medical Management of Obesity: Present and Future Therapy

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The major goal of obesity therapy is to eat fewer calories than are expended in order to consume endogenous triglyceride stores as fuel. Although altering eating and activity behaviors is the cornerstone of therapy, achieving successful long-term weight loss by attempting to change lifestyle has proved to be extremely difficult in modern society. This frustration in obesity management, in conjunction with recent scientific advances in our understanding of the regulation of energy balance, has led to an increased interest in the potential for pharmacotherapy to treat obesity. In this report the current status of the long-term use of drug therapy for obesity, and the pharmacologic treatment options that may become available in the future, will be reviewed.

OVERVIEW

The medications currently approved by the United States Food and Drug Administration (FDA) for treating obesity are listed in Table 1. With the exception of orlistat, which inhibits intestinal fat digestion and absorption, these medications act as anorexiants by either increasing satiation (hunger during a meal, which affects the amount of food consumed) or satiety (hunger after a meal is consumed, which affects the frequency of eating), or both. Current anorexiant medications exert their effects by altering monoamine (norepinephrine, serotonin, and dopamine) metabolism in the hypothalamus. Methamphetamine and benzphetamine are addictive and should be avoided.

The FDA has approved the use of weight loss drugs for persons who have a BMI $\geq$30 kg/m^2, or a BMI between 27 and 29.9 kg/m^2 in conjunction with an obesity-related medical complication such as type II diabetes. Most of the medications listed in Table 1 are only approved for short-term use (i.e., a few weeks), whereas sibutramine and orlistat are approved for long-term use. This complicates the pharmacologic approach to obesity, which is a chronic disease that will relapse when effective treatment is stopped. Therefore pharmacotherapy for obesity should not be provided as a short-term option, because patients who respond to drug therapy usually regain weight when therapy is stopped.[1,2] In addition, pharmacotherapy alone is not as effective in achieving weight loss as pharmacotherapy that is given in conjunction with a comprehensive weight management program, including behavior modification therapy and a structured meal plan.[3] Therefore standard weight management principles, including behavior modification, diet education, and activity counseling, should be included as part of the therapeutic approach for all patents who are given weight loss medications.

SIBUTRAMINE

Sibutramine increases satiation by inhibiting the reuptake of norepinephrine, serotonin, and dopamine in the brain. The effect of sibutramine on body weight depends on the dose, across a range of doses from 1 to 30 mg/day.[4] The current recommended starting dose is 10 mg/day, which can be decreased or increased to 5 mg/day or 15 mg/day in those who do not tolerate or who do not respond to the initial dose.[5]

The results from two studies evaluating the clinical weight loss efficacy of sibutramine in long-term (1-year) randomized controlled trials are presented in Table 2.[6,7] In both trials, mean weight loss and the percentage of subjects who lost $\geq$5% or $\geq$10% of their initial weight was greater in subjects treated with sibutramine than with placebo. Moreover, data from a recent randomized controlled study suggest that intermittent sibutramine therapy can be just as effective as continuous therapy; weight loss with sibutramine given daily during weeks 1 through 12, 19 through 30, and 37 through 48, and placebo given

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Table 1. Drugs approved by the FDA to treat obesity

Generic name	Trade name(s)
Methamphetamine hydrochloride	Desoxyn
Benzphetamine hydrochloride	Didrex
Phendimetrazine tartrate	Bontril, Plegine, Prelu-2, X-Trozine
Phentermine	
Hydrochloride	Adipex-P, Fastin, Oby-trim
Resin	Ionamin
Diethylpropion hydrochloride	
Immediate release	Tenuate
Controlled release	Tenuate Dospan
Mazindol	Sanorex, Mazanor
Sibutramine hydrochloride	Meridia
Orlistat	Xenical

Adapted from Klein S, Wadden T, Sugerman HJ. American Gastroenterological Association Technical Review: Obesity. Gastroenterology 2002;123:882–932.

during the other weeks) was equivalent to weight loss with continuous sibutramine therapy.[8]

Sibutramine therapy has been shown to maintain long-term weight loss in those who have been able to achieve successful initial weight loss with either diet or sibutramine therapy.[2,9] In one randomized controlled trial, subjects who lost at least 6 kg after 4 weeks of therapy with a very-low-calorie diet were assigned to 1 year of treatment with sibutramine or placebo.[9] The group given sibutramine lost an additional 5.2 kg, whereas the group given placebo gained 0.5 kg. In another randomized controlled trial, subjects who were able to lose more than 5% of their initial weight at the end of 6 months of sibutramine treatment were randomized to 18 months of dietary counseling and treatment with either sibutramine or placebo.[2] On average, subjects who continued to receive sibutramine maintained their weight loss for 1 year, followed by a slight weight increase in the last 6 months of the study. In contrast, weight increased progressively in those randomized to placebo. In subjects who completed the study, almost three times as many subjects treated with sibutramine (43%) as compared to placebo (16%) maintained 80% or more of their original weight loss.

The most common side effects of sibutramine treatment are dry mouth, headache, insomnia, and constipation. Although sibutramine also causes small increases in blood pressure (approximately 2 to 4 mm Hg) and heart rate (approximately 4 to 6 beats/min),[2,4] some patients experience much larger increases that require dose reduction or discontinuation of therapy. Therefore sibutramine is contraindicated in patients with poorly controlled hypertension but can be given safely to hypertensive patients who have good blood pressure control.[6]

ORLISTAT

Orlistat inhibits the digestion and absorption of dietary fat by binding to intestinal lipases secreted

Table 2. Randomized controlled trials that evaluated 1 year of treatment with sibutramine or orlistat

Reference	No. of subjects randomized	Weight loss at 1 yr: Mean (% initial weight)		≥5% (% Subjects)		≥10% (% Subjects)	
		Placebo	Drug	Placebo	Drug	Placebo	Drug
Sibutramine trials							
McMahon et al.[6*]	224	0.7	4.7	9	40	4	13
Smith and Goulder[7]	485	1.8	7.3	20	57	7	34
Orlistat trials							
Sjöström et al.[1]	688	6.1	10.2	49	69	18	39
Davidson et al.[12]	892	5.8	8.8	44	66	25	39
Rössner et al.[13]	487	6.6	9.8	44	63	19	38
Finer et al.[14]	228	5.4	8.5	21	35	17	28
Hauptman et al.[15†]	422	4.2	7.9	31	51	11	29
Hollander et al.[16‡]	391	4.3	6.2	23	49	9	18
Lindgarde[17*†‡§]	376	4.6	5.9	41	54	15	19

*Subjects with hypertension.
†Primary care setting.
‡Subjects with type II diabetes mellitus.
§Subjects with dyslipidemia.
Adapted from Klein S, Wadden T, Sugerman HJ. American Gastroenterological Association Technical Review: Obesity. Gastroenterology 2002;123:882–932.

into the lumen of the gastrointestinal tract.[10] At the therapeutic dosage of 120 mg three times a day with meals, approximately 30% of ingested triglycerides are not absorbed and excreted in stool.[11]

Data from studies evaluating the clinical weight loss efficacy of orlistat in long-term (1-year) randomized controlled trials are shown in Table 2. The results from these studies demonstrate that mean weight loss and the percentage of patients who lost ≥5% or ≥10% of their initial weight were both greater in subjects treated with orlistat than with placebo.[1,12–17] Subjects who had type II diabetes[16,17] and those involved in studies conducted in a primary care practice setting without formal behavior therapy or visits to a dietitian[15,17] did not lose as much weight as those enrolled in trials that provided behavior modification therapy and dietary counseling.[1,12,13] Several of these studies were continued for another year and demonstrated that weight loss was still greater with orlistat therapy than with placebo at 2 years.[1,12,13,15]

The most common adverse effects of orlistat therapy are gastrointestinal complaints; these include increased defecation, soft and liquid stools, fatty or oily stool, fecal urgency, and fecal incontinence.[1,12–17] Approximately three fourths of subjects treated with orlistat experienced one or more gastrointestinal events, compared with approximately half of those treated with placebo. Most gastrointestinal side effects occurred within the first 4 weeks of therapy, were mild or moderate in intensity, and resolved despite continued treatment with orlistat. The gastrointestinal side effects of orlistat can be minimized or prevented by concomitant therapy with a gel-forming fiber (psyllium mucilloid).[18]

Orlistat treatment impairs the absorption of fat-soluble vitamins[19] and lipophylic medications such as cyclosporin.[20,21] Therefore all patients who are treated with orlistat should take a daily multivitamin and any lipophilic drugs at least 2 hours before or after orlistat ingestion. In addition, plasma drug concentrations should be monitored whenever possible.

FUTURE THERAPY

Obesity is a major target for future pharmacotherapy because of the marked and increasing prevalence of this disease and unmet therapeutic needs. Developing successful pharmacologic approaches to obesity is difficult because of complex genetic, molecular, cellular, physiologic, and environmental interactions. However, the scientific advances made during the past 10 years have revolutionized the potential for effective therapy. Table 3 lists emerging treatments for obesity that are currently under investigation by the pharmaceutical industry. Most of these agents are in the early stages of development, so it is premature to predict their future efficacy.

Table 3. Emerging weight loss drugs

Centrally acting appetite suppressants
Leptin-related compounds
Recombinant human leptin
Second-generation leptin
OB-R modulators
Leptin gene promoter modulators
Leptin pathway modulators
Ciliary neurotrophic factor (Axokine)
5 HT_{2c} receptor agonists
Melanocortin-4 receptor agonists
Selective neuropeptide Y_1 and Y_5 antagonists
Mahogany gene modulators
Tub protein modulators
Galanin antagonists
Cannabinoid receptor antagonists
Orexin A and B receptor antagonists
Thermogenic agents
β_3-adrenoreceptor agonists
Uncoupling protein modulators
Gastrointestinal hormones
Cholecystokinin-A
Bombesin
Glucagon-like peptide 1
Amylin
Enterostatin
Apolipoprotein A-IV
Novel lipase inhibitors
Adipocyte differention modulators
PPARγ antagonists
Metabolic agents
Fatty acid oxidation modulators
Carboxypeptidase enzyme inhibitors
Medications already approved for other uses
Buproprion (antidepressant; antismoking)
Topiramate (anticonvulsant)

Adapted from Mosaic Study #33. Obesity. Decision Resources, Inc. April, 2002. Huberman AB. Next-generation Metabolic Disease Therapeutics: An Analysis of Eight Therapeutic Pipelines for Diabetes and Obesity. Decision Resources, Inc. November, 2000.

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Open and Laparoscopic Surgical Modalities for the Management of Obesity

Philip R. Schauer, M.D.

INDICATIONS AND RATIONALE FOR SURGICAL MANAGEMENT OF OBESITY

Most surgeons and medical insurance providers today adhere to the guidelines for surgical management of obesity established at the 1991 National Institutes of Health Consensus Conference on Gastrointestinal Surgery for Severe Obesity.[1] The panel of experts reviewed the long-term data on safety and efficacy of medical and surgical weight loss and concluded that surgical therapy should be offered to morbidly obese patients who are unresponsive to nonsurgical therapy for weight loss. The rationale for surgery was based on a large volume of studies indicating that "dietary weight reduction with or without behavioral modification or drug therapy had an unacceptably high incidence of weight regain in the morbidly obese within 2 years after maximal weight loss." Despite the introduction of new pharmacologic therapies since then, results of nonsurgical therapy for weight loss in the morbidly obese remain poor. According to the guidelines, patients are eligible for surgery if they have failed attempts at nonsurgical weight loss and have a body mass index (BMI) $\geq$35 with comorbidity or a BMI $\geq$40 with or without comorbidity. The only operations endorsed by the panel were gastric bypass and vertical banded gastroplasty, which at the time were the primary procedures performed in the United States with well-documented long-term data. Since this conference, there has been a dramatic increase in acceptance of bariatric surgery, with a corresponding increased understanding of alternative procedures and new approaches, particularly laparoscopic bariatric procedures. Because of the significant increase in information regarding outcomes of many different operations, as well as new questions regarding existing indications, many have suggested that a new consensus conference be held to address these issues.

STRATEGIES FOR SURGICALLY INDUCED WEIGHT LOSS

Three primary approaches for surgically induced weight loss affecting the gastrointestinal tract have arisen over the past 50 years. These include restrictive, malabsorptive, and intermediate operations. The restrictive procedures cause early satiety by creation of a small gastric pouch and prolong satiety by creating a small outlet to that pouch. They include the many varieties of gastroplasty (Fig. 1) and gastric banding (Fig. 2). In these procedures the outlet is reinforced by prosthetic material to prevent dilation. The pouch and the outlet must be small enough to adequately restrict intake yet not so small as to cause obstruction. The adjustable gastric banding procedures (Fig. 1), LAP-BAND Adjustable Gastric Banding System (BioEnterics Corp., Carpinteria, CA) and the Swedish Band (Obtech Medical, Barr, Switzerland), allow for fine adjustments of the outlet diameter, which may offset the disadvantages of a fixed, nonadjustable outlet. Significant dietary compliance is required because the intake of high-calorie liquids or soft foods is not inhibited by the narrow outlet and will result in failure to lose weight. Benefits include technical simplicity with no anastomoses or bypasses of any of the intestinal tract. There is also no protein-calorie malabsorption and no vitamin or mineral deficiencies. Relative disadvantages include less weight loss than with alternative procedures and more late failures due to pouch or anastomosis dilation or maladaptive eating behavior. Excessive narrowing by the reinforced outlets may cause frequent vomiting and gastroesophageal reflux. The prosthetic material at the outlets may erode into the gastric lumen. Malabsorptive procedures include the jejunoileal bypass, biliopancreatic diversion, with or without duodenal switch (Fig. 3), and the distal gastric bypass. These operations depend on bypass of various lengths of small intestine to cause malabsorption akin to a "controlled short-gut syndrome." Benefits include greater sustained weight loss that is less dependent

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on dietary compliance. Problems include increased risk of malnutrition and vitamin deficiencies, with a need for constant follow-up to reduce these risks. Intermittent diarrhea or steatorrhea is likely. The malabsorptive procedures are generally more technically complex than the restrictive operations, with two or more anastomoses and, with the biliopancreatic diversion, partial gastric resection. The standard Roux-en-Y gastric bypass (RYGB) (Fig. 4) has historically been considered a restrictive operation, although many argue that there is a degree of malabsorption due to the foregut bypass, with associated vitamin and mineral deficiencies.

THE GOLD STANDARD FOR OPEN BARIATRIC SURGERY

In order to assess new laparoscopic bariatric operations, it is appropriate to establish benchmark outcome goals for comparison. The RYGB is most suitable for comparison because there is significant evidence to document both short-term and long-term outcomes, and it is considered by most surgeons in North American to have the most favorable risk/benefit profile. Table 1 demonstrates selected series of open RYGB published primarily over the past decade with key outcome parameters.[2–12] These studies varied considerably with regard to which outcome parameters were reported. Notably absent are data reflecting operative time and perioperative recovery, such as hospital stay and return to work (not reported in any of the studies). Routinely reported data reflecting recovery after surgery have apparently only recently been considered important. Collectively these studies suggest that open RYGB results in a hospital stay ranging from 4 to 8 days with a perioperative complication rate of 3% to 20% and a mortality rate of approximately 1%. The most common major complications occurring early (<30 days) include pulmonary embolus (1% to 3%), gastrointestinal leak (1% to 5%), and anastomotic stricture (3% to 10%). Common late complications include hernia (5% to 24%), marginal ulcers (3% to 10%), and bowel obstruction (1% to 3%). Vitamin B_{12} deficiency and iron deficiency anemia are the most common nutritional sequelae after gastric bypass, although both can be prevented in most patients with supplementation. Significant malnutrition or hypoalbuminemia is extremely rare in the absence of infection, obstruction, or other medical disorders. Long-term weight loss at 5 to 14 years appears to be 49% to 62% of excess body weight. Pories et al.[9] have the longest reported follow-up for gastric bypass demonstrating a nadir weight loss of 65% excess body weight at 2 years, with an approximate 15% weight regain over 14 years that appears to stabilize (Fig. 5).

Table 1. Outcomes for open gastric bypass: Selected series

	N	Patient size (BMI, kg, or %IBW)	OR time (min)	Hospital stay (day)	Early complication rate (%)	Mortality (%)	PE rate (%)	Leak rate (%)	Hernia (%)	Follow-up (mo)	Weight loss
Mason 1969[2]	26	42	—	—	19	7.7	3.4	0	11.5	12	43 kg
Griffin 1981[3]	402	134 kg	—	—	4.2	0.75	0.25	5.47	3.5	6	35 kg
Linner 1982[4]	174	126 kg	—	—	10.4 (all)	0.57	0	0.57	0	24	64% EWL
Sugerman 1989[5]	182	213%	—	6–7*	—	1	0	1.6	18*	12	67% EWL
Hall 1990[6]	99	198%	120	8	20	0	3	0	2	36	67% lost >50% EBW
Brolin 1992[7]	90	62	—	—	5	0	1.1	0	6.6	43	64% EWL
MacLean 1993[8]	106	50	—	—	—	0	—	5.6	—	33	58% lost >50% EBW
Poires 1995[9]	608	50	—	5–6*	25.5	1.5	—	—	23.9	168	49% EWL
Capella 1996[10]	560	52	—	—	1	0	0	0†	—	60	62% EWL
Fobi 1998[11]	944	46	—	4*	2.7	0.4	0.6	3.1	4.7	24	80% EWL
MacLean 1999[12]	243	49	—	—	—	0.41	—	—	16	66	BMI 44→29‡

BMI = body mass index; EBW = excess body weight; EWL = excess weight loss; IBW = ideal body weight; PE = pulornonary embolism; — = not reported.

From Schauer PR, Ikramuddin S, Gourash W, et al. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Ann Surg 2000;232:515–529.

*As reported by the investigator, without mean and standard deviation of the mean.

†One subphrenic abscess.

‡Change in BMI for patients with initial BMI 40–50.

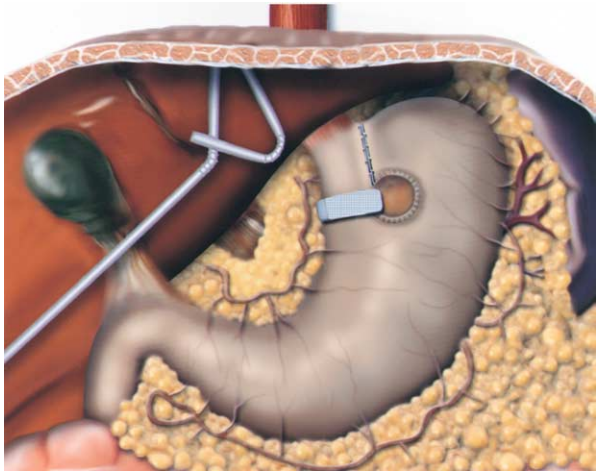

Fig. 1. Vertical banded gastroplasty (open or laparoscopic).

LAPAROSCOPIC SURGERY FOR OBESITY

Laparoscopic approaches to bariatric operations, including vertical banded gastroplasty (VBG), adjustable silicone gastric banding, and gastric bypass, all emerged at about the same time in the early to mid-1990s in the wake of laparoscopic cholecystectomy. Because of the complexity of these procedures in morbidly obese patients, the transition to common practice has been slower than some of the second-generation procedures such as laparoscopic hernia repair and Nissen fundoplication. Currently there is sufficient early experience to review technique and outcomes of three bariatric operations including laparoscopic VBG, gastric banding (with adjustable bands), and gastric bypass. Laparoscopic malabsorption operations are just beginning to emerge. Hybrid procedures that use hand-assisted laparoscopic techniques have been developed with the intention of providing similar benefits seen with completely laparoscopic procedures. A major element of laparoscopic bariatric surgery that should be addressed is the importance of adequate training in both advanced laparoscopic surgery and bariatric surgery.

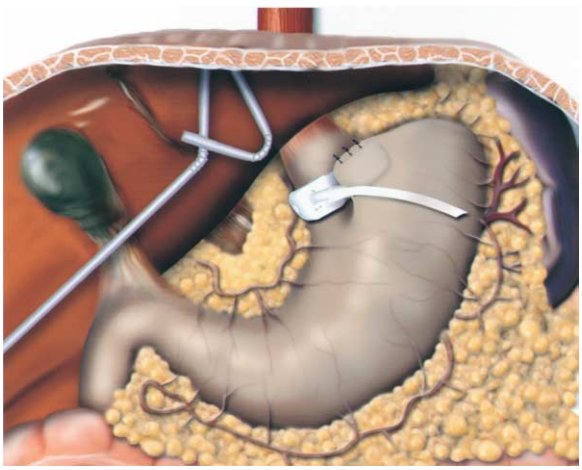

Fig. 2. Adjustable gastric band (open or laparoscopic). The device in the figure is the Lap Band (BioEnterics, Carpinteria, CA).

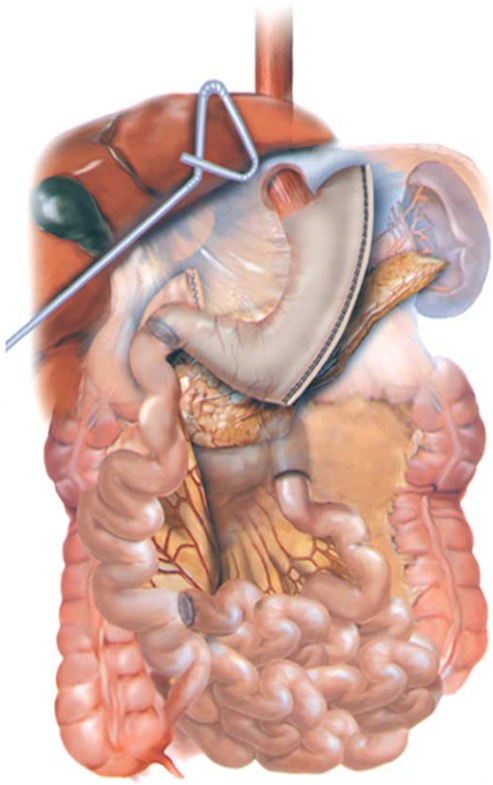

Fig. 3. Biliopancreatic diversion with duodenal switch (open or laparoscopic).

Although perioperative morbidity for bariatric surgery has steadily diminished, cardiopulmonary and wound complications remain a major problem.[13,14] Furthermore, recovery after these bariatric procedures may take many weeks or months. The access laparotomy is largely responsible for the prolonged recovery and perioperative morbidity. By minimizing the access incision, a laparoscopic approach to bariatric procedures has a strong potential to significantly enhance recovery and reduce morbidity (Fig. 6). Because conventional bariatric procedures require extended abdominal incisions in patients with high comorbidity, the relative reduction in perioperative morbidity after laparoscopic bariatric procedures may be even greater than what has been observed for laparoscopic cholecystectomy.

Laparoscopic Vertical Banded Gastroplasty

Most laparoscopic versions of VBG are derived from the Mason gastroplasty.[15] Current experience with a laparoscopic approach to VBG is limited (Fig. 1).

There appears to be reluctance among surgeons, at least in the United States, to consider laparoscopic VGB, perhaps because long-term results of open VBG appear to be less favorable than those of RYGB. A recent study from the Mayo Clinic showed only a 26% success rate for VBG after 10 years of follow-up.[16] At the present time, only a few studies primarily from Europe have been published.[17,18] These studies include patients with a lower mean BMI (low 40s) than what is encountered in North American studies. The laparoscopic approach appears to have an advantage over the open approach in terms of length of hospital stay (4 days) and rapid recovery. Conversion rates have generally been less than 5%. Early and late complication rates (2% to 6%) appear comparable to those for open VBG. Short-term weight loss also is comparable with a mean excess weight loss of 61% to 75% at 18 months to 3 years. The greatest concern regarding the laparoscopic VBG is that, similar to the open VBG, it will likely not achieve good long-term weight control.

Laparoscopic Gastric Banding

Laparoscopic adjustable silicone gastric banding (LASGB) was first introduced outside the United States in the early 1990s, and only recently (in June 2001) was it approved by the FDA for use in the United States. It is a purely gastric restriction procedure that involves the use of an adjustable silicone band that is placed around the gastric cardia creating a small gastric pouch, 15 to 20 ml, with a narrow outlet similar in concept to the VBG (Fig. 4). It differs from the VBG in that the band diameter may be increased to minimize side effects (i.e., vomiting) or decreased to enhance weight loss. Multiple series with 3- to 5-year follow-up have been published primarily by surgeons from Europe and Australia.[19–22] These studies suggest that the technique is associated with a short hospital stay, rapid recovery, and minimal perioperative morbidity. Weight loss with follow-up (less than 5 years in most cases) appears to be similar to that achieved with VBG (i.e., 40% to 70% excess body weight loss). Potential advantages include complete reversibility on removal of the device and no stapling or dividing of native tissue. Disadvantages include the development of device-specific complications such as band migration, band erosion into the gastrointestinal tract, esophageal dilatation, and foreign body reaction. Experience with laparoscopic gastric banding in the United States is limited. One recently published study by DeMaria et al.[23] demonstrated that 15 (41%) of 37 patients required band removal for complications or poor weight loss. Although LASGB remains the most popular bariatric operation in Europe and Australia, its role in the United States population remains in question until more United States based studies are completed.

Laparoscopic Gastric Bypass

A laparoscopic approach to RYGB was first described by Wittgrove et al.[24] Their technique involves creation of a 15 to 30 ml gastric pouch isolated from the distal stomach, a 21 mm stapled circular anastomosis, a 75 cm retrocolic retrogastric Roux limb, and a stapled side-to-side jejunojeunostomy. They have reported on their experience with 75 patients with 3 to 30 months' follow-up. The operating time was 159 to 343 minutes. The mean hospital stay and recovery time were 2.8 days (range 2 to 75 days) and 15 days (range 7 to 30 days), respectively. Excess weight loss at 12 to 30 months was 81% to 95%. The incidence of major complications was 11%, and the leakage rate was 5% (4/75). The mortality rate was zero. The majority of comorbid conditions such as hypertension or non–insulin-dependent diabetes mellitus were either resolved or significantly improved. Their experience with 500 patients with a 5-year follow-up has been similar with good long-term weight loss. Several other large series with follow-up ranging from 1 to 3 years show equally good results.[25–30]

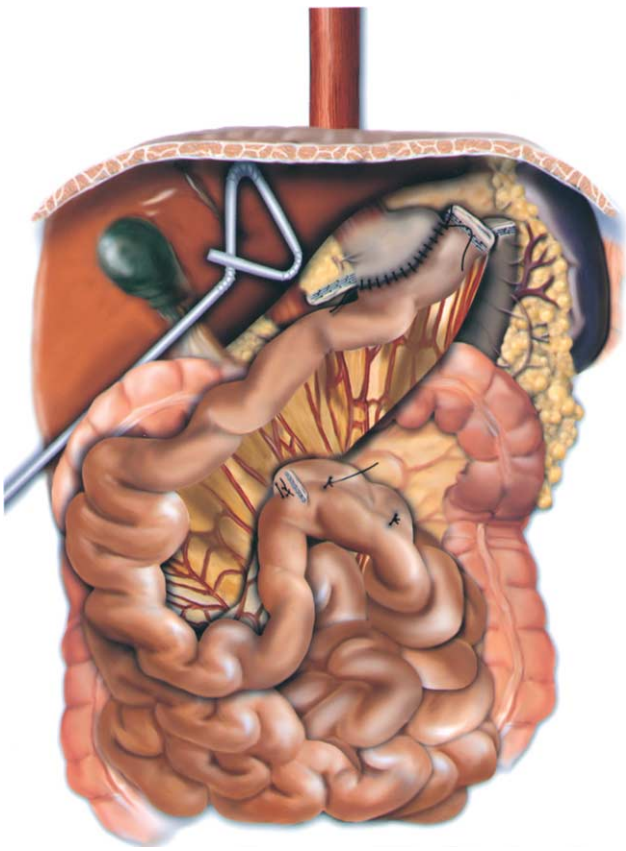

Fig. 4. Roux-en-Y gastric bypass (open or laparoscopic).

Our approach to laparoscopic RYGB at the University of Pittsburgh is shown in Fig. 4.[30] Consecutive patients (n = 275) who met the National Institutes of Health criteria for bariatric surgery were offered laparoscopic RYGB between July 1997 and March 2000. A 15 ml gastric pouch and a 75 cm Roux limb (150 cm for superobese patients) were created using five or six trocar incisions. The conversion rate to open gastric bypass was 1%. The start of an oral diet began a mean of 1.58 days after surgery, with a median hospital stay of 2 days and return to work at 21 days. The incidence of early major and minor complications was 3.3% and 27%, respectively. One death occurred, which was related to a pulmonary embolus (0.4%). The hernia rate was 0.7%, and wound infections requiring outpatient drainage only were uncommon (5%). Excess weight loss at 24 and 30 months was 83% and 77%, respectively (Fig. 7). In patients with more than 1 year of follow-up, most of the comorbid conditions were improved or resolved, and 95% reported significant improvement in quality of life (Table 2). Our experience suggests that laparoscopic RYGB is effective in achieving weight loss and in improving comorbidity and quality of life while reducing recovery time and perioperative complications.

The early results of laparoscopic RYGB compare favorably with those of open RYGB (see Table 1), particularly with regard to perioperative morbidity and recovery. Nygen et al.[31] reported, in a prospective randomized study, that the laparoscopic approach resulted in less blood loss, fewer admissions to the intensive care unit, a shorter hospital stay, and faster recovery compared to the open approach, with no difference in total cost. This same group also showed that the laparoscopic approach resulted in a significant reduction in postoperative pulmonary impairment.[32] The laparoscopic approach appears to significantly reduce wound-related complications, which may be its greatest advantage over open RYGB.

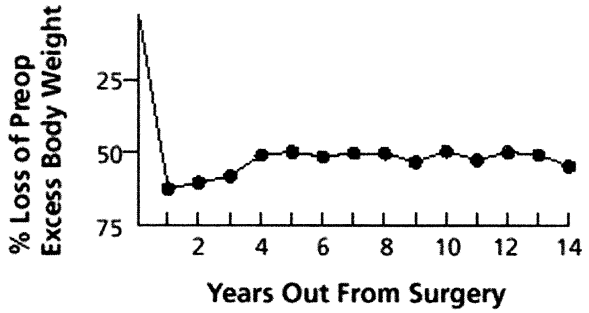

Fig. 5. Excess body weight loss after gastric bypass. Reprinted with permission from, MacDonald KG Jr, Long SD, Swanson MS, Brown BM, et al. The gastric bypass operation reduces the progression of mortality of non-insulin-dependent diabetes mellitus. J GASTROINTEST SURG 1997;1(3):213–220.

Because cardiopulmonary complications are less common, comparison of results from larger series will be necessary to detect differences from open RYGB.

The laparoscopic approach for RYGB, however, is not without developmental challenges. The learning curve is very steep, and long operating times are required. The incidence of intestinal leakage at the gastrojejunal anastomosis may be higher after the laparoscopic approach than after open RYGB during the learning curve. Measures to reduce staple line leaks, such as minimizing tension at the gastric pouch/Roux limb junction, careful endoscopic examination of the anastomosis, and oversewing of the staple line, may reduce leaks. The laparoscopic approach is technically more difficult in superobese persons, especially those with a preponderance of abdominal adipose tissue. Patients with prior abdominal surgery may also pose significant challenges with respect to managing complex adhesions. Finally, the laparoscopic approach may be exceedingly difficult in patients with enlarged livers because of inadequate exposure of the esophagogastric junction.

Laparoscopic Malabsorption Procedures

Laparoscopic approaches to malabsorption procedures, such as the biliopancreatic diversion operation developed by Scopinaro et al.[33] and the duodenal switch operation advocated by Marceau et al.,[34] are currently being developed (Fig. 3). Ren et al.[35] have published the only study to date evaluating early results of a laparoscopic malabsorption procedure. They performed a laparoscopic approach to biliopancreatic diversion with duodenal switch (BPD-DS) in 40 patients with a mean BMI of 60 kg/m^2. The operation involved a 150 to 200 ml sleeve gastrectomy with the remaining stomach anastomosed to the distal 250 cm of divided ileum, leaving a common channel of 100 cm. The conversion rate was 2.5% with a mean operating time of 210 minutes and a hospital stay of 4 days. Major morbidity occurred in 15% and the mortality rate was 2.5%. Median follow-up at 9 months showed a loss of 58% of excess body weight. This study showed that laparoscopic BPD-DS is feasible with a reasonable perioperative morbidity and mortality. Whether it offers significant advantages over other open or laparoscopic procedures remains to be seen.

Hand-Assisted Laparoscopic Bariatric Surgery

Because of the formidable technical challenges of laparoscopic approaches to bariatric operations, hand-assisted modifications are emerging to facilitate these operations. Hand-assisted approaches involve the use of devices that allow the surgeon to insert one hand intra-abdominally through a small access

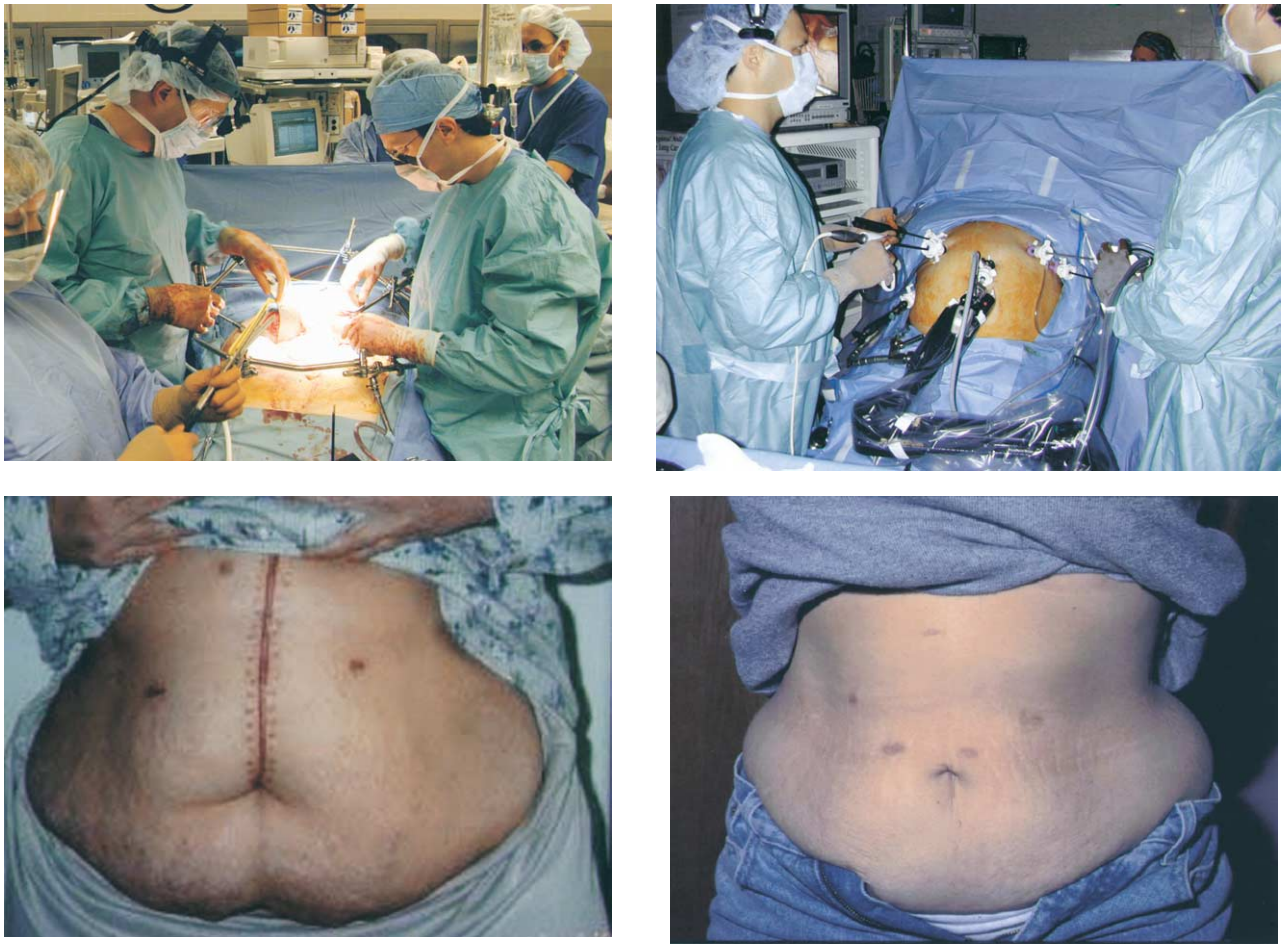

Fig. 6. Operative set-up and postoperative scars for open gastric bypass (*top left* and *bottom left* respectively) versus laparoscopic gastric bypass (*top right* and *bottom right* respectively).

incision (6 to 8 cm) to assist with the laparoscopic procedure.[36] These devices form an airtight seal around the surgeon's arm to prevent leakage of the pneumoperitoneum. In concept, hand-assisted laparoscopy is a hybrid between open surgery and laparoscopy, and attempts to maximize the benefits of both approaches. Two currently available devices include the Dexterity Pneumo Sleeve (Dexterity Surgical, Roswell, GA) and the HandPort System (Smith and Nephew, London, UK). Early reports of hand-assisted bariatric operations suggest that the technique may facilitate the arduous learning curve for laparoscopic bariatric surgery, but advantages over conventional surgery are not clear.[32,36–38]

TRAINING ISSUES FOR LAPAROSCOPIC BARIATRIC OPERATIONS

Laparoscopic bariatric surgery, particularly the laparoscopic RYGB and malabsorption procedures, are technically very challenging because they require skills not required of many advanced laparoscopic procedures. Both the obese patient and the complexity of these reconstructive procedures create the major technical barriers. Patient factors such as massive obesity (BMI >60), severe hepatomegaly, prior abdominal surgery, and reoperative bariatric surgery may increase the degree of difficulty by several magnitudes. This high degree of difficulty translates into a steep learning curve and potentially a higher rate of perioperative technical complications such as intestinal perforation, anastomotic leaks, bleeding, bowel obstruction (failure to adequately close mesenteric defects), and inadvertent visceral injury. Other undesirable consequences attributed to the complexity of this operation include a longer operating time (at least initially) and potentially higher conversion rate. Acquisition of advanced laparoscopic skills is essential for safe and effective performance of laparoscopic bariatric operations. Surgeons who do not have the benefit of experience with at least some of the other advanced laparoscopic procedures will be at a significant disadvantage. Equally important to success is

Table 2. Changes in comorbidity after laparoscopic Roux-en-Y gastric bypass

Comorbidity	Total	% Aggravated	% Unchanged	% Improved	% Resolved
OA/DJD	64	2	10	47	41
Hypercholesterolemia	62	0	4	33	63
GERD	58	0	4	24	72
Hypertension	57	0	12	18	70
Sleep apnea	44	2	5	19	74
Hypertriglyceridemia	43	0	14	29	57
Depression	36	8	37	47	8
Peripheral edema	31	0	4	55	41
Urinary incontinence	18	0	11	39	44
Asthma	18	6	12	69	13
Diabetes	18	0	0	18	82
Migraine headaches	7	0	14	29	57
Anxiety	7	0	50	17	33
Venous insufficiency	7	0	71	29	0
Gout	7	0	14	14	72
CAD	6	0	0	75	26
COPD	3	0	33	67	0
CHF	3	0	33	67	0
OHS	2	0	0	50	50

CAD = coronary heart disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; GERD = gastroesophogeal reflux disorder; OA/DJD = osteoathritis/degenerative joint disease; OHS = obesity hypoventilation syndrome.
From Schauer PR, Ikramuddin S, Gourash W, et al. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Ann Surg 2000;232:515–529.

the knowledge and experience with management of the bariatric patient including appropriate indications for surgery, preoperative evaluation, perioperative management, and long-term follow-up care. Either fellowship training or extended mentoring by an experienced surgeon are the two most optimal methods of obtaining the necessary skills. Both fundamentals of bariatric surgery and advanced laparoscopic surgery should be mastered before performing laparoscopic RYGB or laparoscopic malabsorption procedures.

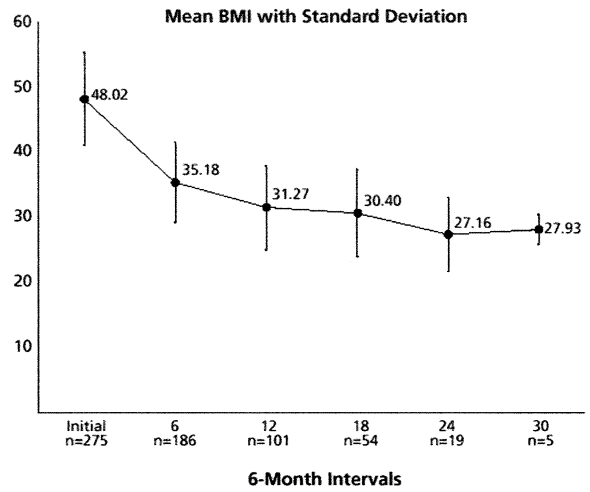

Fig. 7. Excess body weight loss after laparoscopic Roux-en-Y gastric bypass. Reprinted with permission from, Schauer PR, Ikramuddin S, Gourash W, Ramanathan R, Leketich J. Out-comes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Ann Surg 2000;232(4):515–529.

CONCLUSION

Two major advances in surgery for morbid obesity over the past decade are responsible for the dramatic transition from skepticism to widespread adoption. The first involves the accumulation of many studies documenting reproducible long-term weight loss in the range of 50% to 70% excess weight loss for gastric bypass, with profound reduction in comorbidity and improvement in quality of life while maintaining major operative morbidity and mortality under 10% and 1%, respectively. Apart from the gastric bypass, LASG or malabsorption procedures appear to have favorable risk/benefit ratios but do not have the same weight of evidence. Although surgical management does carry a higher risk than medical management of severe obesity, it clearly is superior in terms of long-term weight loss, which at best is 10% to 15% of excess body weight for the best medical (nonsurgical) therapy. The second major advance is the development of less invasive bariatric operations that use laparoscopic techniques. The reduction in perioperative morbidity particularly related to wound complications and recovery clearly provides significant advantages over the conventional (open) approach. Essentially all major bariatric operations can now be performed laparoscopically. Patient

demand is rising steadily for the laparoscopic technique, and it probably accounts for at least some of the increase in patients seeking bariatric surgery. As more surgeons learn the laparoscopic technique, it should become the norm. Among the many challenges ahead are determining which operations are most suitable for specific patients, and whether expanding indications for surgery to include adolescents, the elderly, and those with moderate obesity (BMI less than 35) is appropriate and justifiable. In summary, the weight of recent evidence suggests that surgical management is the most effective therapy currently available for treating severe obesity, with a favorable risk/benefit ratio. Primary physicians should be obliged to discuss surgical options with all of their patients who suffer from morbid obesity.

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Treatment of Obesity

Harvey J. Sugerman, M.D.

The presentations we have just heard provide a thorough update on the clinical management of the severely obese patient. Clearly, obesity has become an epidemic throughout the world. Even for countries where obesity is not believed to be a problem, such as China, Japan, and Korea, this is no longer true. A significant part of the epidemic may be due to the influx of fast-food restaurants into these countries. Our lifestyle has become increasingly sedentary. Physical education is no longer strongly supported in many of our elementary or high schools. Children have become "couch potatoes." They sit in front of the TV screen, play computer games, or live on the Internet. Also, the complications of obesity, including diabetes, hypertension, and sleep apnea, usually thought to be problems in adults, are exploding in our adolescents.

Unfortunately, the long-term efficacy of nonsurgical weight loss leaves much to be desired. Although the loss of 10% of excess body weight will have a significant benefit in terms of obesity-related morbidity, we have found that the greater the weight loss after surgery, the greater the likelihood that hypertension and diabetes will be corrected.[1] As with the adverse effects of the discredited jejunoileal bypass operation, pharmaceutical adjuncts to weight loss have also had their major complications with valvular heart disease and pulmonary hypertension following treatment with Redux. Although the newer agents appear to be safe, the amount of weight loss achieved with orlistat or sibutramine is underwhelming, and these medications are quite expensive. Newer agents are in the pipeline and, hopefully, these will be both safe and more effective. Clearly, as Dr. Klein has emphasized, similar to diabetes or hypertension, medical treatment of obesity will require life-long therapy. It has been shown in many studies that once pharmaceutical therapy is withdrawn, weight recidivism will occur.

Dr. Schauer has shown us, both in his own work as well as that of others, that laparoscopic Roux-en-Y gastric bypass has become an effective procedure for the treatment of severe obesity. The operation has evolved over the past several years at many centers to become a very safe procedure. More and more bariatric surgeons, with significant support and motivation by the corporate surgical instrument companies, are learning how to do the procedure. Some have charged into the operation without adequate training, to the detriment of their patients. However, this problem is resolving as did the transient marked increase in common bile duct injury with the development of laparoscopic cholecystectomy. From an endoscopist's point of view, the two major long-term complications that can occur with gastric bypass are a marginal ulcer, especially in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs), and stenosis at the gastrojejunal anastomosis. The latter responds to endoscopic dilatation and may be urgently needed to prevent the dehydration or recurrent vomiting that can lead to Wernicke-Korsikoff encephalopathy or peripheral neuropathy from thiamine deficiency.

The FDA approved the laparoscopic adjustable silicone gastric band procedure last June for use in the United States. During the initial evaluation we and others at centers throughout the United States had major concerns regarding the safety and efficacy of this procedure, including the significant problem of esophageal dilatation and dysphagia. Centers in Australia and Europe have reported much better results with this device. The reason for this discrepancy is not clear. Its use is associated with a very low mortality risk. No randomized studies have been performed, to date, comparing these results to those of Roux-en-Y gastric bypass.

There is a real concern about late weight recidivism following Roux-en-Y gastric bypass. Our data in adolescents who have undergone obesity surgery show excellent weight loss with correction of obesity comorbidity up to 10 years after mostly gastric bypass surgery, and these patients still show a significant weight loss at 14 years after surgery.[2] However, a few of them, as well as our adult patients, have regained all or most of their weight 10 or more years after the operation. Long-term follow-up in this population is extremely difficult. In a study by Pories et al.,[3] with 98% follow-up that included phone contact and primary care physician data, the average loss of excess weight was 66% at 2 years, 60% at 5 years, 50% at 10 years, and 47% at 14 years. Thus

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weight recidivism clearly exists. This appears to be primarily a result of nibbling high-fat junk foods (potato or corn chips). In some instances patients do not develop "dumping" symptoms with the ingestion of carbohydrates, and some even crave sugar. A few have marked dilatation of the gastrojejunal anastomosis and claim that they do not achieve early satiety. This could be prevented by placing a band above the gastric outlet, such as a combination vertical banded gastroplasty with gastric bypass. Perhaps in the future this problem may be treated endoscopically with injection of a polymer being developed for gastroesophageal reflux disease.

Many surgeons believe that these severely obese patients need a malabsorptive procedure for long-term maintenance of weight loss. Currently the most popular malabsorptive operation is a partial biliopancreatic bypass with duodenal switch. Unfortunately there has been no randomized trial comparing this operation to the gastric bypass. At present, there is no "legal" CPT billing code for the duodenal switch procedure. We have had institutional review board approval to perform this randomized trial; however, private insurance companies will not support "research" studies. The National Institutes of Health will not fund surgical treatment of patients. Thus it is now extremely difficult to perform the necessary clinical studies.

In summary, we need better drugs for the treatment of obesity. Surgery is currently the most effective treatment and, with rare exception, the best approach for the severely obese patient with a BMI greater than 40 who has significant obesity-related comorbidity problems. However, we have yet to determine the optimal surgical procedure. Surgery is a very expensive solution to our worldwide massive obesity problem. What is clearly needed is a much more aggressive and effective worldwide prevention program beginning in elementary school.

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Overview—Current Clinical and Preclinical Use of Robotics for Surgery

Mark A. Talamini, M.D.

The first device for abdominal and thoracic surgery was approved for use by the FDA on June 16, 1999. This ushered in a new and exciting age of surgery, with potential limited only by surgeons' dreams and engineers' capabilities. An early challenge is that of definitions. A robot is defined as "a machine that resembles a human and does mechanical, routine tasks on command" or "any machine or mechanical device that operates automatically with humanlike skill" (*Webster's Universal College Dictionary*). Although the machines developed for surgery currently do not resemble humans on a large scale, two important aspects of the system resemble human capabilities—three-dimensional visualization and wristlike movements of the end effectors. However, they do not execute preprogrammed independent actions. Rather, these devices are designed to enhance the capabilities of surgeons. The implication that these devices act independently, created by using the term robot, may cause appropriate apprehension among patients and the public. A more precise term might be *computer-enhanced telemanipulator*. However, the simpler and more exciting term *robot* is already in common usage.

Robotic technology has been used to great advantage in nonmedical applications for a long time. Maintenance of the nuclear arsenal, production of automobiles, and manipulations in space all benefit from the field of robotics. Surgery has been slower to take advantage of this technology for obvious reasons. But engineers and forward-thinking surgeons have been thinking, dreaming, and working toward the introduction of robotic technology into the world of surgery. Dr. Russ Taylor, while working at IBM and after joining the Johns Hopkins faculty, was performing such work, in consultation with a variety of surgeons. One potential disadvantage of robotic devices is the lack of feedback regarding the amount of pressure they may be exerting on tissues. In a series of experiments, using a robotic device designed by Dr. Taylor's team, we sought to determine whether a robotic device would be better or worse than human force during organ retraction.[1] To accomplish this, we modified a laparoscopic retraction device by adding pressure sensors. We then compared the pressures generated during porcine laparoscopic operations in which the robotic device applied retraction pressure or a human did so. We found that the robot applied a more consistent retraction pressure and less overall retraction pressure than did the human. Thus this seems to be an instance where a robotic device can perform a boring, repetitive task in a more consistent, and perhaps safer, manner. Retraction pressures applied during open and laparoscopic operations on humans have not been measured, so we really do not know what an appropriate pressure is for retracting an organ such as the liver. We are working to accomplish such studies now. This is an example of preclinical work that will likely contribute to the evolution of surgical robotic devices.

One of the first devices used clinically in human surgery was the "Robo-doc" system for orthopedic surgery.[2] Its intention was to improve on a task performed by hand by surgeons. The task, in this instance, was bone drilling to fit a hip prosthesis, to create a more ideal fit between prosthesis and bone. This system continues to be used clinically.

Experience has rapidly accumulated since the approval by the FDA of the daVinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA). We recently reported a combined series of clinical cases from four institutions at the SAGES meeting in New York. In that presentation, four institutions (East Carolina University, Johns Hopkins University, Ohio State University, and the University of Illinois at Chicago) reported on a prospective analysis of 211 robotically assisted procedures performed between June 2000 and June 2001 using the daVinci system. The procedures

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undertaken included antireflux surgery (n = 69), cholecystectomy (n = 36), Heller myotomy (n = 26), bowel resection (n = 17), donor nephrectomy (n = 15), left internal mammary artery mobilization (n = 14), gastric bypass (n = 7), splenectomy (n = 7), adrenalectomy (n = 6), exploratory laparoscopy (n = 3), pyloroplasty (n = 4), gastrojejunostomy (n = 2), distal pancreatectomy (n = 1), duodenal polypectomy (n = 1), esophagectomy (n = 1), gastric mass resection (n = 1), and lysis of adhesions (n = 1). In this series of patients, the average operating room time was 188 minutes (range 45 to 387 minutes, standard deviation [SD] = 83), surgical time was 143 minutes (range 35 to 462 minutes, SD = 63), and the actual robot use time was 90 minutes (range 12 to 235 minutes, SD = 47). The median length of stay was 1 day (range 0 to 37 days). There were eight technical complications (4%) during these procedures—five minor (4 hook cautery dislodgement and 1 slipped robotic trocar) and three major (system malfunctions, 2 of which required conversion to standard laparoscopy). In all cases, technical problems caused only delay, without apparent altered outcome. Medical/surgical complications occurred in nine patients (4%). Six (3%) were considered major, including one death unrelated to the robotic procedure. The group concluded that the results of robotic-assisted surgery compared favorably with those of commonly reported conventional laparoscopy with respect to mortality, complications, and length of stay.

A number of other interesting reports are also beginning to appear in the literature. A series of 146 cases from a single institution in which the daVinci system was used was reported by Cadiere et al.[3] The authors opine that the daVinci system is most effective for fine manipulations in a small space. The two most popular systems (daVinci Surgical System and ZEUS Robotic Surgical System; Computer Motion, Goleta, CA) were compared in an animal study reported by Sung and Gill.[4] They concluded that the operative times and the learning curve were shorter with the daVinci system, although both systems were effective. A group from France reported an initial experience with 25 robotic laparoscopic cases, all cholecystectomies.[5] They also concluded that computer-assisted surgery is feasible and safe, with operative times and recovery comparable to laparoscopic cholecystectomy. The group from Ohio State compared computer-assisted and laparoscopic antireflux operations. Although the operating times were longer for the robotic group, there were no other differences seen in the perioperative course or the clinical outcomes.[6]

The world of surgery is rapidly changing. The current generation of robotic systems for general surgical applications is only a beginning, but it is an impressive beginning. Issues with these systems certainly exist, such as the additional time necessary and the cumbersome nature of the machinery. As surgeons and engineers continue to work together, future systems will evolve into tools that are beyond our current imagination.

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Robots in Surgery: Advanced Gastrointestinal Applications and Credentialing

W. Scott Melvin, M.D.

ADVANCED GASTROINTESTINAL APPLICATIONS

Advances in laparoscopic surgery have allowed the application of standard laparoscopic tasks to encompass most aspects of gastrointestinal surgery. New instrumentation, including advanced surgical systems (e.g., the da Vinci Surgical System; Intuitive Surgical, Inc., Sunnyvale, CA), are a continuation of this progress. Discussions of systems such as da Vinci require strict definitions. The term *computer-assisted/enhanced telesurgery* is most accurate. Other terms such as *robotic surgery* are frequently used but are imprecise in that they imply preprogrammed, autonomous devices, which currently are not available for widespread use.

Computer-enhanced telesurgery can further define and enhance many aspects of advanced gastrointestinal surgery. The current limitations of laparoscopic surgery are well recognized. Rigid, unarticulated instruments that rotate around a fixed point in the abdominal wall reduce precision. Tissue manipulation and the ability to reach certain environments within the abdomen are limited. Moreover, standard laparoscopic instrumentation does not provide true-depth or three-dimensional imaging. The computer-enhanced devices do. Additionally, the new devices offer motion scaling, which significantly adds to all fine-motor aspects of advanced gastrointestinal surgery. This level of enhancement is important when manipulating small structures or fine tissues and, at this time, provides the most apparent benefit of a computer-enhanced telesurgical device.

The indications and actual advantages of the new devices for performing standard laparoscopic gastrointestinal surgery remain unclear, however. Numerous reports concur, including the largest combined series of 211 cases from four institutions describing a variety of completed gastrointestinal and intra-abdominal procedures. The series by Talamini et al.[1] reported no device failures or complications directly related to the instrument. Although no objective evidence has yet shown the clear advantages of this device subjectively, many authors have suggested that it may provide some benefit. Further ongoing studies comparing different procedures will tell more. A single trial comparing standard laparoscopic to "robotic" laparoscopic antireflux surgery has been reported.[2] The robotic surgery required longer operative times, but no significant clinical differences were found.

Laparoscopic approaches to solid-organ disease have been limited to end-organ excision. Procedures performed with computer-enhanced devices, including splenectomy, adrenalectomy, nephrectomy, and pancreatectomy, have been described.[3] No trials, however, have compared the robotic procedures to standard laparoscopic procedures. One promising use for the new device may be in the treatment of liver disease, including biliary tract and excision of small lesions, and perhaps even allowing for vascular control in lobar resections. Approaches to the common bile duct are formidable and most often approached through an endoluminal technique; however, with the fine motor control, motion scaling, and high-definition three-dimensional imaging provided by these computer-enhanced devices, approaches to the biliary tree to treat common duct pathology may be more appropriate. Biliary tract reconstructions using fine-suturing techniques, as well as open bile duct exploration, are certainly possible and have been reported in anecdotal form.

Another possible area for application may be in laparoscopic surgery for obesity. A particularly demanding step of the surgery is creation of a proximal gastrojejunostomy and a small gastric pouch. A variety of stapling techniques have been described, but many surgeons continue to advocate hand suturing of the anastomosis. Facile, multiarticulated instruments

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have generally resulted in significantly improved laparoscopic suturing skills. The quality of the anastomosis, although not yet studied, appear to meet standards. It may be that the added use of a computer-enhanced device during performance of a hand-sewn gastrojejunostomy may provide a clear benefit.

New technology has the potential to enhance surgical techniques. Applications for computer-enhanced devices should be studied in a professional and scientific manner, so that the true advantages can be presented both ethically and appropriately for improved patient care.

ISSUES IN CREDENTIALING NEW TECHNOLOGY

As new technology becomes available to assert itself between the physician and patient, a framework must exist that ensures proper credentialing. Most nationally recognized guidelines require individual institutions to appropriately delineate privileges for individual practitioners based on training and experience. Physician leaders within any health care institution must develop credentialing systems with patient safety as the top priority. When a new technology is identified, certain steps should be taken, including defining the new technology and criteria and providing appropriate definitions. Once new credentialing guidelines are developed and the technology is clearly defined, the basic tenets of any credentialing process must be in effect. Physicians should be practicing within the scope of their training, and the new technology studied in reference to existing techniques, with clinical trials proving efficacy as well as benefits. Any technology causing major changes in patient care algorithms needs to be carefully studied before being widely implemented.

In credentialing robotic surgery, many institutions think it reasonable to identify the individual instrument, such as the ZEUS Robotic Surgical System (Computer Motion, Inc., Goleta, CA) or the da Vinci surgical system. It is important that all members of a credentialing committee and/or team identify the fact that a surgeon needs to be credentialed to perform certain procedures. The device itself has no independent preprogrammed motions that make it a credentialed entity. It should be recognized that computer-enhanced surgery is, in fact, an incremental improvement in minimally invasive surgery and, perhaps, other surgical procedures. The surgeon should have acquired knowledge and experience with the instruments specific to a machine and have clinical experience, gained either in the laboratory or the operating room. Many situations of proctoring by an "expert" surgeon seem reasonable, and all surgeons should subscribe to an ongoing quality assurance program. Financial analysis may be appropriate in some situations to determine the cost-effectiveness of these instruments, as well. Appendix A is an example of credentialing guidelines at The Ohio State University.

The credentialing procedure for computer-enhanced surgery is the same as for all technology. New technology should be assessed first for patient safety. Surgeons should operate within the scope of their practice and training, and gain practical experience with new devices outside of the operating room before approaching a patient. Once a limited clinical experience is identified, then expert preceptors should be identified to help new surgeons apply the new technology. With the cooperation of hospital personnel, administrators, surgeons, educators, and engineers, maximum safety procedures can be undertaken to provide the benefit of the new computer-enhanced technology to provide optimal patient outcomes.

APPENDIX A
Guidelines for Credentialing of Computer-Assisted Surgery at The Ohio State University

Introduction. Computer-assisted surgery consists of utilizing advanced technology that couples high-resolution imaging to remotely controlled surgical arms. Surgical intervention is accomplished by manipulation of the device under three-dimensional video imaging, which reproduces motions that affect patient tissue. Computer-assisted technology allows a more precise manipulation of tissue by "scaling" hand motions and three-dimensional imaging. It is the purpose of these guidelines to provide and grant privileges in the use of computer-assisted surgical devices.

Basic Qualifications. The following criteria will be a prerequisite for all individuals for the performance of computer-assisted surgery:

1. The completion of a formal training program in surgery or a surgical subspecialty in an ACGME-approved program
2. Certification or active engagement in the certification process by the American Board of Surgery or the certifying agency of the surgical subspecialty
3. Eligibility and active privileges at The Ohio State University to perform the open and laparoscopic procedures. The use of computer-assisted surgical instrumentation should be limited to the level of intervention already privileged under the guidelines of advanced laparoscopic procedures

4. Active participation in the ongoing quality assurance program at the Department of Surgery and The Ohio State University
5. One of the following criteria must be met:
   - Practical experience via an accredited fellowship or residency program and clinical experience in a minimum of 10 computer-assisted procedures
   - Training in the use of the computer-assisted device with didactic and practical experience in a laboratory setting
   - Successful completion of at least two procedures under the supervision of an expert preceptor*

Monitoring. It is anticipated that for the first year of cases performed, the cases will be entered into a database to allow periodic review of quality care.

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*A preceptor should be identified as a surgeon who has met the above outlined qualifications for credentialing at The Ohio State University and has practical experience in the successful use of the computer-assisted surgical devices. Additionally, the preceptor should be approved by the Division Chief of the individual seeking credentialing as an appropriate preceptor for completion of the surgical procedure.

Outcome After Pancreaticoduodenectomy for Periampullary Cancer: An Analysis from the Veterans Affairs National Surgical Quality Improvement Program

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The aim of this study is to define the risk factors that predict adverse outcomes for patients undergoing pancreaticoduodenectomy for periampullary cancer in the Department of Veterans Affairs Healthcare System (VA). The VA National Surgical Quality Improvement Program prospectively collected data on 462 patients undergoing pancreaticoduodenectomy in 123 VA medical centers from 1990 to 2000. Independent variables included 68 preoperative and 12 intraoperative variables. The main outcome measures were 30-day postoperative mortality and morbidity, as measured by a set of 20 pre-defined complications. Predictive models for 30-day morbidity and mortality were constructed using logistic regression analysis. The 30-day morbidity rate was 45.9% (212/462). The 30-day postoperative mortality rate was 9.3% (43/462). Significant predictors of mortality included: preoperative serum albumin, American Society of Anesthesiologists classification, preoperative bilirubin >20mg/dl, and operative time. The use of preoperative biliary tract instrumentation did not predict postoperative death or septic complications. This study provides a set of preoperative risk factors that are predictive of adverse outcome following pancreaticoduodenectomy. These factors may assist in patient selection for this procedure and are likely to facilitate risk-adjusted comparison of pancreaticoduodenectomy outcomes between different health care systems. (J GASTROINTEST SURG 2003;7:484–491) © 2003 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Pancreatic neoplasms, surgery, adverse effects, postoperative complications

Pancreaticoduodenectomy (PD) remains one of the most complex and technically demanding procedures in the general surgical repertoire. In the recent era, however, a number of specialty centers have reported consistently low operative mortality rates.[1–3] As the majority of these series are retrospective reviews from single institutions, the applicability of these results to patients treated for pancreatic malignancies in other hospitals or health care systems is not known. There is evidence that suggests that institutional and surgeon volume may contribute to favorable outcomes,[4–7] however, other specific predictors of mortality and the reproducible processes of care that lead to favorable outcomes have not been well defined.

In order to identify preoperative indicators of surgical risk and facilitate the comparative assessment of the quality of surgical care among multiple facilities, the Department of Veterans Affairs (VA) established the National VA Surgical Quality Improvement Program (NSQIP). The NSQIP oversees the prospective collection of presurgical, surgical, and 30-day outcome information for surgical patients throughout the VA healthcare system. One of the

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primary goals of this program is to use prospectively collected data to develop and validate risk adjustment models. These models allow for the prediction of surgical outcome as well as providing a basis for comparative assessment of the quality of surgical care among multiple facilities.[8] On the basis of these data, risk adjustment models have been developed for 30-day mortality and morbidity for both cardiac and noncardiac surgery including the majority of the surgical subspecialties.[9,10]

The objectives of this study are to define the mortality and morbidity rates for patients undergoing PD for periampullary cancer within the VA healthcare system and to use the prospectively collected data from the NSQIP to define the predictors of surgical risk related to this procedure. This study also aims to develop a risk adjustment model for PD that will facilitate accurate comparison of risk-adjusted outcomes of pancreaticoduodenectomy between different institutions and health care systems.

MATERIAL AND METHODS

The methods of the NSQIP were developed during the National VA Surgical Risk Study (NVASRS).[11] This study was designed to collect reliable, valid, and accurate data about patient risk and surgical outcome. In 1994, the validated methods of the NVASRS were extended to all VA Medical centers performing surgery and the National VA Surgical Quality Improvement Program was established. The program now functions as an ongoing quality improvement initiative. The program relies on the efforts of trained nurse-reviewers who are based at Veterans Affairs medical centers (VAMC). These individuals collect prospective data on patients undergoing non-cardiac operations in 123 VAMCs. At low volume centers (<140 eligible operations per month), all eligible operations are included. At high volume centers (>140 operations per month), the first 36 eligible procedures are entered into the study in each consecutive 8-day period, beginning with a different day each period.

Data collection includes patient variables that are collected for the purpose of risk-adjusted analysis of outcome. These data include 68 preoperative, 12 intraoperative variables, and 33 outcome variables. Logistic regression analysis is then used to develop predictive models of postoperative death and complications.

The present study was reviewed and approved by the Institutional Review Board of the University of Washington. All patients undergoing pancreaticoduodenectomy during the period October 1, 1990 through September 30, 2000 were selected from the NSQIP database. This included Current Procedural Terminology (CPT) codes 48150 (pancreaticoduodenectomy) and 48153 (pancreaticoduodenectomy with pylorus preservation). Patients that underwent a pancreaticoduodenectomy without pancreaticojejunostomy (48152, 48154) were excluded from this analysis. Patient diagnosis, as indicated by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM),[12] was reviewed, and patients with benign diseases of the pancreas were excluded from this analysis. All patients were diagnosed with a carcinoma of the pancreas (ICD−9 157.0–157.9), ampulla of Vater (156.2), duodenum (152.0), or bile duct (156.1). Additional treatment related information including the use of preoperative biliary stents was gained by linking NSQIP data to data in the Patient Treatment File (PTF), which contains detailed records on hospital procedures. NSQIP data were also linked to the VA outpatient treatment files to gain information on procedures performed on an outpatient basis.

Patients' vital status as of November 2000 was determined by matching social security numbers from the NSQIP data set with records in the VA Beneficiary Identification and Records Locator Subsystem (BIRLS). This system is designed to track mortality of veterans for the proper assignment of benefits to dependents. The BIRLS has a 95% sensitivity for identification of death in veterans who have ever been admitted to a VA hospital.[13,14]

Data from the NSQIP database were used to develop a logistic regression model for 30-day postoperative mortality for patients undergoing pancreaticoduodenectomy within the VA system. The purpose of this model was to identify important predictors of 30-day postoperative mortality. When laboratory tests had missing values, a regression technique was employed to impute missing values.[10,15] Independent variables examined included 68 presurgical clinical parameters, including a variety of laboratory test values and 12 intraoperative risk factors.[11] We also examined additional clinical variables including operative time and the use of preoperative biliary tract instrumentation. Outcome variables included 20 adverse outcomes and postoperative mortality. Postoperative mortality was defined as death from any cause inside or outside of the hospital within 30 days of operation. To analyze the bivariate relationship between morbidity and mortality and candidate variables we used the t test for continuous variables and the chi square test for categorical variables. Measures of logistic regression model fit included the c-index[16,17] and the Hosmer Lemeshow test.[18]

RESULTS

Demographic and Clinical Characteristics

Four hundred and ninety-five patients who underwent pancreaticoduodenectomy for periampullary malignancy in the VA health care system from October 1, 1990 to September 30, 2000 were identified from the NSQIP data. Thirty-three patients were excluded from the analysis because they were identified by the NSQIP reviewer as having "disseminated cancer" at the time of the operation. The remaining 462 patients comprise the study group. The patients were predominantly male with a mean age of 65 years (Table 1). The majority of the patients (72.5%) had a pancreatic tumor. The remainder of the patients had disease involving the bile duct, duodenum or ampulla. Approximately 25% of patients were coded in the Patient Treatment File as undergoing preoperative biliary tract instrumentation. A standard pancreaticoduodenectomy was used as the operative procedure in 84% of the study group and all other patients were treated with a pylorus-preserving pancreaticoduodenectomy.

Postoperative Mortality and Logistic Regression Modeling

Forty-three patients died within 30 days of the operative procedure (9.3%). Three preoperative factors were predictive of postoperative mortality (Table 2). The presurgical albumin was inversely associated with 30-day mortality. American Society of Anesthesiologists (ASA) classification, and a preoperative total bilirubin greater than 20 mg/dl were also significantly associated with increased postoperative mortality (Table 3). Additional logistic models were developed using intraoperative variables (Table 4). Increasing operative time (hours) was associated with an increased risk of 30-day mortality. The addition of biliary tract instrumentation to the model did not predict postoperative mortality. The model that includes operative variables including operative time and biliary tract instrumentation predicted well (c = 0.733) with no gross lack of fit. Additional modeling was performed to examine the potential role of institutional surgical volume on postoperative mortality. When forced into the logistic regression model, the number of procedures performed at the institution did not predict postoperative mortality.

Table 1. Clinical and demographic data

Characteristic	n	%
Age (mean ± sd, range)	65.3 ± 9.6 (37–89)	
Sex		
Male	455	98.5
Female	7	1.5
Race		
White	332	71.9
Black	80	17.3
Other	50	10.8
Tumor location		
Ampulla of Vater	69	14.9
Bile duct	21	4.6
Duodenum	37	8.0
Pancreas	335	72.5
Procedure		
PD	388	84.0
Pylorus-preserving PD	74	16.0
Biliary instrumentation		
−instrumentation	349	75.5
+instrumentation	113	24.5

PD = pancreaticoduodenectomy.

Table 2. Thirty-day mortality: Logistic regression analysis of preoperative variables

Variable	Parameter estimate	*P* value	Odds ratio
Intercept	−1.686	0.148	
Preoperative albumin (mg/dl)	−0.640	0.024	0.53
ASA classification	0.625	0.042	1.87
Preoperative bilirubin >20 (mg/dl)	1.110	0.010	3.04

Model fit: c index = 0.692; R-square = 0.05; Hosmer-Lemeshow goodness of fit = 5.36 ($P = 0.719$).

Postoperative Morbidity

The overall postoperative complication rate was 45.9%. Major medical complications such as cardiac arrest, acute renal failure and pulmonary failure had the greatest association with 30-day mortality (Table

Table 3. Observed mortality and preoperative serum total bilirubin

Preoperative total bilirubin (mg/dl)	No. of cases	No. of postoperative deaths	Mortality rate (%)
0.0–4.9	233	18	7.73
5.0–9.9	93	7	7.53
10.0–14.9	52	4	7.69
15.0–19.9	45	3	6.67
20.0–24.9	16	4	25.00
25.0–29.9	13	4	30.77
30.0+	10	3	30.00

Table 4. Thirty-day mortality: Logistic regression analysis of preoperative and operative variables

Variable	Parameter estimate	*P* value	Odds ratio
Intercept	−3.265	0.011	
Preoperative albumin (mg/dl)	−0.669	0.018	0.51
ASA classification	0.694	0.027	2.00
Preoperative bilirubin >20 (mg/dl)	1.115	0.011	3.05
Operative time (ho)	0.192	0.003	1.21
Preoperative biliary stent	−0.179	0.661	0.836

Model fit: c index = 0.733; Hosmer-Lemeshow goodness of fit = 11.13 ($P = 0.195$).

5). Surgical complications such as systemic sepsis, and blood loss requiring >4-unit transfusions were also associated with a high mortality rate. The rates of systemic sepsis were 13.3% (15/113) for patients with preoperative biliary tract instrumentation and 8.9% (31/349) for patients without evidence of instrumentation. Although this shows a trend, it is not statistically significant ($P = 0.205$). Separate logistic regression models were run for systemic sepsis and wound infections as outcomes. For systemic sepsis, a history of congestive heart failure, age and operative time were significant predictors. For wound infection, only a history of congestive heart failure was predictive. The use of a preoperative biliary stent was not predictive for either systemic sepsis or wound infection.

Relationship Between Institutional Volume and Postoperative Mortality

Only eight hospitals performed more than 10 pancreaticoduodenectomies during the study period. In these hospitals the postoperative mortality rate was 5.9%. Institutional volume was not predictive of postoperative mortality in logistic regression modeling. We performed univariate modeling of the relationship between volume and mortality using a variety of cut-points. We compared postoperative mortality rates for institutions performing 5 or more versus fewer procedures, 8 or more procedures, and 10 or more procedures (Table 6). Volume was significantly associated with mortality in this univariate analysis when hospitals performed <5 procedures versus ≥5 procedures.

DISCUSSION

In spite of the technical complexity of the procedure, pancreaticoduodenectomy has become an increasingly safe operation. In a small number of

Table 5. Observed mortality associated with individual complications

Complication	N	Complication rate (%)	No. of deaths*	Mortality rate (patients with complications) (%)
Cerebral vascular accident	1	0.22	1	100
Cardiac arrest	13	2.81	12	92
Acute renal failure	10	2.16	7	70
Coma >24 h	4	0.87	2	50
Peripheral neurological deficits	2	0.43	1	50
Unplanned intubation	48	10.39	19	39
Progressive renal insufficiency	11	2.38	4	36
Systemic sepsis	46	9.96	16	35
Myocardial infarction	6	1.30	2	33
Bleeding requiring >4 units transfusion	35	7.58	11	31
Failure to wean >48 h	55	11.90	15	27
Graft failure	4	0.87	1	25
Wound infection	46	9.96	7	15
Prolonged ileus	43	9.31	6	14
Pneumonia	50	10.82	6	12
Urinary tract infection	32	6.93	3	9
Wound disruption	12	2.60	1	8
Superficial infection	31	6.71	2	6
Pulmonary embolism	1	0.22	0	0
Deep venous thrombosis	0	0	0	NA

NA = not applicable.
*Deaths within 30 days of operation.

Table 6. Observed postoperative mortality by hospital volume

Hospital group (cases)	No. of hospitals	No. of cases	No. of deaths	Mortality rate (%)	*P* value
≤5	48	130	18	13.9	0.05
>5	38	332	25	7.5	
≤8	69	274	28	10.2	0.52
>8	17	188	15	8.0	
≤10	78	360	37	10.3	0.25
>10	8	102	6	5.9	

high-volume centers the operation is performed with mortality rates consistently less than 5%[1,3,19] Successful outcomes following pancreatic surgery are likely to be related to experience of the surgeon and the institution, and patient selection. There has also been speculation that such clinical variables as the use of preoperative biliary stents may impact on the safety of the procedure.[20] The aim of this study was to use a large, prospective, multi-institutional, clinical data set to identify presurgical and operative predictors of postoperative mortality. These predictors may serve to guide patient selection as well as providing guidelines for risk-adjusted analysis to facilitate comparison of outcomes between different health-care systems.

A recently published study of pancreaticoduodenectomy outcomes among more than 10,000 Medicare recipients indicates that postoperative mortality is 10%.[21] In the current study we have used NSQIP data to show that postoperative mortality (9.3%) for patients undergoing pancreaticoduodenectomy within the VA system are within the range of Medicare recipients treated in the private health care arena. However, mortality rate is somewhat above that reported by single, specialty institutions. This study identifies preoperative albumin, preoperative total bilirubin >20 mg/dl, and ASA class as significant predictors of postoperative mortality. These results are consistent with previous studies of general surgical procedures using the NSQIP data set. Albumin in particular has proven to be a consistent and reliable predictor of mortality. Albumin is a powerful predictor of postoperative mortality following proctectomy,[22] colectomy,[23] gastrectomy,[24] and a variety of other surgical procedures.[25] The predictive power of serum albumin is logical given its role as an accurate indicator of overall nutritional status. In the current study it is not evident from the data if diminished preoperative albumin represents poor nutritional status existing as a premorbid condition, or if it relates to patients presenting with more advanced disease and cancer-related cachexia.[26] Regardless of etiology, decline in preoperative serum albumin is a significant predictor for adverse postoperative outcome.

ASA classification has also proven to be a consistent predictor in other studies of predictors of outcome in general surgical procedures. In previous NSQIP studies, ASA classification is the second most predictive indicator of both postoperative morbidity and mortality, following serum albumin.[8] A variety of other groups have also studied the predictive value of ASA and found that some global measure of health status, such as ASA classification or APACHE II score serves as a consistent predictor of postoperative mortality and morbidity.[27–29]

The role of preoperative biliary drainage and the potential deleterious effects of preoperative jaundice both remain controversial topics within pancreatic surgery. In the past, surgeons proposed that significant elevations in preoperative bilirubin were associated with a multiplicity of complications, particularly postoperative renal dysfunction and hemorrhage.[30,31] After the advent of endoscopic biliary drainage procedures, preoperative biliary drainage was proposed as a method to reduce postoperative death and complications in jaundiced patients.[32,33] However, in recent years a variety of investigators have suggested that not only is preoperative biliary drainage not beneficial, but it may even be harmful.[20,34–37]

In the present study we find that after adjustment for other characteristics, such as albumin, bilirubin, and ASA classification, the use of preoperative biliary tract drainage is not a predictor of postoperative mortality. In the VA system as in many other health care systems, preoperative biliary stents are placed in patients with obstructive jaundice, particularly when a delay is anticipated before the patient undergoes surgical treatment. Although one large retrospective study has suggested that preoperative drainage increases mortality,[20] we find no evidence of increased postoperative mortality related to preoperative drainage in this group of patients. We believe our data demonstrate that although preoperative biliary drainage does not necessarily decrease postoperative complications, it also does not appear to increase postoperative mortality. These data support the continued selective use of preoperative stenting, particularly for patients that require additional evaluation or referral to a tertiary care center for surgical therapy.

Given the number of studies that have demonstrated no clear benefit from preoperative biliary drainage, a variety of investigators have sought to determine if there exists a threshold value of preoperative bilirubin at which preoperative drainage is likely to provide a clear benefit. In the current era no such

subgroup of patients has been clearly identified.[38] This may in part be due to lack of uniformity in the studies that have addressed this question. The data presented in this report suggest that postoperative mortality increases significantly for patients with a preoperative total bilirubin of ≥20 mg/dl, as shown in Table 3. It is not clear from these data if jaundice has a causative link with the mortality rate or if severe jaundice accompanies another process such as the local extension of the tumor. This group of patients with severe jaundice may derive the most benefit from preoperative biliary drainage. However, this will only be confirmed with a large-scale, prospective, clinical trial to evaluate outcome with and without drainage in this subpopulation of patients. The most significant aspect of this finding may relate to the fact that both surgeons and patients need to be aware that this group of patients with severe jaundice will be at increased risk for complications and possibly death following pancreaticoduodenectomy.

We believe it is appropriate to reiterate the fact that there were 33 patients who underwent pancreaticoduodenectomy during the study period who were excluded from the analytic group because they were identified by the NSQIP clinical review staff as suffering from "disseminated cancer" at the time of the operation. The confidentiality restrictions inherent in the use of this data prevent us from accessing the medical records of these individual patients for more intensive review. However, we believe it unlikely that VA surgeons actually proceeded with pancreaticoduodenectomy in patients with known metastatic disease at the time of operation. Because the process of data abstraction generally occurs after the hospitalization, the reviewers have access to the pathology reports, as well as dictated operative notes. Given the information available to the reviewers we believe it likely that the term "disseminated" may be applied in cases in which the pathology report indicates diffuse pancreatic disease, multiple lymph node metastases, or other foci of extrapancreatic disease, rather than obvious metastases seen in the operating room.

Because we could not access more detailed information about this group, and because we wished to make the study group representative of the majority of patients undergoing PD, we elected to exclude these individuals from the study group. Nevertheless, their postoperative mortality is high and deserves further review. Nine of 33 patients (28%) with "disseminated cancer" died in the postoperative interval. If this group of patients is included in the analysis, the overall postoperative mortality rate increases to 10.5% and "disseminated cancer" becomes a significant predictor of postoperative mortality along with albumin, ASA classification, and bilirubin >20 mg/dl.

One of the central aims of the NSQIP is to function as a tool for ongoing process improvement. Although the designation of "disseminated cancer" may be subject to variability in identification and coding, the postoperative mortality of this subset of patients points out potential targets for process improvement. It is clear that surgeons need to be particularly vigilant in preoperative staging, and intraoperative exploration to avoid resecting this group of individuals who have particularly high mortality.

The additional process of care variables examined in this study includes operative time and the practice volume of the VA center performing the operation. Not surprisingly, increasing operative time is associated with increased postoperative mortality. It is not clear if increased operative time reflects the technical experience of the involved operative teams, or if the procedural duration is a marker for technical difficulty and possibly, extent of disease. The analysis of volume is also complex. A number of studies have demonstrated the association between operative volume and favorable pancreaticoduodenectomy outcome.[4,7,39] In the current study, volume is not predictive in the logistic regression modeling. These results need to be interpreted with considerable caution for a variety of reasons. Within the VA system, there are no institutions that perform the same volume of pancreatic cancer surgery that is performed at a number of large cancer centers that specialize in pancreatic cancer surgery. As such, this study lacks true "high volume" centers for benchmarking. The comparison of different centers, all with a relatively low volume of practice, limits the utility of the analysis in this healthcare system. The situation is also confounded by the fact that the attending surgeons who supervise these operations may also have non-VA practices that are not captured in this analysis. As such, a high-volume pancreatic surgeon may be supervising the procedure in a hospital that appears to perform only a low volume of pancreatic surgery. Given these limitations in our study, we do not dispute the findings of a number of previous investigations that have demonstrated the importance of volume–outcome relationship in complicated surgical procedures. We do believe our results serve to point out the importance of heterogeneity in case mix and the importance of risk adjusting for clinical variables such as albumin, bilirubin, and ASA classification when examining PD surgical outcomes, particularly when comparing results between institutions. When comparing risk-adjusted results between institutions, only the preoperative risk factors should be included in the model and not the intraoperative factors, which may be confounded with quality of surgery (e.g., longer

operative times may be partially affected by intraoperative complications).

One of the greatest benefits of the NSQIP data set is that it provides a progressively expanding set of prospectively collected data for use in modeling of postoperative outcomes. The most significant utility of this study is likely to result from the fact that this study has identified several preoperative variables that serve as predictors of risk for mortality following pancreaticoduodenectomy. These predictors will be useful tools for performing risk-adjusted analysis of outcomes within the VA system. These indicators will also facilitate potential comparisons of outcome to non-VA healthcare systems, in a clinically meaningful way. In this manner, we will continue to aim toward process of care improvements and identification of best practices both from within the VA system as well as other institutions.

CONCLUSION

We have identified several clinical characteristics that are independently associated with an increased risk of postoperative mortality for patients undergoing pancreaticoduodenectomy in the VA healthcare system. Low preoperative albumin, a high ASA classification, and serum bilirubin >20 mg/dl all serve as significant predictors of risk of adverse outcome and death following pancreaticoduodenectomy. In this study, we find no indication that preoperative biliary drainage increases the risk of postoperative sepsis or death. In addition, our study underscores the need to perform careful risk adjusted analyses, including these clinical factors when comparing surgical outcomes between different groups of patients or different healthcare systems.

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Transcystic Common Bile Duct Exploration in the Management of Patients With Choledocholithiasis

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Common bile duct stones are found in approximately 16% of patients undergoing laparoscopic cholecystectomy. If the diagnosis of choledocholithiasis is made at the preoperative workup, it is common practice to refer the patient for endoscopic retrograde cholangiography and endoscopic sphincterotomy. However, if the diagnosis is established during intraoperative cholangiography, the surgeon is confronted with a therapeutic dilemma—that is, the choice between laparoscopic common bile duct exploration, conversion to open surgery, or postoperative endoscopic sphincterotomy. We have opted to treat patients with choledocholithiasis in only one session during the laparoscopic cholecystectomy; we use the transcystic common bile duct exploration technique employing the choledochoscope. We report our early experience in terms of success of stone removal, operative time, morbidity and mortality, and length of hospital stay. From 1992 to 2002, we performed 350 laparoscopic cholecystectomies. Selective cholangiography was used in 105 patients (30%); 40 of them were found to have common bile duct stones, for an incidence of 11.4%. Among this group, we performed laparoscopic transcystic common bile duct exploration in all but six patients. Our success rate for stone removal was 94.1% (32 of 34 patients), with only two failures related to multiple stones and impaction at the ampulla, for a conversion rate of 5.8%. The mean operative time was 120 ± 40 minutes. The morbidity rate was 8.8%, and there were no deaths. Length of hospital stay was 24 to 48 hours. Mean recovery time was 7 days, and time to return to work was 15 ± 3 days. We concluded that most of the patients with common bile duct stones found during laparoscopic cholecystectomy could be treated successfully by means of the transcystic technique with choledochoscopy, with no increase in morbidity or mortality and a shortened hospital stay and recovery time, similar to patients who undergo only laparoscopic cholecystectomy. On the basis of our results, we recommend that this method become the primary strategy in the great majority of patients with common bile duct stones found during intraoperative cholangiography. (J GASTROINTEST SURG 2003;7:492–496) © 2003 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Common bile duct stones, laparoscopic transcystic bile duct exploration

Common bile duct stones are found in approximately 16% of patients undergoing cholecystectomy.[1] In the present laparoscopic era, the best treatment for patients with choledocholithiasis is a matter of debate. Until very recently it was generally agreed that if stones were detected in the common bile duct on preoperative imaging studies, or if they were suspected on the basis of abnormal laboratory liver function tests, it seemed reasonable to remove the stones prior to cholecystectomy by endoscopic sphincterotomy (ES).[2] Although endoscopic retrograde cholangiography plus ES allows successful removal of more than 90% of common bile duct stones, consideration must be given to the extra expense per patient and the potential complications associated with this procedure. Even in the hands of experienced surgeons, the rate of complications is reported to be in the range of 4% to 6%. These complications may include acute pancreatitis, bleeding, perforation, and cholangitis.[3] Another potential problem may occur when the diagnosis of choledocholithiasis is made during transoperative cholangiography, which can create a therapeutic dilemma between laparoscopic common bile duct exploration, conversion to open surgery, or even the possibility of postoperative

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ES. Petelin[4] and Phillips et al.[5] described two different techniques for extraction of common bile duct stones by laparoscopy, which challenged the routine use of preoperative ES in all patients with choledocholithiasis. They recommended that common bile duct stones be managed surgically, allowing patients to be treated in only one session, as had previously been the case prior to the laparoscopic era. In order to treat our patients who had common bile duct stones during laparoscopic cholecystectomy, we adopted the technique described by Phillips et al.[6] in which laparoscopic transcystic common bile duct exploration (LTCBDE) was used. We report herein our initial results in terms of successful stone removal, operative time, morbidity and mortality, and length of hospital stay.

METHODS

From May 1992 to August 2002, we performed 350 laparoscopic cholecystectomies for symptomatic gallstone disease. Our patients included 280 women (80%) and 70 men (20%). Median age was 51.5 years (range 17 to 86 years). All patients underwent preoperative abdominal ultrasound imaging, liver function tests, and serum amylase studies, and they were also questioned about any history of pancreatitis or jaundice. On the basis of elevated bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels, a history of pancreatitis or jaundice, or the presence of a dilated common bile duct or common bile duct stones on preoperative ultrasound examination, selective cholangiography was performed. These were all considered risk factors for stones in the common bile duct. This was our standard practice at the beginning of our series, but during the past 2 years we decided to perform routine dynamic cholangiography, which consisted of fluoroscopic imaging with the use of a C arm and an image-intensifier system. When choledocholithiasis was found on the transoperative cholangiogram, we had to choose the best available method for treating it in each case. Within the past 5 years we have adopted LTCBDE as a routine procedure. We use a balloon angioplasty catheter (8 Fr) to dilate the cystic duct through a new incision made with microscissors at 1.5 cm from the common bile duct; then we introduce a bidirectional flexible choledochoscope (12 Fr; Olympus Corp., Puebla, Mexico). Then with warm saline irrigation of the cystic duct and gentle manipulation down the common bile duct, we attempt to find the stone(s). When a stone is identified, a 2.5 or 3 F four-wire basket is inserted into the working channel and under direct endoscopic vision is used to capture and remove the stone passing through the cystic duct. The maneuver is repeated as necessary until all of the stones are cleared and the ampulla can be seen. The cystic duct is then closed using a ligature and clips, and routine retrograde laparoscopic cholecystectomy is performed, with placement of a suction drain near the duct stump in all cases.

RESULTS

We obtained 105 intraoperative cholangiograms from 350 patients (Table 1), thus yielding a 30% risk for harboring stones among patients undergoing selective cholangiography, according to previously mentioned risk factors. In 42 cases (40%) the cholangiograms were positive for stones in the common bile duct (Fig. 1). We found stones in 40 patients, with false positive results in two cases, for a sensitivity of 95% for intraoperative cholangiography (IOCG). The incidence of choledocholithiasis was 11.4% in our group (40 of 350 patients). At the beginning of our series, two patients had to undergo conversion to open common bile duct exploration, and four were referred for postoperative ES, with successful stone removal in all six cases. In the remaining 34 patients, LTCBE was performed. We found common bile duct stones in all of them, which varied in number from one to eight per patient. The mean operative time was 120 ± 40 minutes. Transcystic extraction of stones was completed in 32 patients for a 94.1% success rate. In all cases the choledoscope was used. Two cases could not be resolved by this technique; failure occurred in one patient because of multiple lithiasis (8 stones), which varied in diameter from 0.5 to 1.5 cm. In the other unsuccessful case, an impacted stone was found in the ampulla (Table 2). Conversion to open surgery was necessary in both cases; one was resolved by means of choledochoduodenostomy

Table 1. Laparoscopic transcystic common bile duct exploration (LTCBDE) in the management of patients with choledocholithiasis found during intraoperative cholangiography (IOCG)

IOCG*	Common bile duct stones (%)	LTCBDE (%)	Success (%)	Morbidity (%)	Mortality
105/350	40 (11.4)	34 (85)	32 (94.1)	8.8	0

*Number of patients with IOCG/total number of patients operated.

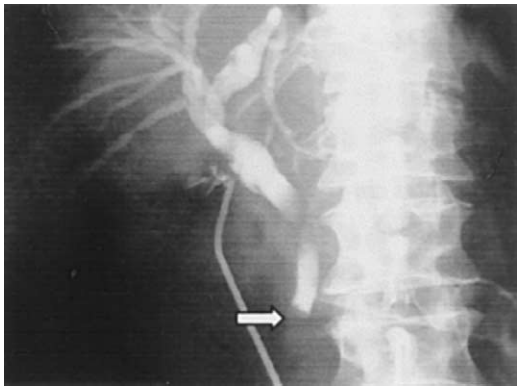

Fig. 1. Intraoperative cholangiogram showing distal common bile duct obstruction secondary to choledocholithiasis.

and the other by transduodenal sphincteroplasty, accounting for a 5.8% rate of conversion to open surgery. Postoperative complications included pulmonary atelectasis in two elderly patients (>75 years of age) and urosepsis in another patient, for an 8.8% morbidity rate. The suction drain was removed within 24 to 48 hours if no bile was observed, which was possible in all patients with 0% of bile leaks. There were no deaths. All patients were discharged from the hospital on the second day after the operation, with minimal discomfort, which was very similar to results in the laparoscopic cholecystectomy group who did not undergo common bile duct exploration. The mean recovery time was 7 days, and the time to return to work and full physical activity was 15 ± 3 days. Follow-up from 1 to 10 years has been possible in 310 patients (88.5%), and we have encountered only two patients with residual choledocholithiasis (0.6%); in both cases IOCG was not performed during the cholecystectomy because neither of these patients had any risk factors suggesting common bile duct stones. In both cases, the residual choledocholithiasis was resolved by endoscopic sphincterotomy. There have been no instances of residual stones in the LTCBDE group.

DISCUSSION

The best treatment of choledocholithiasis must be simple, reliable, readily available, and cost-effective for most patients. Unfortunately, there is no consensus in the medical community as to how best to deal with common bile duct stones.[7] However, according to the reported incidence of choledocholithiasis, which is estimated to be 10% to 16% among patients undergoing cholecystectomy,[1,8] the surgeon must be prepared to manage the choledocholithiasis appropriately, depending on whether the diagnosis is established or suspected in the preoperative scenario or during laparoscopic cholecystectomy. When choledocholithiasis is suspected at the time of the preoperative workup, it is recommended that endoscopic retrograde cholangiopancreatography (ERCP) be performed, and if the choledocholithiasis is confirmed, the patient should then undergo sphincterotomy.[9] The only situations in which preoperative ERCP is hardly ever considered include the following: choledocholithiasis confirmed on preoperative ultrasound examination or CT scan, acute cholangitis, severe gallstone pancreatitis, and comorbid conditions that render cholecystectomy too high-risk.[10–12] Other less frequent findings are altered anatomy in patients with Billroth II or Roux-en-Y gastrojejunostomy, in which ERCP is successful in approximately 70% and 50%, respectively. However, there are important variables to consider: first, ES allows successful removal of more than 90% of common bile duct stones in most series, but depends on the availability of an experienced and skilled endoscopist with a high success rate in achieving biliary cannulation and stone extraction. Another consideration is cost, which varies from one institution to another but could reach approximately $1500 with professional and facilities charges. ERCP is a procedure with potential complications. Acute pancreatitis occurs in approximately 6% of patients who undergo ERCP, and when sphincterotomy for stone extraction is performed, another 4% of patients will have additional complications including bleeding, perforation, and cholangitis.[3] A recent prospective multicenter study of ES in 1494 patients showed a procedure-related morbidity of 7.4% when ES was performed in conjunction with laparoscopic cholecystectomy, for a procedure-related mortality of 0.5% and a total mortality of 2.2%.[13] Another issue is the potential risk of delayed stricture at the sphincter, which is something to be aware of in the long-term follow-up of younger patients.[14] In the early days of laparoscopic cholecystectomy, ERCP plus ES was usually recommended for any patient who had jaundice, recent pancreatitis, or a dilated bile duct on ultrasonography, but this approach led to a high incidence of normal ERCP findings ranging from 40% to 70%.[2] At the present time, these indicators are considered minor risk factors for the presence of common bile duct

Table 2. Risk factors for conversion during laparoscopic transcystic common bile duct exploration

Multiple lithiasis (>8 stones)
Large stones (>1.5 cm)
Impacted stone in the ampulla

stones in most patients. With these more inclusive morbidity figures, the decision to refer patients for preoperative ERCP-ES as the best management of common duct stones must be based on the previous considerations of risk factors suggesting a high likelihood for harboring stones, comorbidity, cost, success rate of stone removal by ES, and availability of skilled endoscopists.

Another situation is when the diagnosis of choledocholithiasis is established intraoperatively. In these cases, consideration should be given to the availability of the most successful method of treatment, which can vary from one institution to another. At the present time, the surgeon is faced with the intraoperative dilemma of whether to perform laparoscopic bile duct exploration, convert to open surgery, or refer the patient for postoperative ERCP. The decision must rest with the surgeon and depends on several factors including patient age, surgical risk, stone characteristics, availability of the extra equipment needed, and the surgeon's level of expertise. The laparoscopic approach offers the patient the advantage of a minimally invasive operation in which the disease can be resolved in one session. A recent randomized trial of laparoscopic exploration vs. endoscopic postoperative ERCP was reported by Rhodes et al.[15] They found that the laparoscopic approach was as effective as ERCP in clearing the common bile duct of stones and led to a significantly shorter hospital stay.

In our series of 350 laparoscopic cholecystectomies, we found 40 patients with stones in the common bile duct, for an incidence of 11.4%. All of them were diagnosed during IOCG, which was performed in a selective manner in 105 patients during the first years of our experience. The sensitivity of the cholangiography was 95%. In our earliest years of laparoscopic cholecystectomy, we decided to perform open bile duct exploration in two patients, and four more were referred for ERCP-ES. All of them account for the 15% of the total number of patients with choledocholithiasis, and were treated without complications but with a longer hospital stay of 5 to 6 days and an increased recovery time of 25 to 30 days. In the remaining 34 patients (85%) with common bile duct stones, LTCBDE was performed. It was successful in 32 patients for a 94.1% rate of stone clearance. We found that multiple common bile duct stones (n = 8), stones larger than 1.5 cm, and stones impacted at the ampulla are risk factors for conversion. Two patients (5.8%) had to be converted because of these risk factors. The overall complication rate was 8.8%, and was related to pulmonary atelectasis in two elderly patients and urosepsis in one. There were no deaths. All patients were discharged from the hospital within the first 48 hours. We did not observe biliary fistulas in our patients, and this was attributed to secure ligation of the cystic stump in all cases. Recovery time was the same as in the laparoscopic cholecystectomy group, and ranged from 7 to 10 days.

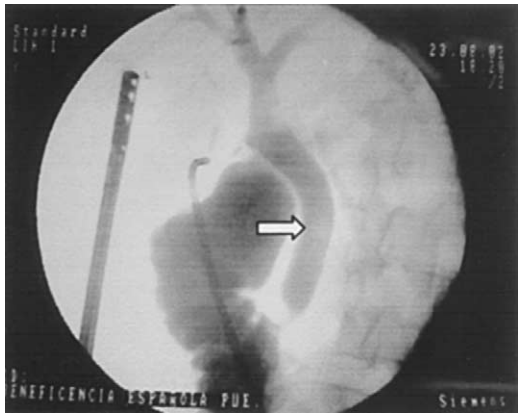

Fig. 2. Intraoperative dynamic cholangiogram with filling defects related to stones.

At the present time, we have every confidence in the technique of LTCBDE; our operative time has decreased as all of the team has become more familiar with the equipment, and the average mean time is now 90 minutes. We are performing routine dynamic IOCG (Fig. 2), which adds less than 10 minutes to the laparoscopic cholecystectomy, in order to avoid residual choledocholithiasis, which was present in 0.6% of the present series. We have also eliminated the false positive results of the previous nondynamic IOCG and the extra waiting time. We have adopted the transcystic laparoscopic approach as the primary strategy for treating common bile duct stones found intraoperatively. Although we still rely on postoperative ERCP-ES for high-risk patients, or patients with multiple stones who are not suitable for the transcystic extraction. We are aware of patients with multiple stones, large stones, or stones in the hepatic ducts and hope to treat them by laparoscopic choledochotomy in the future to avoid conversion.[16] Open common bile duct exploration should be rarely needed at the present time.

Our results are similar to previous reports[4,6,7,8] in terms of success of stone removal, minimal complications, a short hospital stay, and rapid recovery time. The optimal management of choledocholithiasis remains unclear in the present laparoscopic era, but we encourage more surgeons to train in this technique because we are convinced that most patient with stones in the common bile duct can be managed by this gentle technique with good results. Management in one session is the optimal approach in terms of safety, patient satisfaction, and cost-effectiveness. It is now time to return the management of common

bile duct stones to the surgeons as the standard of care in "minimaly invasive treatments."

CONCLUSION

Common bile duct stones were detected in 11.4% of patients during laparoscopic cholecystectomy. Because most of these patients (94.1%) were treated successfully using LTCBDE, with no increases in morbidity or mortality; it seems reasonable to remove the stones during the laparoscopic procedure to avoid the possibility of postoperative ERCP-ES or conversion to open surgery. The complications, length of hospital stay, and recovery time were very similar to outcomes in patients who underwent only the laparoscopic cholecystectomy. We found that multiple or impacted distal stones are risk factors for conversion to an open procedure. The benefits attained by minimal access surgery confirm that LTCBDE should become the primary strategy in the great majority of patients with common bile duct stones found during IOCG.

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Biliary Obstruction Reduces Hepatic Killing and Phagocytic Clearance of Circulating Microorganisms in Rats

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Septic complications are common in patients with biliary obstruction. This is thought to be related, in part, to dysfunction of the hepatic reticuloendothelial system (RES). It has been reported that nearly 80% of circulating microorganisms are phagocytosed and killed within the liver and that clearance of circulating pathogens is significantly impaired in patients with jaundice. However, the effect of biliary obstruction specifically on phagocytic killing within the liver is less well described. Therefore this study was designed to quantify the effect of biliary obstruction, simultaneously and discriminately, on two important components of hepatic RES function (phagocytosis and phagocytic killing). Rats were divided into three experimental groups: control, sham, and jaundiced (common bile duct ligation). At 7, 10, 14, and 21days after operation, *E. coli* labeled with both ^{125}I and ^{51}Cr were injected intravenously. Using the previously validated double-labeled in vivo *E. coli* technique, hepatic phagocytic clearance (HPC), hepatic killing efficiency (HKE), and net hepatic killing (NHK) were measured. Common bile duct ligation resulted in a significant decrease in the HPC of *E. coli* 10, 14, and 21days postoperatively. Similarly, HKE was significantly decreased in jaundiced animals by postoperative day 10, but returned to baseline values by day14. The net effect of these changes in HPC and HKE values were reflected in a significant reduction in NHK in jaundiced animals. Results of the present study suggest that obstructive jaundice impairs both phagocytosis and phagocytic killing within the liver. These findings may help to explain the susceptibility of patients with biliary tract obstruction to the morbidity and mortality of septic complications. (J GASTROINTEST SURG 2003;7:497–506) © 2003 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Obstructive jaundice, reticuloendothelial system, phagocytosis, phagocytic killing

Despite improvements in operative technique and the development of potent broad-spectrum antibiotics, patients with jaundice due to either benign or malignant extrahepatic biliary obstruction still experience a high incidence of postoperative complications and death. Clinical and experimental studies have demonstrated a relationship between obstructive jaundice and the development of sepsis.[1–7] High serum levels of toxic substances including bilirubin, bile salts, and endotoxin facilitate the development of sepsis,[8] which is the major cause of death in obstructive jaundice. Recent experimental studies have shown that bacterial translocation (into the systemic circulation) occurs in obstructive jaundice.[6–9] However, clinical studies have shown that preoperative biliary drainage has no benefit,[10–12] and even increases the risk of developing positive (bacteria) intraoperative bile cultures and increased postoperative infectious morbidity and mortality after pancreaticoduodenectomy.[13] Furthermore, postoperative bacteremia is a common complication of hepatectomy for hepatobiliary malignancy, especially in older patients with obstructive jaundice who are undergoing major hepatectomy.[14] These findings suggest that an impaired host defense system, which allows bacteria and endotoxin into the systemic circulation,[6,7,15,16] may

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contribute to the development of sepsis in patients with obstructive jaundice. Although the pathophysiologic mechanisms responsible for the well-documented relationship between obstructive jaundice and sepsis are not fully defined, two main factors are believed to predispose patients to systemic bacteriotoxemia: increased endotoxin absorption and bacterial translocation from the gut into the portal vein,[15,16] and impaired hepatic reticuloendothelial system (RES) function allowing "spillover" of bacteria or endotoxin into the systemic circulation.[5,7]

RES function is an important component of host defense and is responsible for removing circulating particulate matter, such as bacteria, immune complexes, foreign proteins, senescent erythrocytes, dead or damaged cells, tumor cells, and tissue debris from the circulation.[17,18] The RES is composed primarily of fixed macrophages in the liver (Kupffer cells), spleen, and lung. These cells phagocytose and degrade (kill) circulating pathogens that have been trapped. The liver is quantitatively the largest reticuloendothelial organ, and under normal conditions approximately 80% of the dose of an intravenously injected particulate substance is cleared by Kupffer cells.[16,17] When biliary obstruction occurs, normal function of the Kupffer cells is impaired.[6,9,15] Depressed Kupffer cell clearance capacity permits spillover of endotoxin into the systemic circulation.[6,7,15,16,19] Previous analyses of RES function in models of obstructive jaundice have been performed using dead/live bacteria or nonbacterial particulate test substances.[5,7,9,15,20–23] A recent in vitro study has shown decreased killing activity of Kupffer cells isolated from jaundiced animals.[9] Although impairment of the hepatic phagocytic capacity of the RES function in animals with obstructive jaundice has been well documented,[19–24] we are unaware of studies that have specifically measured hepatic phagocytic *killing* in animals with obstructive jaundice in vivo. Obstructive jaundice may impair not only hepatic phagocytic clearance but also the ability of the phagocyte to kill injected pathogens. We have described and validated an in vivo assay of hepatic RES function in the rat, which quantitatively discriminates its two essential components: phagocytic uptake and phagocytic killing.[25] The present study was designed to quantify the effect of biliary obstruction, simultaneously and discriminately, on these two distinct components of hepatic RES function.

MATERIAL AND METHODS

Experimental Animals

All studies were conducted in accordance with standard criteria for the humane care and treatment of animals, following protocols previously approved by the Animal Care and Use Committee of Johns Hopkins University School of Medicine. Male Sprague-Dawley rats (Harlan, Indianapolis, IN), weighing 250 to 300 g, were maintained on a diet of standard laboratory chow (Labdiet, PMI Feeds, St. Louis, MO) under clean conditions in individual cages in a light-cycled room.

Obstructive Jaundice Model and Operative Procedure

Rats were anesthetized with ketamine (50 mg/kg) and xylazine (10 mg/kg), and prepared with betadine and alcohol before an upper midline abdominal incision was made. In the rats undergoing common bile duct ligation (CBDL), the common bile duct was identified and double ligated with 5-0 silk and then divided between ligatures,[14,15,17,19] whereas in the sham-operated control animals the bile duct was dissected free from surrounding soft tissue without ligation and transection. The abdomen was then closed, and the animals were allowed to recover. All operations were performed under clean but not sterile conditions. Throughout the experiment all rats were kept in a temperature-controlled environment and given free access to water and food.

Quantitative Assay of Hepatic Phagocytic Clearance and Hepatic Phagocytic Killing

We have previously found that hepatic RES phagocytosis and killing can be discriminated quantitatively.[25] The methodologic details and quantitative validation of the use of double-labeled *Escherichia coli* to simultaneously measure hepatic phagocytic clearance and phagocytic killing have been described previously.[25] In brief, ampicillin-resistant *E. coli* (XLI-BLUE strain; American Type Culture Collection, Rockville, MD) grown on Mueller-Hinton agar were transferred to trypticase soy broth and incubated for 2 hours at 37° C (Becton Dickinson, Cockeysville, MD), and subsequently labeled with 0.1 mCi of 5-[^{125}I]-iodo-2′-deoxyuridine (^{125}IUdR, IM-355V, Amersham, Arlington Heights, IL). Cultures were incubated for 18 hours at 37° C, washed three times with normal saline solution, pelleted, and then incubated with 0.05 mCi of $Na_2{}^{51}CrO_4$ (^{51}Cr, CJS-11; Amersham). The washed suspension, stored for up to 4 hours at 4° C, contained less than 2% free ^{51}Cr or ^{125}IUdR. The bacteria concentrations in the final suspension were calculated by measurement of optical density in a spectrophotometer at 600 nm after calibration with actual bacteria colony counts from serial 10-fold dilution of a stock suspension of bacteria. We have confirmed that the ^{51}Cr and ^{125}I remain

bound to the bacteria (cytoplasm and DNA, respectively) for at least 90 minutes in vivo and in vitro.[25]

Under ketamine and xylazine anesthesia, 1.0 ml of the double-labeled *E. coli* (10^8) suspension was injected into the dorsal vein of the penis of the nonoperated, sham-operated, or CBDL rats 7, 10, 14, or 21 days after operation. Ninety minutes after *E. coli* injection, the rats were anesthetized again and killed. The liver, lungs, and spleen were excised, washed free of blood by dipping into a beaker containing physiologic saline solution, blotted on gauze, and weighed. Whole-organ ^{51}Cr and ^{125}I levels were determined by gamma scintillation counting (Gamma 4000; Beckman Instruments, Palo Alto, CA) using windows of 50 to 175 keV and 0 to 20 keV, respectively, with appropriate correction for crossover activities. Total hepatic ^{51}Cr and ^{125}I content were calculated, and the data were expressed as a percentage of the inoculum. Hepatic ^{51}Cr uptake is rapid (maximum uptake in <10 minutes), remains stable for 24 hours after systemic intravenous injection, and accurately reflects hepatic bacterial phagocytosis.[25] The hepatic phagocytic clearance (HPC = hepatic ^{51}Cr) quantifies the percentage of ^{51}Cr injected that is trapped in the liver 90 minutes after *E. coli* injection:

$$\text{Hepatic}^{51}\text{Cr}(\%) = \text{HPC} = [\text{hepatic}^{51}\text{Cr(cpm)}/\text{injected}^{51}\text{Cr(cpm)}] \times 100$$

The activity of ^{125}I was also measured in the same manner:

$$\text{Hepatic}^{125}\text{I}(\%) = [\text{hepatic}^{125}\text{I(cpm)}/\text{injected}\ ^{125}\text{I(cpm)}] \times 100$$

Although hepatic ^{125}I and ^{51}Cr are similar at 10 minutes, hepatic ^{125}I declines over time in parallel with bacterial killing. The hepatic ^{125}I content reflects the proportion of residual live bacteria in the liver.[25] To compare the degree of intrinsic hepatic bacterial killing under conditions of *variable* phagocytic uptake, the hepatic killing efficiency (HKE) was calculated:

$$\text{HKE}(\%) = [(\text{hepatic}^{51}\text{Cr} - \text{hepatic}^{125}\text{I})/\text{hepatic}\ ^{51}\text{Cr}] \times 100$$

Net hepatic killing (NHK) reflects the percentage of the total number of injected organisms that have been degraded in 90 minute:

$$\text{NHK}(\%) = \text{hepatic}\ ^{51}\text{Cr} - \text{hepatic}\ ^{125}\text{I} = \text{HPC} \times \text{HKE}$$

This radioisotope assay has been validated previously under a variety of conditions known to upregulate or downregulate hepatic RES phagocytosis and/or phagocytic killing.[25]

Liver Function Tests

Blood samples were taken from the rat femoral vein prior to double-labeled *E. coli* injection. The blood samples were centrifuged at 3000 rpm for 10 minutes, and the serum was collected from each blood sample and stored at −20° C. Frozen serum samples were shielded from direct light, thawed to room temperature, and assayed for total bilirubin (T-Bil), albumin (Alb), aspartate aminotransferase (AST), and alkaline phosphatase (ALP).

Experimental Protocol

The rats were divided into three experimental groups as follows: (1): normal rats, with no laparotomy, were assayed at day 0 to provide baseline values (control group, n = 10); (2) sham-operated rats were assayed at 7, 10, 14, or 21days after operation (sham groups, n = 10 for each group); (3) CBDL rats were assayed at 7, 10, 14, or 21 days after operation (jaundiced groups, n = 10 for each group).

Statistical Analysis

The data were expressed as means ± standard error of the mean (SEM). Statistical calculations were made with two-factor factorial analysis of variance (ANOVA) or Student's *t* test. Values of $P \leq 0.05$ were considered to be significant.

RESULTS

Obstructive jaundice was confirmed in rats by their clinical appearance, the yellow discoloration of their fur coats, and the production of dark urine. During final laparotomies, CBDL led to cystic dilatation of the proximal common bile duct, and the liver was found to be enlarged macroscopically. The hepatic parenchyma was heterogeneous with yellow or green pigmentations, and the hepatic edges were blunted. The color of the intra-abdominal organs reflected the presence of bile pigments, and ascites was present. No recanalization of the bile duct was found at the time the animals were killed. Postoperative mortality rates at 7, 10, 14, and 21 days after CBDL were 0%, 11%, 28%, and 36%, respectively, without injection of bacteria. The cause of death in each case was evaluated to be infection (sepsis) or liver failure.

The body weight of each rat in the jaundiced group was significantly decreased compared to values in the corresponding sham group (7, 10, 14, or 21days after operation: $P < 0.001$, < 0.001, $< 0.001 = 0.008$, respectively; data not shown). Postoperative weight recovery was also delayed in jaundiced rats compared to sham-operated control rats. Liver-to-body weight ratios in each jaundiced rat were significantly higher than values in the corresponding sham group ($P < 0.001$, respectively; data not shown). Lung-to-body weight ratios in all jaundiced rats were also significantly increased when compared with values in corresponding sham and control groups ($P < 0.001$, respectively).

Liver Function Tests

T-Bil, AST, and ALP levels were significantly elevated in the jaundiced group compared with the sham group (Fig. 1, *A–C*). T-Bil, AST, and ALP levels in jaundiced rats rose rapidly, reaching a peak at postoperative day 7. Alb levels in the jaundiced group were significantly decreased compared to values in the sham group (Fig. 1, *D*).

Organ Distribution of Radiolabled *E. coli*

Table 1 summarizes organ distribution of intravenously injected radiolabeled *E. coli*. Normal distribution of *E. coli* in the liver, lungs, and spleen was

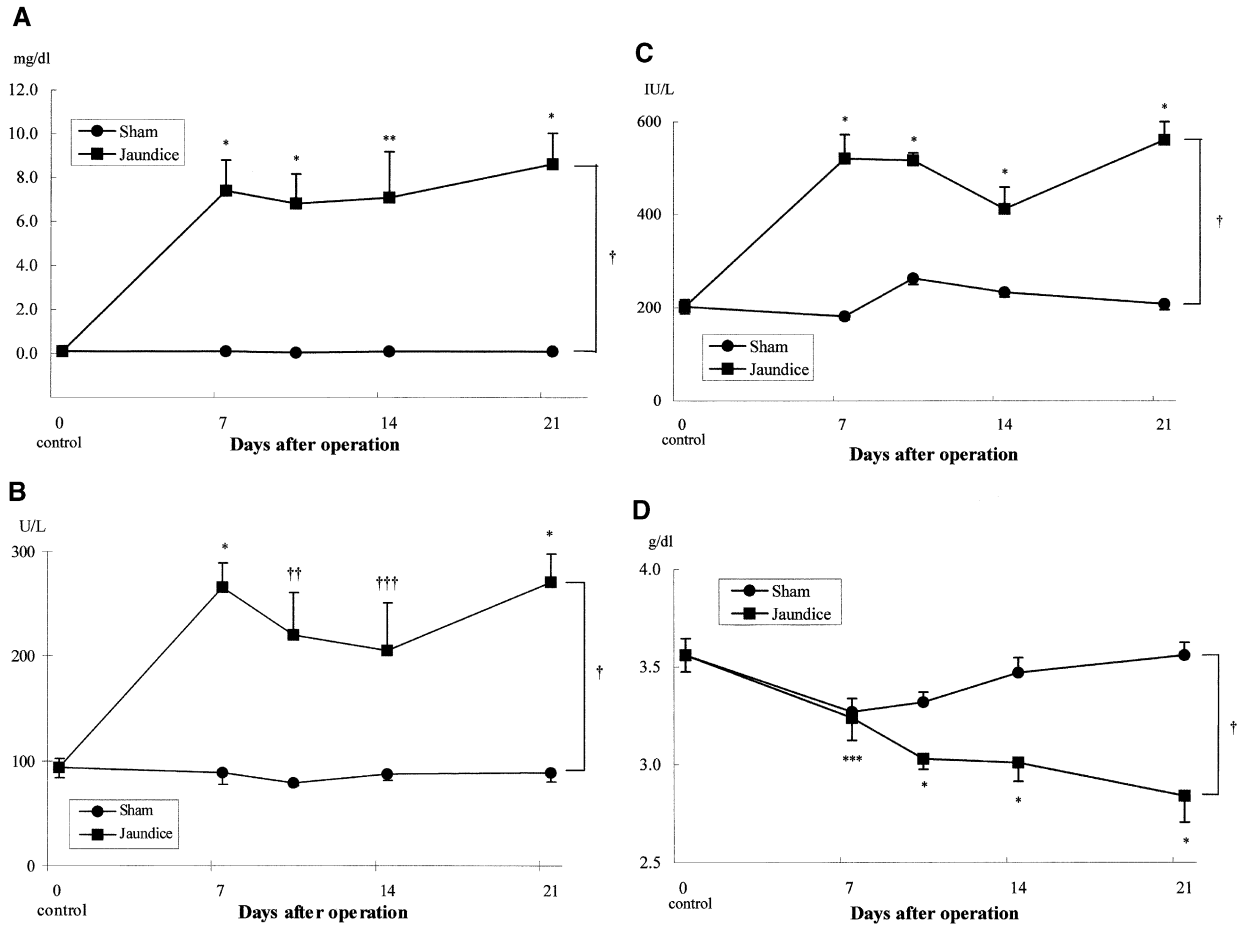

Fig. 1. Liver function test. Total bilirubin (**A**), aspartate aminotransferase (**B**), alkaline phosphatase (**C**), and albumin (**D**) levels were measured before intravenous bacterial challenge. Total bilirubin, aspartate aminotransferase, and alkaline phosphatase levels were elevated in the jaundiced group compared with the sham group. Albumin in the jaundiced group was decreased when compared with the sham group. Data were expressed as means ± SEM. $^{\dagger}P < 0.001$ jaundiced vs. sham group (two-factor factorial ANOVA). $^{*}P < 0.001$ vs. sham and control groups. $^{**}P < 0.003$ vs. sham and control groups. $^{***}P = 0.817$ vs. sham (NS) and P = 0.030 vs. control group. $^{\dagger\dagger}P = 0.005$ vs. sham and control groups. $^{\dagger\dagger\dagger}P < 0.020$ vs. sham and control groups (Student's *t* test).

similar to what we have previously reported[25]; more than 80% of the organisms were trapped within the liver. In jaundiced animals the liver distribution of *E. coli* was decreased, whereas the percentage of bacteria that localized in the lung was increased. Splenic bacterial trapping was unchanged.

Hepatic Phagocytic Clearance in Jaundiced Rats: Measurement of Reticuloendothelial System Function

Sham-operated animals did not show evidence of altered HPC compared with control animals. CBDL resulted in significantly decreased HPC of *E. coli*, as reflected by decreased hepatic ^{51}Cr content at 90 minutes by day 10 (Fig. 2). This depression of HPC persisted through the 21 days of observation, reaching a nadir 21 days after CBDL.

Hepatic Killing Efficiency in Jaundiced Rats

In order to compare the bacterial killing capacity of individual rat livers showing variable levels of phagocytosis, the HKE was calculated as described earlier. Although the HKE was unchanged by sham operation, CBDL caused significant suppression of HKE in the jaundiced group (Fig. 3). By postoperative day 7 the HKE in the jaundiced rats was significantly depressed. HKE suppression reached a nadir on day 10 (see Fig. 3) but returned to sham operated levels by day 21 (see Fig. 3).

Table 1. Organ distribution of radiolabeled *E. coli*

Groups	Liver	Lungs	Spleen
Controls	83.2 ± 1.4	5.5 ± 0.7	7.1 ± 0.7
7 days jaundice	80.1 ± 1.8	8.3 ± 1.1*	5.1 ± 0.9
7 days sham	82.8 ± 1.4	4.2 ± 0.4	7.1 ± 0.3
10 days jaundice	79.1 ± 2.3*	10.8 ± 1.6*	6.0 ± 1.0
10 days sham	86.6 ± 0.7	4.0 ± 0.3	6.8 ± 0.5
14 days jaundice	71.2 ± 4.9*	15.4 ± 4.6*	6.9 ± 0.8
14 days sham	81.4 ± 1.7	3.8 ± 0.3	6.9 ± 0.5
21days jaundice	69.3 ± 3.6*	12.6 ± 2.5*	9.2 ± 1.0
21days sham	84.5 ± 0.6	3.9 ± 0.4	8.5 ± 0.4

The distribution of radiolabeled *E. coli* was determined by ^{51}Cr uptake in various organs (% of injected dose) 90 minutes after intravenous bacterial challenge. Normal distribution of *E. coli* in the liver, lungs, and spleen were 83.2% ± 1.4%, 5.5 ± 0.7%, 7.1 ± 0.7%, respectively (mean ± SEM). In jaundiced animals the distribution of *E. coli* in the liver, lungs, and spleen was decreased, increased, and unchanged, respectively.
*$P < 0.05$ vs. sham-operated and control (Student's t test).

Net Hepatic Killing in Jaundiced Rats

The net effect of these changes in HPC and HKE were reflected in the net hepatic killing (NHK). Jaundiced animals demonstrated significantly lower NHK than sham-operated animals, indicating that more bacteria remained viable within the liver (Fig. 4). There were no differences between the control and sham-operated rats. The NHK in the jaundiced group decreased sharply by day 10 after CBDL, and then continued to decline gradually through the remainder of the 21-day observation period.

Localization of Radiolabeled *E. coli* in the Lungs and Spleen

The pulmonary ^{51}Cr uptake was significantly increased in jaundiced animals compared with sham operated animals (Fig. 5). Splenic ^{51}Cr uptake in the jaundiced rats did not differ from that of the sham group (data not shown).

DISCUSSION

Untreated jaundice can result in major complications such as cholangitis, coagulation defects, and progressive hepatic parenchymal damage which, if unchecked, can evolve into biliary fibrosis and cirrhosis.[26–28] When mechanical biliary obstruction is diagnosed, surgical or radiologic therapeutic procedures are frequently performed. Despite improvements in preoperative evaluation and postoperative care, surgical relief of obstructive jaundice still carries a high rate of mortality and morbidity. Many of the postoperative complications are related to sepsis, renal failure, and pulmonary dysfunction. Wound healing is delayed, and herniation and evisceration occur frequently in patients with obstructive jaundice. Experimental and clinical studies have suggested several etiologic factors including immunosuppression, toxicity of bilirubin and bile acids, hypotension, impaired nutritional status, and hepatic parenchymal dysfunction.

The importance of the RES in the prevention of infection and the clearance of toxins and waste products is well established. The RES is a critical component of the efferent immune response. The liver is quantitatively the most important organ of RES function, as the liver accounts for approximately 80% of RES activity. RES *clearance* function is depressed in conditions such as obstructive jaundice,[10,14–25] trauma,[29] surgery, and sepsis.[30] Several studies have reported that the increased incidence of sepsis in obstructive jaundice might be due to impaired RES function.[13–15] In previous experiments,

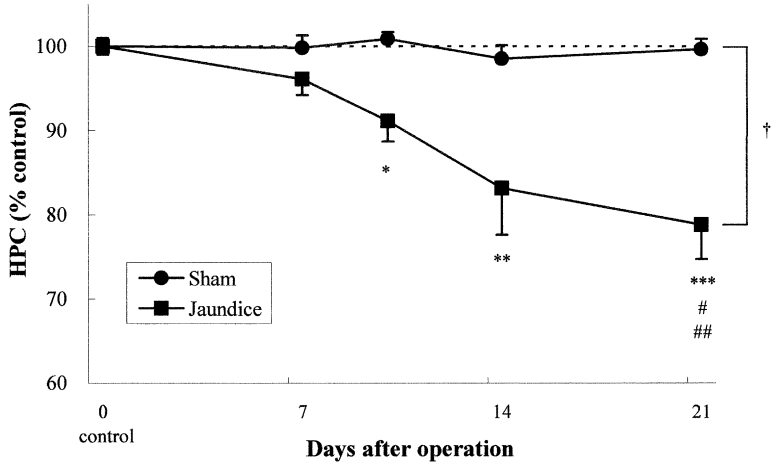

Fig. 2. Hepatic phagocytic clearance. At 10, 14, and 21 days, HPC in the jaundiced group was significantly decreased compared with corresponding sham rats. HPC in jaundiced rats decreased gradually and reached a nadir 21days after CBDL. Data were expressed as percentage of control values (means ± SEM). $^{\dagger}P < 0.001$ overall jaundiced group vs. sham group (two-factor factorial ANOVA). $^{*}P < 0.001$ vs. sham and $P = 0.003$ vs. control group. $^{**}P = 0.011$ vs. sham and $P = 0.005$ vs. control group. $^{***}P < 0.001$ vs. sham and control groups. $P = 0.001$ vs. 7 days jaundice. $^{\#\#}P = 0.014$ vs. 10 days jaundice (Student's *t* test).

various particles such as colloidal carbon, macroaggregated serum albumin, endotoxin, and live/dead bacteria have been selected as targets to evaluate RES *clearance* function in the setting of obstructive jaundice.[10,14–21,23,24,31] Although the impairment of this hepatic phagocytic capacity of the RES in animals with obstructive jaundice is well described, little attention has been given to assessment of the second key component of RES function—that is, phagocytic killing.[16,32] We have previously described an in vivo rat model capable of quantitatively discriminating hepatic RES phagocytosis and killing of bacterial targets.[25] This double-labeled *E. coli* clearance assay provides an efficient, reliable, and reproducible method for discriminately measuring these two distinct components of hepatic RES function.[25] We applied this in vivo RES assay to simultaneously yet selectively measure the capacity of the liver to phagocytose and kill circulating pathogenic bacteria in a model of surgically induced obstructive jaundice.

The present study has confirmed the observation of Ding et al.[15] that HPC of intravenously injected double-radiolabeled *E. coli* is depressed in experimental obstructive jaundice in vivo. The findings were also consistent with in vitro studies of RES function, which reported decreased phagocytic clearance of Kupffer cells in rats with obstructive jaundice 1, 2, and 3 weeks after CBDL.[16,24,33] We found that HPC gradually decreased during the 21-day observation period after CBDL. These findings suggest that the impairment of phagocytic clearance in jaundiced animals is progressive. Previous studies have shown that hepatic arterial and portal venous blood flow is reduced in animals with obstructive jaundice.[16,34] Although this could account, in part, for the decrease in HPC, the dose of intravenously injected *E. coli* was chosen to give values for phagocytosis and killing that were independent of hepatic blood flow. As expected, CBDL resulted in markedly increased serum bilirubin, AST, and ALP levels, weight loss, and decreased hepatic protein synthesis (serum albumin concentrations). Kupffer cell function is influenced by both increased intraductal pressure and altered serum biochemistry, including direct bilirubin toxicity.

Hepatic phagocytic *clearance* alone does not effectively eliminate pathogens from the host. The necessary second step is degradation (killing) of the phagocytosed organisms. Several in vitro studies have reported impairment of bacteria killing activity in biliary obstruction through the observation of superoxide production by Kupffer cells isolated from rats with obstructive jaundice.[16,32] Our present study indicates that the ability of the liver to kill phagocytosed bacteria (HKE) in vivo is markedly decreased in rats with obstructive jaundice. Importantly, this suppressed killing of phagocytosed bacteria was noted in the early postoperative period (postoperative day 7), well in advance of significant alternations to phagocytic clearance. HKE subsequently increased and approached normal levels by 14 to 21 days after CBDL. These results suggest that in the early post-CBDL period, obstructive jaundice selectively impairs the killing capacity of the liver without concomitant depression of HPC.

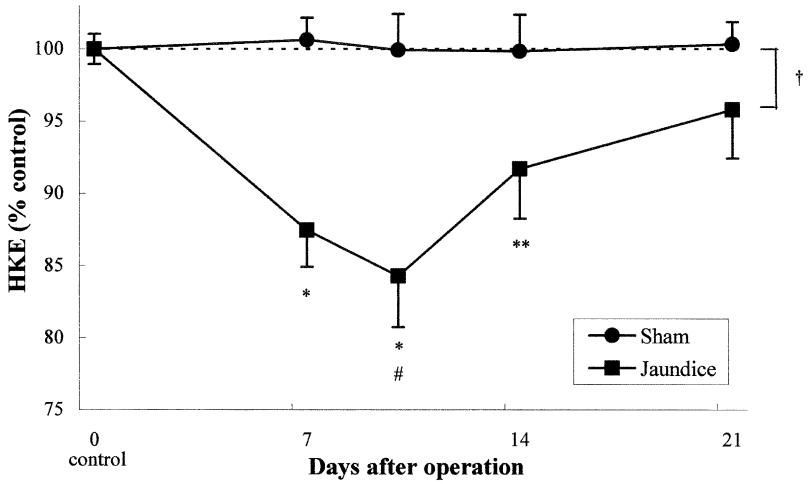

Fig. 3. Hepatic killing efficiency. CBDL caused significant suppression of HKE in the jaundiced group. HKE in jaundiced rats gradually decreased by postoperative day 10, and then returned to baseline values by day 14 after CBDL. Data were expressed as percentage of control values (means ± SEM). $^{\dagger}P < 0.001$ jaundiced vs. sham group (two-factor factorial ANOVA). $^{*}P < 0.001$ vs. sham and control groups. $^{**}P = 0.061$ vs. sham (not significant) and $P = 0.026$ vs. control group. $^{\#}P = 0.023$ vs. 21 days jaundice (Student's *t* test).

NHK reflects the percentage of the total injected bacteria that have been killed in the liver and the net effect of the combination of the separate components of HPC and HKE. NHK may be the best indicator of the resistance to challenge with pathogenic organisms. NHK in obstructive jaundice was markedly suppressed by day 10 after CBDL and remained depressed through the 21-day observation period.

In this study the pulmonary localization of radiolabeled *E. coli* was significantly increased in jaundiced rats. Normally, approximately 70% to 80% of injected bacteria are removed by the liver,[11,12] and the remainder are cleared by the spleen and lungs. After CBDL, organisms are partitioned among the solid organs of the RES in somewhat different proportions. Several studies have determined that decreased levels of radiolabeled targets localize in the liver, with a compensatory increase in lung and other solid organ uptake.[22,35] Viable organisms could be recovered from these extrahepatic sites, suggesting that HPC

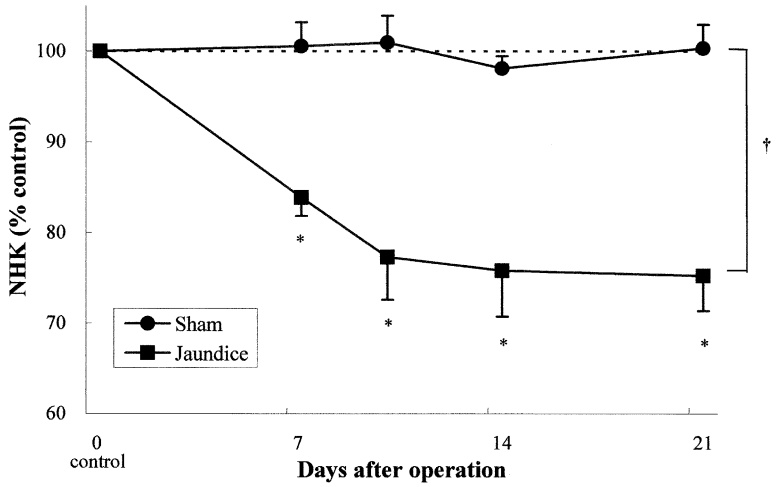

Fig. 4. Net hepatic killing. Jaundiced animals demonstrated significantly lower NHK values compared to sham-operated animals. NHK in obstructive jaundice decreased sharply by day 10 after CBDL and remained suppressed through day 21 after CBDL. Data were expressed as percentage of control values (means ± SEM). $^{\dagger}P < 0.001$ jaundiced group vs. sham group (two-factor factorial ANOVA). $^{*}P < 0.001$ vs. sham and control groups (Student's *t* test).

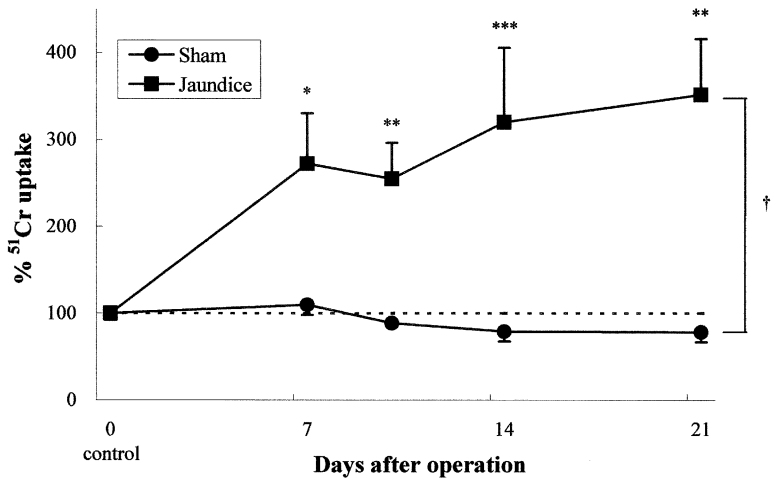

Fig. 5. Localization of radiolabeled *E. coli* in the lung. Localization of radiolabeled *E. coli* in the lung was determined by the pulmonary ^{51}Cr uptake. Trapped *E. coli* in the lung increased in jaundiced animals compared with sham-operated animals. Data were expressed as percentage of control values (means ± SEM). $^{\dagger}P < 0.001$ jaundiced vs. sham group (two-factor factorial ANOVA). $^{*}P = 0.009$ vs. sham and P = 0.006 vs. control group. $^{**}P < 0.001$ vs. sham and control groups. $^{***}P = 0.009$ vs. sham and $P = 0.015$ vs. control group (Student's *t* test).

is relatively ineffective in rats undergoing CBDL.[35–38] This raises the question of whether the pulmonary dysfunction and pneumonia commonly observed in the setting of obstructive jaundice may be explained, in part, by the depressed HPC and HKE observed in our model.

In our model we chose to inject the bacteria through a peripheral vein as opposed to a portal vein tributary, recognizing that bacteria such as *E. coli* often pass first through the liver before entering the systemic circulation. Increased bacterial translocation from the gastrointestinal tract across the gut mucosal barrier into the portal circulation, and impaired hepatic RES, allows "spillover" of bacteria and/or endotoxin into the systemic circulation in obstructive jaundice.[6,7,14,15] This systemic *bacteriotoxemia* (sepsis) is a major cause of morbidity and mortality in animal models of obstructive jaundice. Therefore we chose to inject *E. coli* into a peripheral vein, specifically to reproduce conditions in which microorganisms escape into the circulation in jaundiced rats. Our previous studies have shown that 80% of peripheral veins injected with *E. coli* are phagocytosed by the hepatic RES,[25] which indicates that the majority of circulating bacteria are cleared by the liver rather than other organs, even under conditions in which the inoculum is not first passed through the liver (as occurs with portal vein inoculation).

Obstructive jaundice results in not only high serum levels of toxic substances such as bilirubin and endotoxin but also in a number of associated complications including cardiovascular dysfunction, peripheral vasoconstriction, renal insufficiency, gastrointestinal hemorrhage, immunosuppression, hepatic dysfunction, coagulopathy, and sepsis. Rats with surgically induced jaundice are indeed sick animals that exhibit multiorgan dysfunction. The jaundiced animals lost significant amounts of weight and developed depressed serum albumin levels. In effect, they were profoundly malnourished, especially in the 21-day group. This study was not designed to quantitatively discriminate the effects of jaundice and malnutrition on hepatic phagocytic clearance and killing. Although this would be an interesting study, we are not aware of models of surgical jaundice that avoid the comorbidity of malnutrition, nor are there reproducible means of replicating similar levels of malnutrition (which is incompletely understood in jaundiced animals) in nonjaundiced rats. Of note, it has been reported that vitamin A deficiency can cause impaired phagocyte function.[39] However, a clinical study reported that undernutrition *increases* phagocytic activity of granulocytes in children.[40] The potential effects of jaundice-related malnutrition need to be further elucidated.

CONCLUSION

Results of the present study suggest that obstructive jaundice impairs both phagocytosis and phagocytic killing within the liver. These findings may help

explain, in part, the susceptibility of patients with biliary tract obstruction to the morbidity and mortality of septic complications. The discriminate quantitation of the two primary physiologic components of RES function—phagocytic clearance and bacterial killing—should provide a better understanding of the effects of biliary obstruction on hepatic RES function.

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An Intravital Model to Monitor Steps of Metastatic Tumor Cell Adhesion Within the Hepatic Microcirculation

Jörg Haier, M.D., Timo Korb, Birgit Hotz, Hans-Ullrich Spiegel, M.D., Ph.D., Norbert Senninger, M.D., Ph.D.

Organ-specific tumor cell adhesion within the microcirculation of host organs is an important step in the metastatic cascade. Circulating tumor cells have to adhere within the microcirculatory vessels, quickly stabilize their adhesion and probably leave the circulation to avoid toxic effects of hydrodynamic shear forces of circulating blood. Using intravital fluorescence microscopy we established a new model for the intravital observation of colon carcinoma cell adhesion within the hepatic microcirculation. HT-29 (human) and CC531 (rat) colon carcinoma cells were fluorescence labeled using CalceinAM. Single cell suspensions were injected intraarterially in Sprague-Dawley rats. Using intravital fluorescence microscopy adhesive interactions of circulating tumor cells within the hepatic microcirculation were observed at the liver surface. These interactions were analyzed regarding their time course and the localization within the vascular tree. Autofluorescence of liver parenchyma was sufficient for distinction of hepatic sinusoids. Intravital microscopy enabled the differentiation of early events in adhesion formation within hepatic sinosoids, adhesion stabilization, and extravasation of the tumor cells into the liver parenchyma. Tumor cell adhesion occurred almost exclusively within sinusoidal capillaries; however, the diameter of these vessels was usually larger than that of the tumor cells leaving remaining perfused lumen of the capillaries. Colon carcinoma cells rapidly migrated into the liver parenchyma after successful adhesion within the sinusoids. In contrast to common endpoint assays of the metastatic cascade, this in vivo model allows investigations of metastatic colon carcinoma cell adhesion within the liver microcirculation as specific steps during the formation of hematogenous metastasis and their underlying mechanisms. (J GASTROINTEST SURG 2003;7:507–515). © 2003 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Cell adhesion, colorectal carcinoma, microcirculation, intravital microscopy

Tumor cell adhesion within the microcirculation of host organs is a fundamental event in the formation of distant tumor metastases. Once metastasizing cancers have penetrated into the circulation or body cavities and malignant cells have been released from the primary tumor, they can be transported to near and distant organs and form distant metastases. Circulating tumor cells have to adhere within the microcirculatory vessels, quickly stabilize their adhesion, and probably leave the circulation to avoid toxic effects of hydrodynamic shear forces of circulating blood. The majority of circulating cancer cells delivered to various target organs are trapped, and then rapidly and lethally damaged in the microvasculature, resulting in cell death and "metastatic inefficiency."[1] To survive, most circulating tumor cells probably must adhere to the vessel walls of distant host organs, and eventually penetrate the vascular wall to avoid blood shear forces and host defense mechanisms. If they remain in the circulation, the environmental conditions in the circulation are usually toxic to these cells. For example, shear forces in the physiological range can induce lethal damage in a high percentage of circulating tumor cells, and up to 70% of B16 melanoma cells can be killed within one hour if these cells were exposed to shear stress.[2] However, these complex interactions between circulating tumor cells and host organs usually remain obscure due to lack of observation in most types of metastatic end point studies.

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However, in vivo the ability of tumor cells to survive the mechanical stress appears to be a very important factor in determining the efficiency of formation of distant metastases. The likely mechanism(s) of loss of cell viability under flow seems to be the mechanical damage of cell membranes by shear forces.[3] The sensitivity of tumor cells to mechanical influences may also depend on cell cycle-related morphology.[4] Furthermore, the blood circulation creates shear forces on the adherent tumor cells, and these forces act against the newly formed adhesions and can break adhesive bonds. Therefore, for most tumor entities, cells have to quickly stabilize adhesions to the vessel wall and extravasate from host organ microcirculation.[5]

Fluid flow under physiological conditions of blood circulation can cause a variety of changes within the circulating cells and the endothelium, such as morphological alterations, activation of signaling cascades, modification of gene expression, and other functional changes.[5–9] For example, it has also been shown that different amounts of shear stress comparable to the situation in the microcirculation can induce modifications in surface expression of adhesion molecules in endothelial cells (EC) that may directly influence their adhesive properties.[10–13] In addition to the modulation of cell adhesion molecules, mechanical forces can influence various other cellular functions, and circulating tumor cells can produce EC injury, resulting in exposure of the underlying basement membrane.[14] Furthermore, shear stress caused by different flow rates within the blood circulation can modulate activation of the coagulation cascade and platelet aggregation. For example, the generation of plasminogen activator by tumor necrosis factor-activated EC was stimulated under high-flow conditions, whereas low flow inhibited its formation.[15] In addition, cellular behavior of circulating cells can be modulated by blood albumin or other serum components.[16] Flow rates in the physiological range can decrease consumption of nitric oxide by circulating erythrocytes resulting in altered oxidative stress in vivo compared to in vitro experiments that usually do not use erythrocyte preparations.[17] However, contradictory results have been reported on the effect of shear stress on cellular characteristics suggesting complex interactions between cellular regulation and biophysical factors.[11,13,18,19] These differences may be caused by the different types of EC used, differences of shear stress exposure, and lack of physiological cellular and soluble blood components. In addition, most experimental data were obtained using in vitro systems that likely simplify biological responses and reduce their complexity within organs and the entire organism.

In contrast, in vivo systems have been used to investigate formation of distant organ metastasis, but these assays usually consider macroscopic tumors within target organs after primary tumor induction or tumor cell injection. Therefore, these end-point assays are unable to differentiate between different steps of the metastatic cascade, such as cell adhesion, survival, and growth. We demonstrate a new model for intravital observation of metastatic colon carcinoma cell adhesion within the hepatic microcirculation that allows separate investigation of various cellular events during formation of liver metastasis.

MATERIAL AND METHODS

Cells

Dulbecco-modified Eagle's medium/F12 medium (DME/F12, 1:1 v/v), RPMI1640 medium, and fetal bovine serum (FBS) were purchased from GIBCO-BRL (Karlsuhe, Germany). All other chemicals were purchased from Sigma (Deisenhofen, Germany).

Human HT-29 and rat CC531 colon carcinoma cells were cultured in DME/F12 or RPMI1640 medium, respectively, containing 10% FBS without antibiotics in humidified 5% CO_2/95% air at 37C. Both cell lines are comparable in their tumor characteristics and metastatic properties. Semiconfluent cells were used during their log-phase of growth. After trypsination cells were washed with calcium-magnesium-free phosphate buffered solution (CMF-PBS) and kept in serum-free medium (DME/F12 [1:1], bovine serum albumin [BSA] 1%) for 60 minutes for reconstitution of cell surface proteins. During reconstitution cells were incubated with calceinAM (Molecular Probes, Leinden, The Netherlands) (1 μg/ml) in order to label them for fluorescence microscopy. We have previously shown that this procedure does not interfere with adhesive properties of the cells in vitro.[20,21] After washing with CMF-PBS cells were resuspended as single cell solution in CMF-PBS at a final concentration of 10^6 cells/ml. Cells were used immediately for further experiments.

Animal Model

Male Sprague-Dawley rats (300–350 g, Charles River, Sulzfeld, Germany) were cared for in accordance with standards of the German Council on Animal Care, under an approved protocol of the local Animal Welfare Committee. Rats were anesthetized using intramuscular/intraperitoneal injection of Rompun/Ketanest (Bayer, Leverkusen, Germany) or by inhalation of isofluorane (Curamed, Karlsruhe, Germany). Permanent catheters were introduced into the carotic artery and the jugular vein. Both catheter tips were located central to the heart. After a wide median laparotomy was performed careful mobilization of a left liver lobe was done without disturbing hepatic circulation. Using the heated operating table, the animals were now fixed

under an upright microscope and positioned on their left side. This positioning allowed a partial luxation of the mobilized liver lobe that was placed on a specific holder to investigate its lower surface. The holder was adjustable in all directions and sufficient to avoid disturbances of the local circulation and moving artifacts caused by heart beats or ventilation (Fig. 1). Furthermore, this holder provided the required plane surface of the liver parallel to the optical layer for clear and sharp imaging. During the experiments the liver was continuously irrigated with isotonic saline solution.

Intravital Fluorescence Video Microscopy

An upright epifluorescence microscope (Zeiss, Jena, Germany) was used containing a 20-fold objective which was located over a glass slip covering the liver surface. The microscope was connected with a video enhancer-zoom lens system and a low-light CCD-video camera (Peiper, Duesseldorf, Germany) allowing real-time imaging via a separate monitor. Fluorescence images were recorded using a timer-containing S-VHS videosystem for further analysis. Filter sets used included excitation wave and emission lengths of 488 nm and 515 nm, respectively, that provided high signal-to-noise ratios for the calcein chromophore. For illumination a 100 W-mercury lamp was used (Zeiss, Jena, Germany).[22]

In Vivo Observation of Metastatic Tumor Cell Adhesion

For intravital observation of adhesive interactions between circulating tumor cells and the hepatic microcirculation single cell suspensions (1×10^6 cells) were injected either intraarterially or intravenously over 60 seconds. In some experiments cells were injected via a catheter that was placed in the extrahepatic portal vein. The injected volume of 1 ml did not interfere with cardio-circulatory functions of the animals. For semiquantitative analysis of cell adhesions 30 microscopic fields were monitored every 5 minutes for a total time of 30 minutes.

Various parameters were used for further investigation and semiquantitative analysis of these interactions. First, occurrence of "cell rolling" was monitored. Additionally, the latency was measured until first stable tumor cell adhesions were established within the hepatic microcirculation. The localization of stable tumor cell adhesions within the vascular tree and in relation to the diameter of the involved vessels were evaluated. If tumor cells were able to arrest within the sinusoids, the diameter of the involved vessel was determined compared to the diameter of the tumor cell. Furthermore, remaining blood flow within this vessel or its occlusion was investigated. A semiquantitative analysis of tumor cell adhesions and extravasation was performed over the 30 minute observation period and the numbers of adherent cells were counted for each of the 5-minute intervals. Using a standardized procedure, all fields were analyzed in each observation period and average numbers of adherent cells, migrated cells, and total cells observed per microscopic field were counted. In addition, the latency of tumor cell invasion into liver parenchyma was determined.

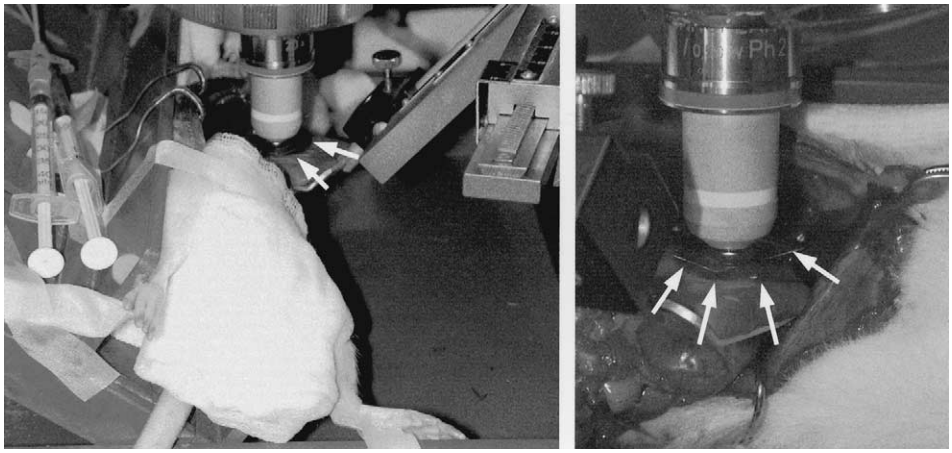

Fig. 1. Intravital fluorescence microscopy. Rats were placed under an upright microscope and a left liver lobe (*arrows*) was partially luxated and fixed on a holder. A 20-fold magnification was used for further experiments.

RESULTS

Intravital Microscopy of Liver Circulation

After exposure of the left liver lobe, a plane surface with minimal moving artifacts autofluorescence was determined using a 488 nm laser beam. The faint autofluorescence of the liver parenchyma caused mostly by hepatocytes enabled a clear visualization of the parenchyma. Distinction between parenchyma and hepatic sinusoids allowed differentiation of various vessel types within the vascular tree of the liver (Fig. 2). Intense green fluorescence of calcein-labeled circulating cells permitted intravital identification of individual tumor cells and their location within the liver circulation (Fig. 3). Furthermore, its differences to the faint yellow autofluorescence of the liver tissue provided sufficient contrast for the determination of the cell extravasation and their migration into the liver parenchyma. Extravasated tumor cells, located within the autofluorescence branches between sinusoids, remained visible over the whole observation period (Fig. 4). Fluorescence labeling of injected tumor cells remained stable in vivo for more than 30 minutes and permitted semiquantitative analysis of cell adhesion and extravasation according to the protocol.

Using this labeling technique we optimized the number of injected cells and the volume of cell suspension to minimize hemodynamic or rheologic side effects. Furthermore, the conditions used were chosen for optimal number of observed events within the microscopic fields and the observation periods. Since intravenous, intraarterial, or intraportal injection can be used for application of cell suspensions we first investigated these methods. It was found that intraarterial injection resulted in the highest numbers of visible cells within the hepatic circulation. In contrast, after intravenous injection the numbers of fluorescence-labeled cells that were observed was much less, probably due to cell trapping within the pulmonary circulation. Furthermore, intravenous injection frequently resulted in severe complications, such as pulmonary and circulatory failure. After injection of cells into the mesenteric vein we found a tendency of disturbed hepatic circulation probably because of the high volume compared to the regular portal blood flow. Therefore, for the preliminary study intraarterial injection of tumor cell suspensions was used.

Tumor Cell Arrest

After the establishment of the experimental model for intravital fluorescence-based observation of hepatic tumor cell adhesion a preliminary study was performed where a small number of rats was investigated for differences between human (HT-29) and rat (CC531) colon carcinoma cells. First tumor cell arrests were observed within 2 minutes after injection of the cell suspension. However, in contrast to adhering leukocytes, rolling of colon carcinoma cells was a very rare event. Cells almost exclusively adhered without reducing their moving velocity. In some cases, adherent cells appeared to lack adhesion stabilization and lost their adhesive bonds after several seconds resulting in recirculation of these cells. Next, we analyzed the location of tumor cell adhesions within the sinusoids and the relationship between the diameters of tumor cells and vessels where the cells arrested was observed. We found that most adherent tumor cells were located within sinusoidal capillaries with a larger diameter compared to the ar-

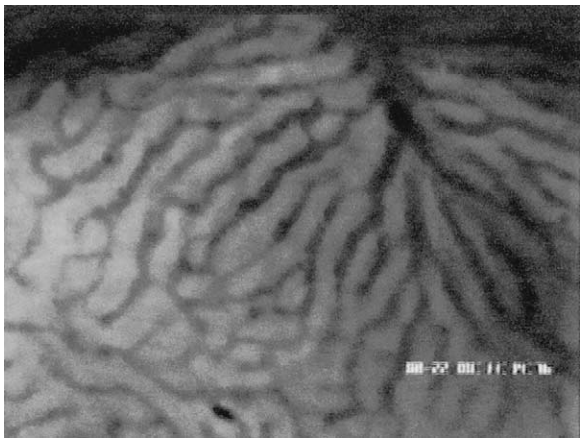

Fig. 2. In vivo fluorescence observation of rat liver. Vascular tree (*dark*) and liver parenchyma (*light*) were easy to differentiate due to the faint autofluorescence of hepatocytes.

Fig. 3. Tumor cell adhesion within liver sinosoids. A carcinoma cell (*arrow*) adhered within a capillary. The diameter of this vessel was larger than the diameter of the tumor cell leaving a remaining lumen for perfusion through this capillary.

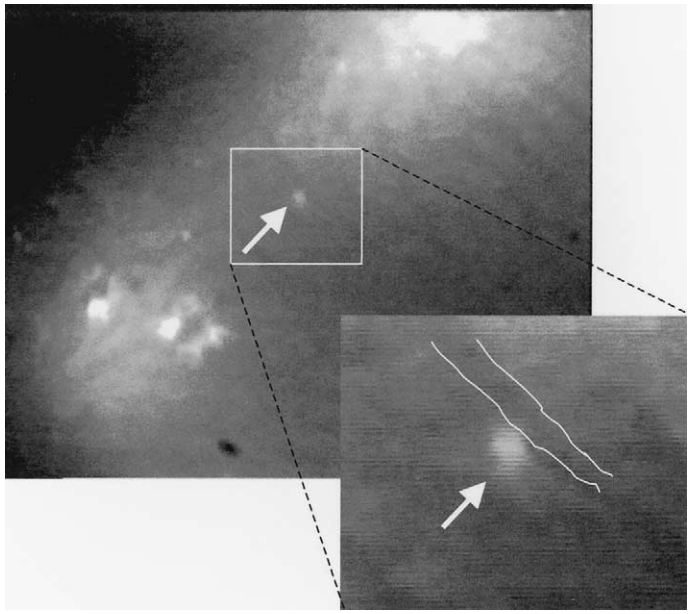

Fig. 4. Extravasation of colon carcinoma cells. HT-29 cell (*arrow*) had left the microcirculation and migrated into the liver parenchyma. Enlargement includes labeling of vessel borders for better contrast.

rested tumor cells. This resulted in a remaining lumen and persistent blood circulation of these capillaries (Fig. 3). However, all of the sinusoidal vessels involved in tumor cell arrest belong to microcirculatory capillaries, and adhesions within vessels of higher order were never found. Differences in the adhesive behavior between HT-29 and CC531 cells were not found, suggesting that heterologous immune reactions did not interfere with cell properties during the observation period.

Migration Into Liver Parenchyma

As described, we were able to differentiate between intravascular adherent tumor cells and fluorescence-labeled cells that had left the microcirculation and were migrated into the liver parenchyma. Therefore, the preliminary analysis was extended to characterize the time course of extravasation within the 30 minute observation period. Surprisingly, first extravasated cells were already found within 5 minutes after injection of the cell suspension. Although the number of animals investigated does not permit statistical evaluation, a high proportion of adherent cells was observed that migrated into the liver parenchyma over time resulting in a very rapid extravasation of the colon carcinoma cells (Fig. 4). After the 30 minute observation the majority of adherent cells were found outside the sinusoids.

Semiquantitative Analysis of Cell Behavior

Adhesive interactions were semiquantitatively analyzed at the liver surface regarding the time course of these interactions for 30 minutes after cell injection. Initially, HT-29 and CC531 cells showed cell adhesion within the liver sinusoids, and cells were exclusively found within the lumen of the vessels. During the next minutes the number of adherent cells slightly increased. In addition, an increasing number of cells was observed that had left the microvessels and were migrated into the liver parenchyma. After more than 15 minutes the total number of cells remained constant, but less adherent cells were found, whereas the numbers of migrated cells increased constantly (Fig. 5). Significant differences between both cell lines were not found.

DISCUSSION

Current evidence indicates that tumor cell adhesion to the microvasculature in host organs during formation of distant metastasis is a complex process involving various types of adhesion molecules. Recent evidence suggested that stabilization of tumor cell adhesion to the microvessels has a very important role for further steps in the metastatic cascade, such as migration and invasion into host organs.

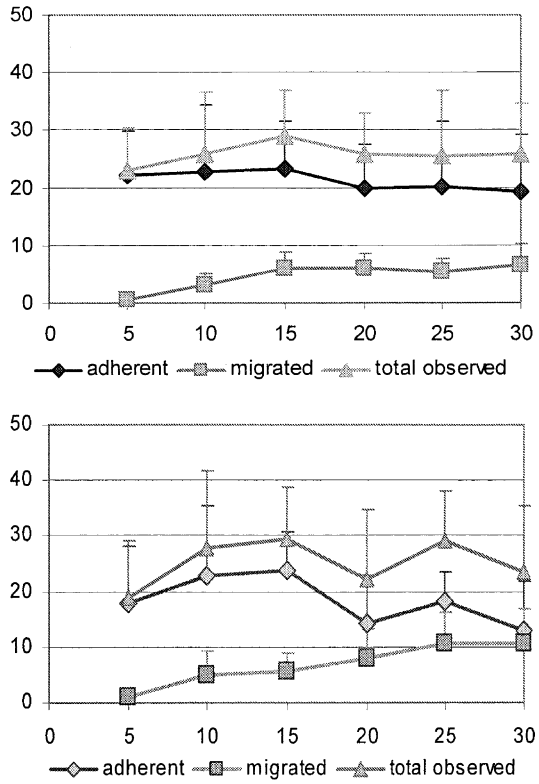

Fig. 5. Time course of metastatic cell adhesion. HT-29 (*top*, n = 9) and CC531 (*bottom*, n = 7) cells were injected. Average numbers of adherent cells, migrated cells, and totally observed cells were counted in each 5 minute observation period per microscopic field.

These studies have shown that tumor cell adhesion within a circulatory system is, in addition to the biochemical interaction between adhesion molecules and their ligands, also influenced by biophysical factors, such as shear stress caused by fluid flow, and cellular and soluble components for the circulating fluid.[5,8,23,24] However, although these complex interactions are not fully represented using in vitro assays, in vivo observation of metastatic tumor cell adhesion and primary migratory processes within host organs is only at the beginning of investigations.

We established a new model for intravital fluorescence-based video-microscopy that allows real-time observation of metastatic tumor cell arrest within the liver microcirculation. Using human and rat colon carcinoma cells we have demonstrated that initial steps of the metastatic cascade within the host organs, such as cell adhesion and migration, can be differentiated. This enables further investigations of various cellular structures, signaling pathways and host organ properties involved in these processes. Using transient or stable fluorescence-labeling circulating tumor cells can be easily observed within hepatic sinusoids and located within the vascular tree or liver parenchyma. In our preliminary study we showed that colon carcinoma cells likely adhere to sinusoidal microvessels by specific interaction, since involved vessels had larger diameters than the adhering tumor cells and these vessels remained perfused. Furthermore, we observed a rapid extravasation of these cells and invasion into the liver parenchyma.

Using an isolated perfused rat lung model Al-Mehdi et al. [25] demonstrated tumor cell arrest of circulating fibrosarcoma cells and embryonic fibroblasts within the pulmonary microcirculation. In contrast to previous results using melanoma cells[26] or CHO chinese hamster ovary cells[27] that arrested due to entrapment within small diameter microvessels in the mouse liver circulation, they found that specific cell adhesions occurred within precapillary arterioles and microcapillaries, and these cells were not trapped by size restriction. Comparable to our results this occurred in microvessels with larger diameters than that of the circulating tumor cells leaving remaining vascular lumen and perfusion of the involved microvessel. Once cells adhered within these vessels, further movement, such as rolling, has usually not been observed in the mice lungs or in our rat liver model. However, this group reported intravascular growth of the adherent sarcoma cells with secondary occlusion of the involved microvessels. In contrast, our preliminary results indicate a rapid extravasation of colon carcinoma cells and migration into the liver parenchyma. Similarly, Chambers et al.[26] and Koop et al.[28] described extravasation of melanoma cells into mice liver parenchyma, but extravasation was much slower compared to the rapid migration in our study. Using a rat tongue carcinoma cell line, Ito et al.[29] reported size-limited mechanical tumor cell arrests within the rat liver without extravasation.

These differences may be explained by different cell types used or by differences in the experimental protocols. Since the study of Al-Mehdi et al.[25] was performed in isolated lungs avoiding blood as perfusate, interactions with other cellular components or soluble factors were excluded. Furthermore, physiologic and biologic characteristics of pulmonary microvessels appear to have significant differences from that of other organs as it was shown by Yamaguchi et al.,[30] using real-time confocal luminescence microscopy. Additionally, species-related differences of the architecture of liver microcirculation, such as diameters of the microvessels or hemodynamic parameters, surface characteristics of sinusoidal EC, such as expression of cell adhesion molecules, or composition of basement membranes, among others, can be re-

sponsible for different adhesive properties in these models. For example, most studies on liver microscopy used inverted microscopes with the advantage of minimizing moving artifacts, but they require positioning of the animals on their abdomen that may interfere with hemodynamic parameters due to increased pressure at the observed surface.

Malignant tumors often show organ preference of metastatic spread suggesting the involvement of specific structures and/or processes in their formation. The sequential model for the development of metastases involves tumor growth, neovascularization and invasion at the primary sites, followed by penetration into lymphatics and blood vessels or into body cavities.[5] One of the most important steps toward understanding metastasis formation was the finding that the development of metastases is a nonrandom process, where the implantation, invasion, survival, and growth of a single cell or small numbers of cells are dependent on both cancer cell and host properties. Similar to other carcinomas, colorectal carcinomas often show organ preference of metastasis formation. Between one century ago and the beginning of this century two major hypotheses on the mechanisms of tumor metastasis formation were proposed. Ewing (1928) proposed that the random mechanical lodgment of circulating tumor cells in the first capillary system encountered was the determining factor. This hypothesis has been almost exclusively used as an explanation for the formation of colorectal metastasis, that the hemodynamics of the vascular system based on specific anatomical structures (portal vein) predicted the locations of secondary cancers (predominance of liver metastasis). However, a direct observation of metastatic tumor cell adhesion has not been achieved until recently.

In contrast, Paget (1889) postulated in his "seed and soil" hypothesis that successful interactions of tumor cells ("seeds") with the microenvironment of a particular target organ ("soil") lead to formation of distant metastases in specific organs. These hypotheses are not mutually exclusive, and the development of distant metastases at specific organ sites is probably determined, in part, by anatomical structures and hemodynamics and specific interactions between unique circulating tumor cells and host organ structures. However, only the latter proposal can explain the unique nonrandom patterns of tumor metastases, which is now supported by the results of our in vivo observation.

Our newly established model permits in vivo investigations of tumor cell interactions within the hepatic microcirculation. Colon carcinoma cells appear to establish stable cell adhesions to the liver sinusoids by specific interactions, and mechanical lodgement may not be quantitatively important. Colon carcinoma cells can rapidly leave hepatic microcirculation after successful cell adhesion and migrate into the liver parenchyma.

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Discussion

Michael G. Sarr, M.D. (Rochester, MN): You have injected these cells intraarterially. Many neoplasms metastasize through the portal venous system. Are there different control mechanisms? Might the regulation of rolling, adhesion, etc., be different intraportal versus intraarterial?

Dr. Haier: I don't think that the cells behave differently if they are injected intraarterially or intravenously or intraportal, but what we will probably see, at least as shown for the first animals that we used, is that the number of cells that finally reach the liver circulation is different. Probably, there are not different control mechanisms depending on the route of application, because after 30 minutes we saw some circulating cells, and they finally had to go through arterial circulation, somewhere, and the behavior of these cells was similar compared to the cells that adhered after two minutes already.

Matthias G. Stelzner, M.D. (Seattle, WA): I think this is very nice work. Similar phenomena are also known for platelet adherence where you also do not see rolling but shear-activated sudden adhesion. Also, in microbiology, similar mechanisms have been described with adhesion of enterobacteriaceae to the vascular endothelium. Such shear-activated processes often get started in direct relation to the involved shear energy. Have you looked in your model, and it would probably be easy to do, whether the speed of the blood flow has any effect on the adhesion? In other words, is there a function between the shear energy and the adhesion of cells?

Dr. Haier: We did extensive studies, not in vivo but in an in vitro model using a laminar plate chamber which simulates the microcirculation. There we found two things; first, the adhesion is clearly dependent on the shear flow rates, and, if the flow is above the shear forces that occur in the capillaries, maybe within the arterioles and venules, then there is no adhesion at all, independent if you use endothelial cells or matrix proteins as the coated surface, it really doesn't matter. The second aspect we found is that the shear flow alone is able to modify cellular signaling like the phosphorylation. Just the presence of the low shear flow comparable to the microcirculation can already enhance the protein phosphorylation.

Kevin E. Behrns, M.D. (Chapel Hill, NC): In a similar question, have you looked at any alterations in the basement membrane in the extracellular composition to see what molecules might be involved with the attachment? Have you done any experiments related to that?

Dr. Haier: We have studied cell adhesion in vitro using different matrix proteins or Matrigel as a mixture. The problem is that it is very likely that the variable composition of basement membranes in different organs is responsible for different behavior and might be responsible for the specific interactions that are organ-specific, such as the

formation of liver or lung metastases. Currently, we are doing studies to identify the adhesion molecules that are involved in the liver.

Reid B. Adams, M.D. (Charlottesville, VA): Beautiful paper and very elegant work. Your last data slide demonstrated what may be a difference in the integrins used to attach to the vasculature versus those that are required to set up and establish metastases in the liver. You showed that you significantly decreased the ability to attach by blocking beta-1 integrins, but it looked like you had a pretty good take once those cells had obtained access to the parenchyma. The green part of your bars, if I remember, looked like you had pretty good take of some of the tumor cells. Do you think that there is a different integrin population besides the beta-1 that may be involved in facilitating tumor establishment versus those that promote vascular attachment and invasion, and have you done studies to distinguish between these two potentially different integrin populations?

Dr. Haier: For the establishment of these techniques, we used beta-1 because it is a very common integrin, and now we are trying to identify the heterodimers that are responsible for these interactions. However, beta-3 is not expressed on these cells, so it is not involved at all, and I don't think that the other beta integrins really play an important role in the establishment of cell adhesions within the liver microcirculation, because the numbers of receptors that are on the cell surface, is probably too low to stabilize adhesions. They might be involved in further requirement for migration or subsequent steps.

Identification of Optimal Harvest Sites of Ileal Stem Cells for Treatment of Bile Acid Malabsorption in a Dog Model

Matthias Stelzner, M.D., Vicki D. Hoagland, B.S., Jacob D. Woolman, B.A.

Ileal mucosal stem cells expressing the sodium-dependent ileal bile acid transporter (IBAT) have been successfully transplanted into the jejunum of rodents in projects aimed at creating a "neoileum" to treat bile acid malabsorption. To find optimal harvest sites for a dog model of stem cell transplantation, the exact location of peak IBAT expression in the donor ileum needs to be known. We therefore mapped IBAT function, IBAT mRNA, and IBAT protein in the ileum of Beagle dogs (N = 3). Mucosal samples were taken every 5 cm in the ileum and every 20 cm in the jejunum of each dog. Sodium-dependent (active) and sodium-independent (passive) taurocholate uptake rates were measured using a standardized everted sleeve technique. IBAT mRNA concentrations were determined by semiquantitative reverse transcriptase–polymerase chain reaction and IBAT protein concentrations by fluorometric immunohistochemical analysis. The small bowel measured 208 ± 17 cm (mean ± standard error of the mean). Active and passive uptake rates were found to follow distinct distribution curves. Significant active uptake was seen only at the terminal 50 cm and peaked at 479 ± 176 pM/mm^2. Depending on location, active uptake accounted for approximately half of the total uptake. IBAT mRNA and protein distributions corroborated uptake curves. The terminal 10 to 50 cm of ileum has the highest bile acid uptake capacity. This short segment appears to be the most promising donor site for ileal stem cell transplants to create a "neoileum" in dogs. (J GASTROINTEST SURG 2003;7:516–522) © 2003 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Ileum, absorption, bile acid, dog

Bile acids are important facilitators of fat and cholesterol absorption in the small intestine. After fulfilling their function as detergents in the intestinal lumen, bile acids are conserved by active ileal uptake and recycled in the enterohepatic circulation. Active uptake in the ileum occurs via the sodium-dependent ileal bile acid transporter (IBAT). Severe disturbances of IBAT function are found in patients with ileitis or after ileal resection and lead to bile acid malabsorption, cholegenic diarrhea, and an increased incidence of gallstones.

Recently, transplantation of ileal mucosal stem cells has emerged as a potential treatment concept for bile acid malabsorption. Our group reported successful transplantation of stem cell clusters derived from the ileal mucosa into a partially de-epithelialized, dormant jejunal segment in rats.[1] However, satisfactory removal of resident mucosal cells in the recipient jejunum segment proved difficult because of tender and thin submucosal and muscular layers of rodent small intestines. Because our group has significant experience performing intestinal mucosectomies in dogs,[2,3] we decided to explore the possibilities of stem cell transplantation in this species.

Among other factors, the clinical success of intestinal stem cell transplantation for the treatment of any malabsorptive condition depends on the availability of stem cells that will give rise to neomucosa with maximal absorptive capacities for the compound in question (in this case, bile acids). To find optimal harvest sites for a dog model of ileal stem cell transplantation, the exact location of peak IBAT expression in the donor ileum needs to be known.

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It was recognized long ago that active bile acid uptake occurs only in the ileum in the dog. Tappeiner,[4] in 1878, was the first to discover that bile acids are absorbed more readily in the ileum than in the jejunum of dogs; one century later, others confirmed that the maximal bile acid uptake occurred in the terminal quarter of the canine small bowel.[5–7] However, exact mapping of active and passive bile acid capacities by measuring inch by inch and mapping of the distribution of the IBAT protein and IBAT messenger RNA have never been performed. Such evidence would be germane to identifying optimal harvest sites for stem cells. Thus, in the present study, we established the exact distribution pattern for the sodium-dependent and sodium-independent components of bile acid uptake in the ileum of dogs. In addition, we determined the exact distribution of the IBAT gene message using a semiquantitative reverse transcriptase–polymerase chain reaction (RT-PCR) technique and visualized the distribution of IBAT protein by immunohistochemical analysis and quantitative fluorimetry.

MATERIAL AND METHODS

Animals

Three Beagle dogs, weighing 3.6 to 4.5 kg, were obtained from Marshall Farms (North Rose, NY). The animals were acclimatized to the new environment in the vivarium and received regular dog chow and water ad libitum. The animals were kept on a 12-hour light/12-hour dark cycle. Animals were allowed to adjust for 7 days before the experiments were begun. All procedures were approved by the institutional review committees at the Seattle VA Medical Center.

The animals were sacrificed by intravenous injection of pentobarbital at 9 A.M. The small intestine was removed from the ligament of Treitz to the ileocecal valve and immediately transferred into 2° C cold mammalian Ringer's solution (128 mmol/L NaCl, 4.7 mmol/L KCl, 2.5 mmol/L $CaCl_2$, 1.2 mmol/L NaH_2PO_4, 1.2 mmol/L $MgSO_4$, and 20 mmol/L $NaHCO_3$, pH = 7.30 to 7.40 at 39° C, 290 mOsm, gassed with continuous 95% O_2/5% CO_2). The intestinal length was measured. In each dog, the small intestine was divided into 5 cm sections from 0 to 75 cm proceeding backward from the ileocecal valve in an oral direction. From 75 cm on, 20 cm long segments were cut and the first 5 cm of each segment was used in the experiments. From each segment, the distalmost 2 cm of intestine was taken for uptake studies. An immediately adjacent 1 cm piece from each segment was used for immunohistochemical analysis and mRNA quantification.

Bile Acid Uptake Measurements

Sodium-dependent and sodium-independent bile acid absorption rates were measured in tissues from the three dogs by a highly standardized everted sleeve method, as previously described.[2,3] Briefly, tissue specimens were kept in 2° C cold mammalian Ringer's solution. Specimens were then everted and secured onto 4 mm thick stainless steel rods using silk ties and stored in oxygenated ice-cold Ringer's solution. Uptake measurements were performed between 1 and 2 hours after excision. Mounted tissues were preincubated for 5 minutes in 39° C warm, oxygenated Ringer's solution, and then incubated for 2 minutes in either sodium-containing or sodium-free Ringer's solution with 1 mmol/L taurocholate. Sodium-dependent transport was defined as the difference between uptake rates in sodium-containing and sodium-free taurocholate-Ringer's solutions.

To measure sodium-independent uptake, sodium-free Ringer's solution was prepared by replacing sodium chloride with choline chloride and $NaHCO_3$ with $KHCO_3$. Taurocholate in the sodium-free solutions was added as a potassium salt. To prepare potassium taurocholate, ion exchange of a 1 mmol/L sodium taurocholate solution with potassium-loaded AmberLyte (Bio-Rad Laboratories, Hercules, CA) was performed. The potassium salt was subsequently recrystallized. Absence of sodium ions after the ion exchange was confirmed by flame-photometry. Tracer amounts of radiolabeled sodium taurocholate (^{3}H- (G) sodium taurocholate; NEN Research Products, Boston, MA) were added to the uptake solutions. 1,2-^{14}C polyethylene glycol (molecular weight 4000 daltons), a marker substance not subject to carrier-mediated transport and with a very low transmembrane diffusion coefficient, was also added to these solutions to account for ^{3}H-radiotracer in the adherent fluid.[2,3,8]

The length of the incubation period was chosen on the basis of initial validation experiments using canine jejunal and ileal tissues, as suggested by Karasov and Diamond.[8] These validation studies showed that at 2 minutes the uptake of radioactive taurocholate still demostrated linear increases over time, while complete equilibration of radioactive polyethylene glycol had occurred (data not shown).

After incubation, tissues were removed from the rods, placed in scintillation vials, and solubilized in 1.5 ml TS-2 tissue solubilizer (Research Products International, Mount Prospect, IL). Vials were incubated at 49° C until the tissues were dissolved and 15 ml acidified Safety-Solve scintillation cocktail (Research Products International) was added. Beta emissions (in disintegrations per minute [DPM]) from

tritium and ^{14}C were counted in a liquid scintillation counter (Tricarb 2200 CA, Packard Instrument Co., Downers Grove, IL).

Immunohistochemistry

For immunohistochemical studies, tissue samples from the small intestine were mounted in OCT compound and frozen on dry ice. Tissues were sectioned on a cryostat (Leitz, Wetzlar, Germany) and mounted on Superfrost/Plus glass slides (Fisher Scientific, Pittsburgh, PA). Polyclonal antibodies were obtained from a commercial source (Research Genetics, Huntsville, AL) against a C-terminal 14 amino acid oligopeptide fragment of hamster IBAT (sequence SFQETNKGFQPDEK). The antibody is then purified from rabbit serum by immuno-affinity chromatography on a "HiTrap" column (Amersham Pharmacia Biotech, Piscataway, NJ) and found to cross-react with the canine, human, mouse, and rat IBAT when used for immunohistochemical analysis. Frozen sections were air-dried at room temperature and fixed in −20º C acetone for 15 minutes. They were then washed briefly in phosphate-buffered saline solution and incubated for 5 minutes with 5% goat serum in phosphate-buffered saline to reduce background staining. A 1:10 dilution of anti-IBAT protein antibodies was applied for 3 hours. Sections were washed and incubated with a 1:100 dilution of a secondary goat antirabbit Cy3 IgG antibody (Jackson Immuno-Research Laboratories, West Grove, PA) for 30 minutes, then washed three times in phosphate-buffered saline for 2 minutes. Slides were mounted using an aqueous medium containing Hoechst 33258 dye as a nuclear stain (Sigma, St. Louis, MO). The slides were evaluated for distribution of the fluorescence signal under a fluorescence microscope (Axioscope II; Carl Zeiss, Thornwood, NJ) equipped with a digital imaging system and a program to measure the intensity of the fluorescence (Axiocam; Carl Zeiss). The fluorescence signal was quantified using an Axiovision image analysis system (Carl Zeiss). Signal density was measured as fluorescence intensity over background. Standardized circular image fields were defined for comparison of villi in different locations along the axis of the gut, one at the villus tip and two in the brush-border area halfway between the villus tip and the crypt-villus junction. A fourth image field of equal size was positioned in the stromal center of each villus and was used to determine the background values. This allowed the assessment of relative signal densities independent of villus height and crypt depth in any given part of the small bowel. Preimmunized serum served as a negative control.

Quantification of IBAT mRNA

Small sections of intestinal tissues (100 to 250 mg) from different locations were used to prepare total RNA as described,[9] incubated with RQ1 DNase (Promega Corp., Madison, WI), and further purified by applying to RNeasy Mini columns (Qiagen, Inc., Valencia, CA). One microgram of purified total RNA from each sample was reverse transcribed and the cDNA used as templates in subsequent PCR reactions. A 331 bp fragment from the coding region of dog IBAT was amplified using the primer pair 5′-CCTTTGACATCCTCCCTCTC-3′ and 3′-ATG GACCCAACCTTGAGTATG-5′. As a normalizing control, a 530 bp fragment from the coding region of dog GAPDH was amplified with the primer pair 5′-TGATGCTGGTGCTGAGTATGTTG-3′ and 3′-CCTGCTTCACTACCTTCTTGATGTC-5′. We first determined the number of PCR cycles at which the two PCR products were accrued by linear increases from these cDNAs. To this end we varied the number of PCR cycles from 20 to 40. Linear increases in all samples were observed with 31 PCR cycles (data not shown). After running all the samples for 31 cycles, PCR products were electrophoresed in a 0.7% agarose gel in 1X triethlanolamine-buffered saline and the dog IBAT and dog GAPDH bands quantified by gel densitometry on a Nucleotech 5000 densitometry unit (Nucleotech, San Diego, CA).

Data Analysis

Data were collected and results expressed as mean ± standard error of the mean (SEM). All quantitative experiments were carried out in triplicate. Mean values of the various groups of samples obtained along the longitudinal axis of the small intestine were compared using single-factor analysis of variance (ANOVA). This was followed by Tukey's least significant difference test as a post hoc test.[10] The data points from the proximal-most jejunum (155 to 215 cm proximal to the ileocecal valve) were considered "jejunal baseline" values. Significance was assumed at a level of $P < 0.05$.

RESULTS

Distribution of Bile Acid Uptake

The length of the canine small intestine from the ligament of Treitz to the ileocecal valve was 208 ± 17 cm (N = 3). High rates of active absorption of taurocholate were found only in the terminal 40 cm of the dog ileum. Active uptake peaked at 479 ± 176 pM/mm^2 × minutes. There was no active uptake beyond 55 cm proximal to the ileocecal

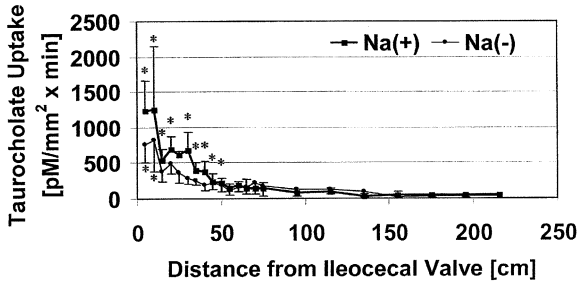

Fig. 1. Distribution of total (sodium-dependent plus sodium-independent) and sodium-independent absorption rates of radiolabeled taurocholate in the canine ileum and jejunum. Measurements were performed on everted mucosal sleeves using sodium-containing Ringer's solution (*filled squares*) and sodium-free Ringer's solution (*filled circles*). Total taurocholate absorption rates were significantly elevated compared to proximal jejunal values in the terminal 50 cm of the ileum ($^*P < 0.05$ by ANOVA/Tukey's test). Increases in sodium-independent values were significant only in the terminal 10 cm of the ileum.

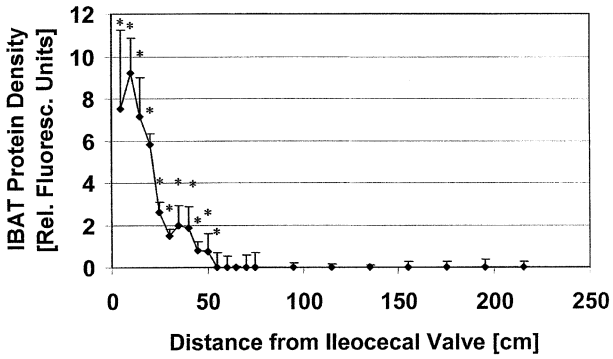

Fig. 2. Distribution of ileal bile acid transporter protein along the axis of the small intestine. Microscopic sections from the jejunum and ileum were treated with anti-IBAT antibodies and fluorescent secondary antibodies. The intensity of the fluorescent signals at the brush-border membranes was quantified. Only the terminal ileum showed significant IBAT protein signals. ($^*P < .05$)

valve (Fig. 1). It was evident that capacities for active bile acid absorption were distributed in a very characteristic pattern. Total uptake rates for taurocholate ranged from 600 to 800 pmol/mm^2 × minutes. Diffusional uptake was also distributed in a very distinctive pattern and was also found to be higher in the terminal ileum. This distribution resembled that of active bile acid transport. Approximately half of the absorption in the terminal ileum was by active absorption and the other half by diffusional uptake (see Fig. 1). No significant differences were found in the amounts of extracellular marker polyethylene glycol attached to tissues from the distal vs. the proximal small intestine (data not shown).

Distribution of IBAT Protein

The immunohistochemistry studies demonstrated a strong fluorescence signal for IBAT protein in the terminal ileum (Fig. 2). IBAT protein densities readily decreased toward the mid-small bowel. The distribution along the axis of the small intestine was similar to the one for taurocholate uptake capacities. Close examination of the distribution of IBAT protein along the crypt-villus axis in the ileum revealed that IBAT protein was relatively evenly distributed along the villus with a slight predominance at the villus tip (Fig. 3). Only small amounts of IBAT protein were detectable in the crypt region. This relative distribution of IBAT protein along the crypt-villus axis did not change as the total signal density decreased toward the more proximal sections of the gut.

Distribution of IBAT mRNA

IBAT mRNA distribution was analyzed by standardized RT-PCR and measured semiquantitatively using agarose gel densitometry. Peak concentrations

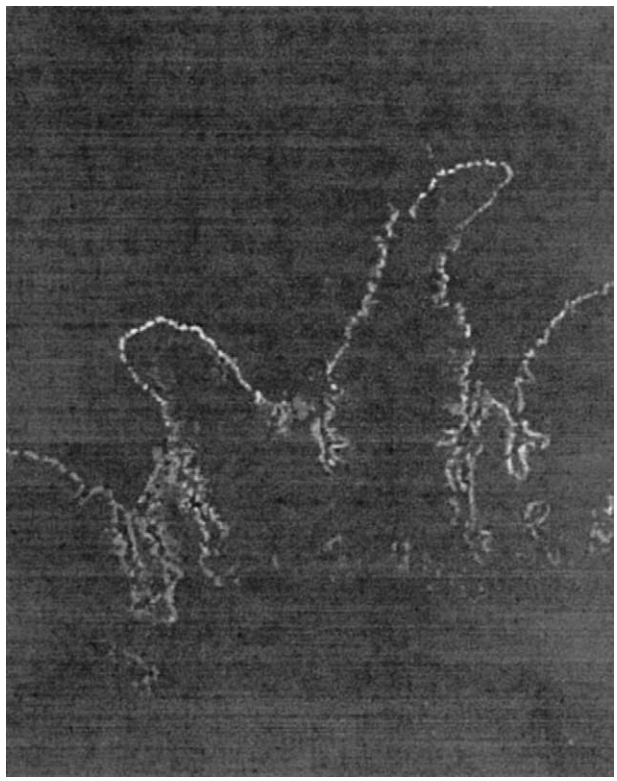

Fig. 3. Detection of IBAT protein in the brush border of two villi in the terminal ileum. IBAT protein was detected immunochemically as described in Fig. 2. IBAT protein was relatively evenly distributed along the crypt-villus with a slight predominance of the villus tip.

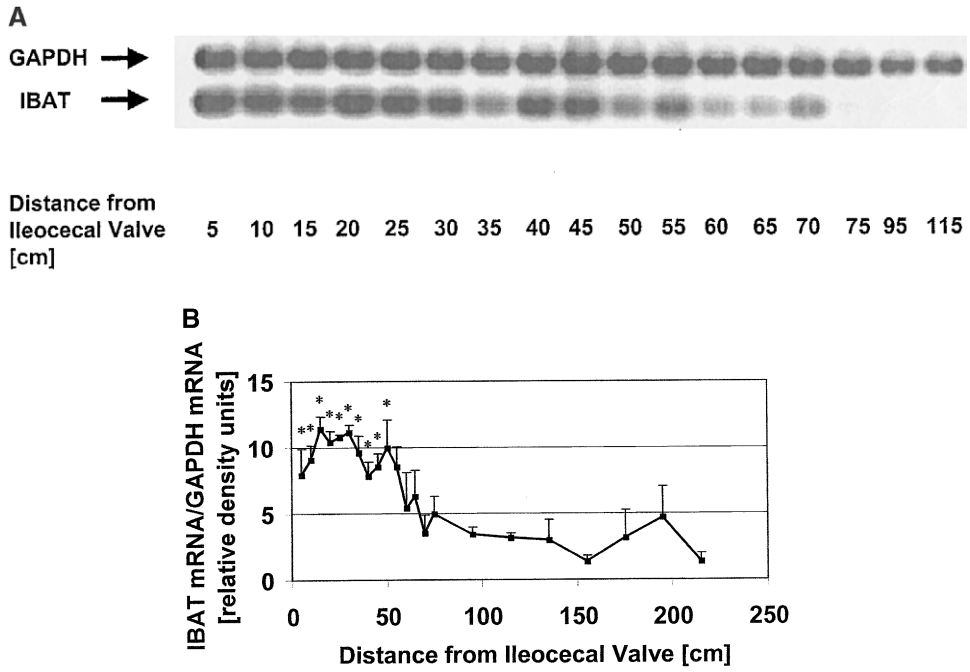

Fig. 4. A, Representative agarose gel of RT-PCR products for GADPH and IBAT mRNA quantification. The figure shows PCR products obtained from tissue samples from the mid-small bowel and the ileum. Strong IBAT signals were found in the terminal ileum. **B**, Distribution of IBAT mRNA—relative to GADPH mRNA—was measured along the axis of the entire small intestine by standardized RT-PCR and subsequent densitometry of all agarose gels. The terminal 50 cm of the ileum showed IBAT mRNA concentrations significantly higher than values from the proximal jejunum. ($^{*}P < 0.05$ vs. jejunum by ANOVA/Tukey's test.)

were again observed in the terminal 40 to 50 cm of the small intestine (Fig. 4, *A* and *B*). Signal densities relative to GAPDH were more variable than those seen for IBAT uptake function or IBAT protein content. This appeared to be partially due to an increased variability in GADPH concentrations. In spite of this variability, densitometric analysis of the IBAT products revealed overall a distribution pattern similar to that of the taurocholate uptake capacities. When the relative mRNA concentrations were quantified and graphed over the length of the small intestine, the resulting distribution curve matched the distribution of IBAT protein and the distribution of active bile acid transport capacities.

DISCUSSION

This investigation provides detailed information about the exact distribution pattern of sodium-dependent and sodium-independent bile acid uptake and the distribution of IBAT gene messages in the canine small intestine.

Distribution of Active Bile Acid Uptake

It has been well established that capacities for active bile acid uptake are concentrated in the terminal ileum in many vertebrates.[11,12] Measurements of the distribution of active and passive bile acid absorption have been performed in several species. In most studies, bile acid uptake rates were measured in long segments, each comprising 10% to 12% of the small intestine.[12–15] The most precise maps of bile acid transport capacities with resolution of 3% (i.e., 3 cm segments from 100 cm total length of the intestine) exist for guinea pig and hamster intestines.[16,17] In the present report, we measured taurocholate uptake in the dog small intestine at 2% resolution in the ileum and at 10% in the proximal small intestine. As in rodents, capacities for active and diffusional bile acid uptake show characteristic distribution curves in the canine ileum. However, the zone of active uptake is shorter than in rodents making up only about 25% of the small bowel. Only about half of the total uptake capacity in the ileum was found to be sodium-dependent uptake compared to approximately 85% in hamsters.[17]

Increased Passive Bile Acid Uptake

We found that sodium-independent taurocholate uptake is very high in the terminal ileum and almost

nonexistent in the jejunum in dogs. Similar increases in diffusional permeability for taurocholate in the ileum have been reported in rabbits and hamsters.[12,18] However, rodents appear to absorb bile acids in the jejunum. Aldini et al.[18] provided evidence that this observation may be explained by differences in the lipid composition of the brush-border membrane. Others found evidence of sodium-independent bile acid transport systems in the jejunum.[12,19] Dogs appear unable to absorb bile acids in the proximal small bowel. It will need to be elucidated whether this is due to a lack of sodium-independent systems that exist in other mammals.

Variations in IBAT mRNA and IBAT Protein

IBAT mRNA and protein levels varied in different segments of the terminal ileum paralleling the variation of sodium-dependent bile acid uptake rates. The jejunum and mid-small intestine showed no active sodium-dependent uptake. These findings corroborate data from studies performed in other species.[12,15] Some investigators have reported the detection of trace amounts of IBAT messenger RNA in the hamster jejunum by Northern blotting.[20] With our methodology we looked at relative changes in IBAT mRNA concentrations in dogs. We found that mRNA concentrations were low throughout the small intestine except for the terminal 50 cm. Our studies also indicate that there is no appreciable sodium-dependent uptake of bile acid in the upper small intestine proximal to a point 50 cm from the ileocecal valve. Finally, we have not detected any IBAT protein in the jejunum and mid-small bowel.

When comparing data from our uptake, mRNA, and immunohistochemistry studies, it appears that the production of IBAT to mRNA along the longitudinal axis of the intestine are closely linked. Similar correlations have been described in investigations of the ileal bile acid transporter of the rat[15] and hamster.[17] Significant IBAT activity appears confined to the terminal 50 cm of the small bowel in dogs. Peak uptake rates are found at 5 to 10 cm proximal to the ileocecal valve.

We mapped bile acid transport capacities because we intend to generate "neoileal" mucosa by transplanting ileal mucosal stem cells into the jejunum in dogs. This neomucosa should be able to absorb bile acids at high rates to serve as a functional substitute for the terminal ileum after ileectomy. Our findings suggest that the "optimal" stem cells are likely found in a small segment located 5 to 10 cm from the ileocecal valve. In addition, only stem cells from the terminal 50 cm of the small intestine would be expected to generate a mucosa capable of significant bile acid absorption. In vivo stem cell transplantation experiments will be necessary to confirm these assumptions.

CONCLUSION

We have established the exact distribution curves for sodium-dependent and sodium-independent bile acid transport capacities in the canine small intestine. Both curves follow similar patterns. Our investigations corroborate findings in other species that the distribution of IBAT mRNA, IBAT protein, and sodium-dependent bile acid uptake rates change synchronously along the axis of the small bowel. The area of highest bile acid absorption capacity and IBAT expression is located 5 to 10 cm proximal to the ileocecal valve. This location is likely the best harvest site for mucosal stem cells in experiments aimed at the generation of a "neoileum" with optimal bile acid uptake capacities. Finally, this study establishes that the areas of high bile acid uptake are characterized by an increase in the expression of IBAT in all enterocytes participating in villus formation in canines.

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Summary of "Current Status of Robotics in General Surgery"

L. William Traverso, M.D.

The invited speakers overall believed that robotics provided technical advances for operations to treat gastrointestinal diseases. This developing technology requires a close collaboration between engineers and surgeons to utilize this modern machinery, but in a way that is cost-effective for our health care system.

Currently there are but a few gastrointestinal operations where the robotic technology has allowed surgeons to provide better operations. A good example is the Heller myotomy, with the virtual elimination of esophageal perforations. The robot was designed to work through laparoscopic trocars. However, this does not mean that the advantages of this technology could not be used during open procedures. An example was the reconstruction of the tiny pancreatic duct to the jejunum during reconstruction after pancreaticoduodenectomy.

The robot offers the surgeon the following advantages: instant ambidexterity, much greater magnification than surgical loupes, reclaiming additional movement (wrist action), and the ability to tie sutures with only several inches of suture material. The down side of the technology includes the following: the lack of haptic feedback to tie sutures without breaking them (the robot is very strong and can break even a 2-0 suture with ease), the bulkiness of the equipment hinders access to the patient by the anesthesiologist, and a surgical assistant that is at the patient's side among the arms of the robot. Another limitation is that the operation must be performed in a small area of the abdomen because moving the instrument arms from the upper to the lower abdomen is currently impossible.

Therefore a good example of a great application is exemplified by the Heller myotomy—fine movement in a confined space under greater magnification with minimal chance of esophageal perforation.

Discussion from the audience following the lectures was interesting. In addition to assessing the robot as allowing a surgical procedure, it was suggested that the robot could be used to record the performance of the surgeon. The new robotic technology could be looked on as a "source of information" on surgical ability. Finally, it was noted that residents in training, although enamored of any new technology, have very little "hands-on" learning opportunity. There is only room for one surgeon at the control station. A resident's discomfort with this new technology is best exemplified by a new term. Because the surgeon is remote from the patient, the new term for the assistant is the "patient-side assistant."

Presented at the SSAT/SAGES Joint Symposium, San Francisco, California, May 22, 2002.
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Institutional Variations in the Management of Patients With Acute Appendicitis

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The purpose of this study was to evaluate institutional differences in preoperative workup, operative approach, complications, and cost in patients with acute appendicitis. A retrospective chart review was performed of all adults operated on for acute appendicitis from June 1999 to November 2000 at the University of New Mexico Hospital (UNMH) and Stanford University Medical Center (SUMC). Variables compared included age, race, sex, duration of symptoms, type of symptoms, results of radiographic evaluation, time from emergency room to operating room, operative approach (open vs. laparoscopic), operative time, length of hospital stay, pathologic findings, and complications. Statistical analysis was performed by means of Fisher's exact test. A total of 154 appendectomies were performed for acute appendicitis at UNMH and 165 at SUMC. Statistically significant differences were found at UNMH vs. SUMC in time from emergency room to operating room (9.1 hours vs. 13.7 hours; $P < 0.001$), operative approach (48% laparoscopic vs. 29% open; $P < 0.001$), and negative appendectomy rate (13% vs. 4.8%; $P < 0.001$). There were no differences in the perforation rate or other complications. Cost analysis showed that $56,744 more was spent at UNMH for the additional negative appendectomy operations, whereas $99,842 more was spent at SUMC for the additional CT scans. Institutional differences in the management of patients with acute appendicitis can result in significant differences in cost without clinically significant differences in outcome. The use of clinical examination and laparoscopy as diagnostic modalities instead of CT scanning resulted in a more cost-effective approach.
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KEY WORDS: Acute appendicitis, laparoscopy, computed tomography

Appendectomy is one of the most frequently performed surgical procedures in the United States. The lifetime incidence of acute appendicitis is 8.6% in men and 6.7% in women, whereas the lifetime risk of undergoing appendectomy is 12% for men and 23% for women.[1] Correct diagnosis of acute appendicitis remains a challenge. The paradigm of acute appendicitis has traditionally been that negative appendectomy rates and perforation rates are inversely proportional. Therefore, a negative appendectomy rate of 15% to 33% in all patient populations is acceptable in order to prevent an increase in the perforation rate.[2,3] An acceptable negative appendectomy rate can reach as high as 40% to 50% in high-risk patients, such as pregnant women, or children.[2–4] In an attempt to decrease the negative appendectomy rate of 15% to 20%, maintain a low perforation rate of less than 10%,[2,3,5] and to better utilize hospital resources, numerous investigators have recommended the use of computed tomography (CT) scanning in patients with suspected appendicitis.[4,6,7] The exact role of CT scans is still highly debated. Some institutions use them routinely without an algorithm.[6,8] Several investigators recommend the use of CT scans only in patients with an atypical presentation,[2,4,9–11] whereas others still rely primarily on clinical diagnosis with the aid of diagnostic laparoscopy in selected patient populations.[4,12,13] This study explores how evaluation of patients with acute appendicitis differs at two university tertiary care centers. One institution performs CT scanning routinely in patients with suspected acute appendicitis, whereas the other rarely obtains routine CT scans. The study was performed to compare the outcomes and cost-effectiveness of these institutional differences in the management of patients with acute appendicitis.

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METHODS

A retrospective review of all patients undergoing appendectomy for presumed appendicitis at the University of New Mexico Hospital (UNMH) and Stanford University Medical Center (SUMC) from June 1, 1999 to November 30, 2000 was performed. The study included only patients with the presumptive diagnosis of acute appendicitis who were taken to the operating room. Patients who underwent incidental appendectomy were excluded from the study. At UNMH 154 patients were identified, whereas at SUMC 165 patients were identified. All charts were reviewed. Variables extracted included preoperative, operative, postoperative, and financial data. Preoperative data encompassed symptoms (nausea, vomiting, chills, diarrhea, and anorexia), temperature, leukocyte count, radiographic studies (CT scanning or ultrasonography), and demographics (age, ethnicity, sex). Operative data included time from emergency room to operating room, operative time, anesthesia time, and type of surgery. Postoperative data examined included length of hospital stay, pathologic findings, and complications. Finally, costs of preoperative radiographic evaluations and operative costs were obtained. Data from UNMH and SUMC were compared and analyzed by means of Fisher's exact test. A P value of less than 0.05 was considered statistically significant.

All CT scans were obtained with a helical CT scanner at 8 mm intervals. At SUMC, a single breathhold helical scan was obtained from the top of the T12 vertebral body to the pubic symphysis. No patients received contrast medium rectally. Most of the patients received intravenous contrast medium. At UNMC all patients received rectal, oral, and intravenous contrast medium and were scanned from lung bases to femoral neck. A resident or fellow read the scans at both institutions initially. For this study the final reading by the attending radiologist was used for data analysis.

RESULTS

Preoperative Data

Statistically significant differences between UNMH and SUMC were found in the incidence of preoperative vomiting, leukocyte count, age, and ethnicity (Tables 1 and 2). The statistical differences found for vomiting, white blood cell count, and age were not thought to be clinically significant.

The false positive rate for CT scans at SUMC was 2% and the false negative rate was 7%. One patient in this group suffered a perforated appendix before the operation. At UNMH, out of eight CT scans there was one false positive and one false negative scan, resulting in a rate of 12.5% for each. As far as can be determined by chart review, there were no CT scans that were initially interpreted as negative that were subsequently definitively read the next day as suggestive of appendicitis.

Table 1. Comparison of UNMH and SUMC data

	UNMH	SUMC	*P* value
Age (yr)	31.8	38.7	<0.001
Sex	53% female	47% female	NS
Vomiting	59%	38%	<0.001
Nausea	51%	62%	NS
Diarrhea	10%	11%	NS
Chills	23%	17%	NS
Anorexia	31%	40%	NS
Temperature	37.2° C	37.4° C	NS
White blood cells	15,000	13,600	<0.03
Ultrasound	2.6%	13.9%	<0.05
CT scan	5.2%	61.8%	<0.001
Emergency room to operating room time (hr)	9.1	13.7	<0.001
Laparoscopic appendectomy	48%	29%	<0.001
Operative time (min)	56.5	55.4	NS
Anesthesia time (min)	105	90	<0.001
Negative appendectomy rate	13%	4.8%	<0.01
Perforation rate	15.7%	16.2%	NS
Length of stay (day)	2.49	2.34	NS
Complications (overall)	18.8%	14.5%	NS
Abscesses	4.5%	4.8%	NS
Wound infections	2.6%	1.2%	NS

NS = not significant.

Operative Data

Statistically significant differences between UNMH and SUMC were found for all variables except operative times with longer anesthesia times, shorter time from emergency room to operating room, and a higher incidence of laparoscopic appendectomies at UNMH (see Table 1).

Postoperative Data

The negative appendectomy rate was significantly higher at UNMH (13% vs. 4.8%; $P = 0.001$), although perforation rates were similar at the two institutions (see Table 1). There were no differences in complication, abscess, or wound infection rates between the two institutions. Of the 20 negative appendectomies at UNMH, 11 were laparoscopic and nine were open operations. Other types of pathologic

Table 2. Ethnic distributions

	African-American (%)	Caucasian (%)	Hispanic (%)	Native American (%)	Asian (%)	Other (%)
UNMH	3.25	26	51.3	6.5	3.9	9.1
SUMC	2.4	69.7	12.1	0	13.9	1.8

conditions were diagnosed in seven patients with pathologically normal appendices. These included ruptured endometrioma in two patients and inflamed Meckel's diverticulum, ruptured ovarian cyst, tuboovarian abscess, small bowel obstruction, and diverticulitis in one patient each. Among these seven patients, three underwent open operations, three had laparoscopic surgery, and one patient with a bowel obstruction required conversion to an open procedure. Of the eight patients with negative appendectomies at SUMC, five had open operations and three had laparoscopic appendectomies. In only one patient was other pathology demonstrated. An enlarged ovary was found in one patient who underwent open appendectomy and ovarian biopsy. CT scans were obtained preoperatively in four of the eight patients with negative appendectomies. The CT scans were read as follows: appendicitis in one patient, early appendicitis with a fecalith in one, appendolith-only in one, and negative for appendicitis in the last patient. No complications were noted in any of the patients with negative appendectomies at UNMH. At SUMC the patient with a bowel obstruction had an enterotomy intraoperatively.

Cost Analysis

At SUMC the cost of a CT scan of the abdomen or pelvis was $1763 including professional fees. Out of 100 patients, an additional 56.63 patients had a CT scan at SUMC compared to those at UNMH (61.8% vs. 5.2%). The additional patients (56.6) multiplied by the cost of the CT scan ($1763) resulted in an additional $99,842 per 100 patients spent at SUMC compared to UNMH because of the increased number of CT scans obtained. In many patients both abdominal and pelvic CT scans were obtained, leading to even higher costs.

Determining the cost differential at UNMH caused by the increased number of patients who underwent surgery for a negative appendix was more difficult. Several assumptions were made. First, it was decided to assume that all of the additional negative appendectomy patients underwent laparoscopic appendectomy. This would result in a higher cost estimate as it was thought that the direct costs associated with a laparoscopic appendectomy would be greater than those incurred with an open approach.[13–16] This was thought to be a reasonable assumption, given that significantly more laparoscopic appendectomies were performed at UNMH. The costs of all laparoscopic appendectomies at UNMH were averaged, resulting in an estimated cost of $6920 per patient. Among 100 patients, 8.2 more negative appendectomies were performed at UNMH compared to SUMC (13 vs. 4.8). The additional patients (7.5) multiplied by the average cost of a negative appendectomy ($6920) resulted in $56,744 per 100 patients spent at UNMH because of the additional patients who had an operation for a negative appendix.

DISCUSSION

Many studies have searched for a more cost-effective way to diagnose and treat acute appendicitis. The goal is to increase diagnostic accuracy without increasing perforation rates.[1–3] In 1998 Rao et al.[6] reported that the use of CT scans in patients with possible acute appendicitis results in a high accuracy rate (98%) and a lower negative appendectomy rate (20% vs. 7%) in comparison to patients who do not undergo CT scanning, thus demonstrating better utilization of hospital resources. The authors concluded that "routine appendiceal CT scanning performed in patients who have suspected appendicitis improves patient care and reduces the use of hospital resources." In their study, routine CT scanning decreased cost both by decreasing the negative appendectomy rate and decreasing the number of admissions for observation. Since the publication of that seminal article, many hospitals have incorporated CT scans into their diagnostic workup of patients with abdominal pain.[2,4,12,17] Some investigators have advocated routine screening with CT scans of this patient population,[6,8] whereas others have recommended more judicious use of CT scans, following algorithms that select patients with atypical presentations who are more likely to benefit from additional diagnostic workup.[2,4,9–11] Increased use of CT scans can lead to a decreased negative appendix rate with improved diagnostic accuracy without an increase in the perforation rate, but with an increase in cost.

Many investigators believe that, at present, CT scanning is overutilized—that is, part of an increasing trend toward including complex diagnostic tests in the evaluation of patients with possible acute appendicitis.[2,7,9,12,17,18] In several recent studies,

Weyant et al.,[2] Lee et al.,[4] Jones,[12] and McDonald et al.[17] found that the use of CT scans at their institutions increased from 10% to 25% up to 60% to 70% following publication of an article by Rao et al.[8] This increase in the use of CT scans resulted in either no improvement in accuracy or perforation rates[2] or else in a decrease in effectiveness from 32% to 10%.[17] The authors concluded that in patients with a clinical suspicion of acute appendicitis, CT scanning does not improve diagnostic accuracy.[4,10]

The overuse of CT scans can lead to a number of problems, including increased time from emergency room to operating room, as was found in the present study. Lee et al.[4] and McDonald et al.[17] found that patients undergoing preoperative CT scanning took 2.6 to 5.4 hours longer to get from the emergency room to the operating room, whereas we found an increased time of 4.6 hours. This longer stay in the emergency room can actually have a negative impact on utilization of hospital resources and money, challenging the findings of Rao et al.[6,8] of an improvement in hospital resources.

The use of CT scans only in equivocal patients can aid in the diagnosis of acute appendicitis, but it is not without its risks and cost. Risks of CT include radiation exposure, false positive examination results leading to unnecessary surgery, and false negative results delaying surgery. The radiation dose per scan is four times that of an abdominal radiograph and nearly 100 times that of a standard chest x-ray examination.[19] Mettler et al.[20] concluded that although CT constitutes 11% of the total studies performed in the radiology department, it accounts for 67% of the total radiation dose. These recent data have produced enough concern that the FDA is currently investigating the unnecessary use of CT scans. The false positive and false negative rates of CT scanning at SUMC of 7% and 2%, respectively, are similar to the reported rates in the literature. Of concern is the patient who had a false negative scan and subsequently had a perforated appendix. Surgery was delayed 12 hours in this patient. Although the overall perforation rates were similar at both centers, missed appendicitis on CT scans should remain a concern. The false positive and false negative CT scan rates at UNMH were higher than those seen at SUMC but were still similar to reported rates. The higher rates are probably not clinically significant and reflect the low numbers of scans performed.

The present study found significant institutional variation in the management of patients with acute appendicitis. AT SUMC more than 60% of patients underwent CT scanning while being evaluated in the emergency room without a patient care algorithm. Typically these were requested before the surgeon was asked to evaluate the patient. Theoretically there could have been numerous patients in this group who, according to the clinical signs and symptoms, clearly had acute appendicitis and therefore did not need CT scans, as has been argued by Safran et al.[18] At SUMC more discriminate use of CT scans could have led to increased cost savings. In actuality, the estimated increased cost probably underestimates the true unnecessary costs, as we did not include the additional costs of patients who underwent ultrasound imaging or patients who had both abdominal and pelvic CT scans.

In comparison, at UNMH, the diagnosis of acute appendicitis was made almost exclusively on the basis of clinical findings. Laparoscopic appendectomy was used more liberally, possibly as a diagnostic tool. The increased use of a laparoscopic approach is probably responsible for the increased anesthesia time at UNMH, as setup times for laparoscopy are typically longer than for open appendectomy. There have been numerous studies investigating the role of diagnostic laparoscopy in suspected acute appendicitis.[4–16,21–23] The consensus is that diagnostic laparoscopy is safe and effective for diagnosing appendicitis as well as other pathologic conditions of the abdomen or pelvis when present. Several investigators strongly recommend diagnostic laparoscopy for all patients with possible acute appendicitis to help improve accuracy, as the rate of an unestablished diagnosis decreases with laparoscopy.[4,13] In the present study we found a decreased incidence of patients with an unestablished diagnosis in the laparoscopic group vs. the open group at both UNMH and SUMC.

Several investigators have found that the negative appendix rate is higher with increased use of laparoscopic appendectomy,[4,5,14,16] as was found in the present study. Some investigators believe this may be due to the controversy regarding whether to remove a grossly normal appendix at laparoscopy.[12,13,24] A different explanation may be that surgeons may be more liberal in their indications for laparoscopic surgery.[16] The negative appendix rate in the present study of 12.4% is within the low range of acceptable limits. It was accompanied by no increase in perforation rate. Despite the increased cost of a laparoscopic appendectomy for a negative appendectomy in this study, clinical diagnosis and judicious use of laparoscopic appendectomy lead to a more cost-effective management of patients with suspected acute appendicitis without an increase in negative patient outcomes. This finding was based on an examination of direct costs only. Examining indirect costs associated with time lost from work may have resulted in even higher cost savings at UNMH compared to SUMC.[13,15]

A negative appendectomy rate within acceptable limits is a critical component of using clinical examination and laparoscopy as diagnostic tools. In addition, there must be no increased morbidity associated with a negative appendectomy. The possibility of a negative appendectomy is discussed with all patients preoperatively. A finding of a negative appendectomy is discussed with patients postoperatively. No patients have indicated any concerns about "unnecessary surgery."

There are several limitations to this retrospective study. We did not gather data on patients who underwent CT scanning in the emergency room and were discharged home. Given the low negative appendectomy rate of 4.3%, these patients may have gone elsewhere for their appendectomies 24 to 36 hours after initial evaluation, or there could have been a potential saving here in terms of patients who might have required admission for observation. In a recent review article by Jones,[12] data were introduced suggesting that active observation of patients with suspected appendicitis could result in negative appendectomy rates in the range of 3% to 10% without increasing the perforation rates. Given the increased time that patients who undergo CT scanning spend in the emergency room, one could question whether frequent reexamination alone would have decreased the negative appendectomy rates and the need for hospital admission for observation. Further studies could include these data.

Another limitation is that we do not know whether laparoscopy was used diagnostically at UNMH. Patients in whom diagnostic laparoscopies were done for presumed appendicitis where the appendix was grossly normal and was not removed would not have been identified with the screening parameters used in this study.

A final limitation is the inherent problems in the nature of this study. Differences in cost-effectiveness could have been due, in part, to institutional differences in cost, charges, and resources. For example, SUMC has access to two rapid CT scanners immediately adjacent to the emergency room, and there are fewer than 1000 trauma admissions per year. UNMH has only one CT scanner, which is near the department of radiology rather than near the emergency room, and they process more than 3000 trauma admissions each year. Also, the general surgeons who take consult call at UNMH do not subspecialize, and thus all of them perform basic laparoscopy. In contrast, at SUMC more surgeons subspecialize and many surgeons, such as the surgeons with a predominant practice of breast diseases, do not perform basic laparoscopy. We expect that this is partially responsible for the increased percentage of open appendectomies at SUMC compared to UNMH.

Many investigators have suggested more directed use of CT scans in the evaluation of patients with possible acute appendicitis.[2,4,7,9,11,17,18] The present study supports that suggestion. Patients with clear clinical signs of appendicitis should be evaluated by a surgeon and taken to the operating room.[4,13,18] Patients with equivocal signs should undergo observation, CT scanning, or laparoscopy depending on presentation, results of surgeon evaluation, and surgeon preference. This study cannot comment on which of those therapies is best suited to patients with atypical findings.

CONCLUSION

Preoperative radiographic evaluation, specifically CT scanning, can significantly reduce the negative appendectomy rate, but at a higher cost. Alternatively, accurate clinical evaluation combined with diagnostic laparoscopy and laparoscopic appendectomy can be used to determine and treat acute appendicitis in a cost-effective manner without an increase in perforation rates and with an acceptable negative appendectomy rate.

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Reduction in Serum Pepsinogen I After Roux-en-Y Gastric Bypass

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The excluded stomach after Roux-en-Y gastric bypass (RYGBP) cannot be readily examined by endoscopy for obvious anatomic reasons. Thus it is difficult to monitor possible changes in the gastric mucosa. However, the type and severity of gastritis can now be assessed by a combination of serologic tests: pepsinogen I and antibodies to *Helicobacter pylori* and H,K-ATPase. Morbidly obese patients were examined before and 1 to 4 years after surgery. A group of 34 patients (mean age 39 years, BMI 44 kg/m^2) underwent RYGBP; another group of 30 patients (mean age 42 years, BMI 44 kg/m^2) had simple gastric restriction and served as control subjects. All patients, except one in the control group, had normal titers of pepsinogen I before surgery. One year after RYGBP, pepsinogen I levels were significantly reduced, as compared to the control group ($P < 0.0001$), and remained low throughout the study. The control group had stable pepsinogen I levels. In both groups, few patients had increased titers of *H. pylori* or H,K-ATPase antibodies, but these abnormalities remained unchanged. Low pepsinogen I levels, similar to those we observed in our RYGBP patients, have been linked to chronic atrophic gastritis. However, the absence of food stimulation in the excluded stomach could also be a reason for the low pepsinogen I levels. (J GASTROINTEST SURG 2003;7:529–535) © 2003 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Pepsinogen, gastric bypass, gastritis, morbid obesity, *H. pylori*

Roux-en-Y gastric bypass (RYGBP) is a standard surgical treatment for morbid obesity[1,2] (body mass index [BMI] >40 kg/m^2) and is increasing in popularity worldwide, mainly because of its laparoscopic feasibility. One problem with RYGBP is that the procedure leaves the main portion of the stomach and the entire duodenum excluded from the normal passage of food. The excluded stomach is difficult to examine by endoscopy or barium studies; hence a delay in diagnosis of serious gastric disease may result. Moreover, the state of the gastric mucosa and the possible development of different types of gastritis cannot be directly assessed by repeat biopsies. Several previous reports have been published on abnormalities in the bypassed segment (i.e., chronic gastritis,[3] development of intestinal metaplasia,[4] bleeding or perforated ulcers,[5,6] and two cases of gastric carcinoma).[7,8] Most patients undergoing obesity surgery are young, and their life expectancy is long as a result of the weight reduction and the improvement in comorbidity achieved with this surgery. Therefore the reports on chronic gastritis must be taken seriously because gastric epithelial changes can develop slowly and proceed unnoticed in the excluded stomach.

The state of the gastric mucosa can now be assessed without endoscopic biopsy using serologic analysis of pepsinogen I (PGI) in combination with determination of antibodies to *Helicobacter pylori* and H, K-ATPase.[9–12] The aim of the present study was to evaluate the mucosa in the excluded stomach by means of serologic testing. Our principal finding

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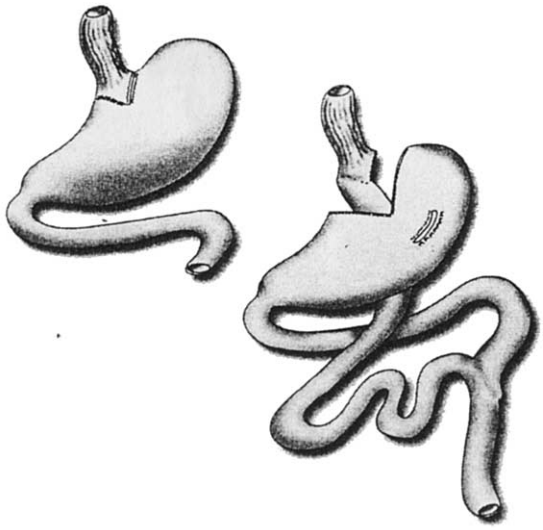

Fig. 1. The principle of Roux-en-Y gastric bypass. The main stomach and duodenum are excluded from the passage of food and not easily accessible for endoscopy. The gastric mucosa is difficult to evaluate, and a delay in the diagnosis of serious disease may result. (Courtesy of WB Saunders.)

was a significant decrease in PGI levels in patients undergoing RYGBP.

MATERIAL AND METHODS

Patients

Between 1992 and 1997, a total of 177 patients underwent first-time surgical treatment for morbid obesity at our center. All patients were recommended for a follow-up program in the Metabolic Unit of the University Hospital, which also included collection of serum samples before and yearly after surgery. For this study we selected 64 patients who had participated regularly in the follow-up program; informed consent was obtained from all of them. The study was approved by the local Ethics Committee of the Medical Faculty at the Uppsala University, and was carried out in accordance with the Declaration of Helsinki. Each patient allowed us to review their medical history and to use stored sera for this study.

Roux-en-Y Gastric Bypass

The RYGBP group included 34 patients (5 men and 29 women) who had a mean age of 39 years (range 23 to 56 years) and mean BMI of 44 kg/m^2 (range 35 to 68 kg/m^2). Gastric bypass was performed by either laparoscopic or open technique. The main portion of the stomach was excluded by transection, and a proximal small pouch (3 × 4 cm) was created. Care was taken to preserve the nerves and vessels near the lesser curvature. The pouch was anastomosed to a 50 to 70 cm retrogastric, retrocolic Roux limb (Fig. 1). All procedures were performed or supervised by one of us (S.G.).

During the study three patients developed stomal ulcers, all within the first 6 months, and were treated with proton pump inhibitors on a long-term basis. Because of epigastric pain, five additional patients were treated with proton pump inhibitors for short periods, three without previous gastroscopy. Five patients requested surgical attention; three were treated conservatively because of suspected small bowel obstruction and two underwent cholecystectomy. The remaining patients reported no disturbing gastrointestinal symptoms except for "dumping" symptoms when overeating. Almost all patients were given vitamin B_{12} supplements. Weight reduction after RYGBP is presented in Table 1.

Control Subjects

The control group consisted of 30 patients (7 men and 23 women) who had a mean age of 42 years (range 29 to 51 years) and mean BMI of 44 kg/m^2 (range 34 to 66 kg/m^2). They underwent a gastric restrictive procedure. Twenty patients were operated on with adjustable gastric banding using the ObTech

Table 1. Body mass index at the study intervals

	RYGBP				Controls			
	Mean	SD	(Range)	n	Mean	SD	(Range)	n
Preop	44	7	(35–68)	34	44	8	(34–66)	22
Year 1	30	6	(21–45)	34	32	6	(25–46)	30
Year 2	30	6	(22–43)	34	34	5	(25–42)	24
Year 3	32	6	(22–44)	30	33	5	(23–42)	25
Year 4	32	6	(21–44)	18	34	7	(22–41)	25

Body mass index (BMI) (in kg/m^2), before and 1 to 4 years after surgery for morbid obesity. Note that patient selection factors probably influenced the interpretation of weight results in the control group.
SD = Standard deviation.

band (Ethicon Endo-Surgery, Cinncinnati, OH). The band was always placed around the upper part of the stomach, and the anatomy of the stomach remained intact. Ten patients were treated by vertical banded gastroplasty (VBG), where a narrow channel was created along the lesser curvature and a strip of Marlex mesh reinforced the outlet. None of the patients in the control group underwent additional bariatric surgery during the study. Thus normal passage of food was maintained through the stomach and duodenum in all patients.

During the study 16 patients were treated with proton pump inhibitors because of esophagitis, which was confirmed by endoscopy. One patient had a biopsy-confirmed Barrett's esophagus and two patients had megaesophagus. No vitamin B_{12} supplementation was given regularly.

Serum Analysis

Serum was obtained before and 1 to 4 years after surgery, and was kept at −70ºC. All serum samples were obtained after an overnight fast. Assay of serum PGI levels was carried out using Gastroset PGI (Orion Diagnostica, Espoo, Finland) according to the manufacturer's instructions. Antigens of *H. pylori* and H,K-ATPase were prepared as previously described.[9] In-house enzyme-linked immunosorbent assay was used to analyze each serum sample in duplicate. All analyses were carried out in the same run in one laboratory.

Statistical Analysis

We calculated the change in PGI for each person by subtracting the actual value from the preoperative value. The primary end-point variables were the changes in PGI levels from year 0 (preoperative) to year 1, year 2, year 3, and year 4, respectively. The groups were compared with regard to their mean changes in PGI with a linear model, with adjustment for the baseline value (year 0). To evaluate whether differences in background factors could explain the differences between groups, further adjustments were made for age, sex, BMI, proton pump inhibitor treatment, smoking, and status of *H. pylori* and H,K-ATPase. The results are all presented as mean, standard deviation, and range unless otherwise stated. Also, in the RYGBP group, univariate and multivariate associations between changes in PGI from year 0 to year 1, along with age, sex, BMI, proton pump inhibitor treatment, smoking, and status of *H. pylori* and H,K-ATPase were evaluated. In one patient in the control group, PGI was 270.6 μg/L, which is well outside three standard deviations from the mean (9.4 standard deviations above the mean). This observation was considered an "outlier" and was therefore excluded from the main statistical analysis, giving the material a normal distribution. Crude comparisons between groups were also made using a nonparametric test when this observation was included, and this did not alter the results.

RESULTS

Serum Pepsinogen I

Before surgery, PGI levels were 69.3 μg/L (range 35.8 to 141.5) and 65.1 μg/L (range 36.9 to 107.5) in the RYGBP and control groups, respectively; the difference was not statistically significant. The patients had values within the reference range for our laboratory (i.e., between 28 and 158 μg/L). One year postoperatively, all RYGBP patients except one had developed a reduced PGI titer (Fig. 2). In addition, eight patients (24%) showed abnormally low values (i.e., below 28 μg/L). The mean PGI value was reduced to 50.6 μg/L (range 20.6 to 108.2). The reduction was 18.7 μg/L at 1 year and remained at similar levels (12.8, 16.6, and 12.5) throughout the study (Table 2).

In the control group the mean PGI at 1 year was 61.4 μg/L (range 30.5 to 114.9), showing a reduction of 3.7 μg/L, but no clear pattern was seen among the individual patients (Fig. 3). The difference between the reduction in PGI (−18.7 μg/L vs. −3.7 μg/L) was statistically significant ($P < 0.0001$). After adjustments for age, sex, BMI, protein pump inhibitor treatment, smoking, and status of *H. pylori* and H,K-ATPase, the difference remained ($P < 0.0001$).

One to 4 years postoperatively, the change in mean PGI for the RYGBP patients was highly significant and constantly lower as compared to the control subjects (see Table 2). The decrease in PGI in the RYGBP patients did not significantly correlate with age, sex, BMI, proton pump inhibitor treatment, smoking, and status of *H. pylori* or H,K-ATPase. The change in PGI during the study is summarized in Fig. 4.

Helicobacter pylori Antibodies

Before surgery, increased titers of *H. pylori* antibodies (>5 units) were seen in three and six patients in the RYGBP and control groups, respectively, which was not significantly different. The values remained almost identical during the study, and no additional patients developed abnormal titers. PGI levels did not differ significantly between *H. pylori*–positive and *H. pylori*–negative patients.

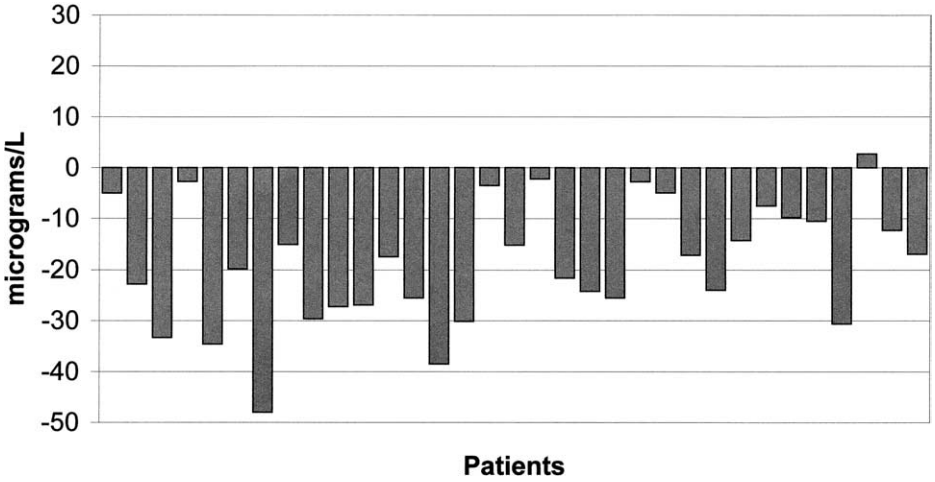

Fig. 2. Changes in serum pepsinogen I levels 1 year postoperatively for each RYGBP patient. All patients except one had decreased levels. In addition, eight patients had values below the reference level.

H,K-ATPase Antibodies

Before surgery, increased titers of H,K-ATPase antibodies (>10 units) were seen in six patients in each group, and the titers remained at the same level throughout the study. No additional patients developed abnormal values.

DISCUSSION

Our main finding was that gastric bypass, in contrast to simple gastric restriction, was followed by a distinct change in one of the three analytes—that is, serum PGI was significantly reduced. The low PGI level was established as early as 1 year postoperatively and remained unchanged for several years. In contrast, only a few patients had abnormal titers for *H. pylori* or H,K-ATPase antibodies, and these parameters did not change significantly over time. No correlation could be found between changes in PGI levels and *H. pylori* or H,K-ATPase.

Pepsinogen is produced in the human gastric mucosa as an inactive precursor of the protein digestive enzyme pepsin (for a review, see Gritti et al.[13]). The synthesis, storage, and secretion are regulated by feedback systems. Pepsinogen is secreted into the gastric lumen as a result of physiologic stimuli, such as food ingestion, and is converted by hydrochloric acid into active pepsin. A small amount of pepsinogen leaks into the blood and can be measured as a marker of peptic secretion and the state of the gastric mucosa.

Pepsinogens are divided into two major groups, PGI and PGII, both of which are produced in the main cells of the gastric corpus and fundus. PGII is also produced by cardiac and pyloric gland cells, the Brunner's glands in the duodenum, and the prostate gland. It has been shown that the serum PGI level is an indicator of the histologic state of the gastric mucosa.[14] High levels are associated with mucosal inflammation: superficial gastritis or *H. pylori* infection. PGI decreases after successful eradication of *H. pylori*.[15] High PGI levels can also be considered a sign of duodenal ulcers.[9,16] Obviously, none of the patients in either the RYGBP group or the control group developed mucosal changes characterized by acute superficial gastritis.

Table 2. Postoperative changes in serum pepsinogen I levels

	RYGBP				Controls				
	Mean	SD	(Range)	n	Mean	SD	(Range)	n	*P* value
Year 1	−18.7	14	(−48.0 to 2.7)	34	−3.7	14	(−40.1 to 23.3)	30	<0.0001
Year 2	−12.8	15	(−43.6 to 18.5)	29	4.9	12	(−14.5 to 21.5)	9	0.0035
Year 3	−16.6	15	(−46.6 to 17.9)	28	−1.4	25	(−76.7 to 29.4)	19	0.0211
Year 4	−12.5	16	(−40.9 to 17.3)	15	4.3	18	(−26.8 to 32.6)	21	0.0099

Changes in pepsinogen I levels (in μg/L) calculated for each patient at 1 to 4 years postoperatively.
SD = Standard deviation.

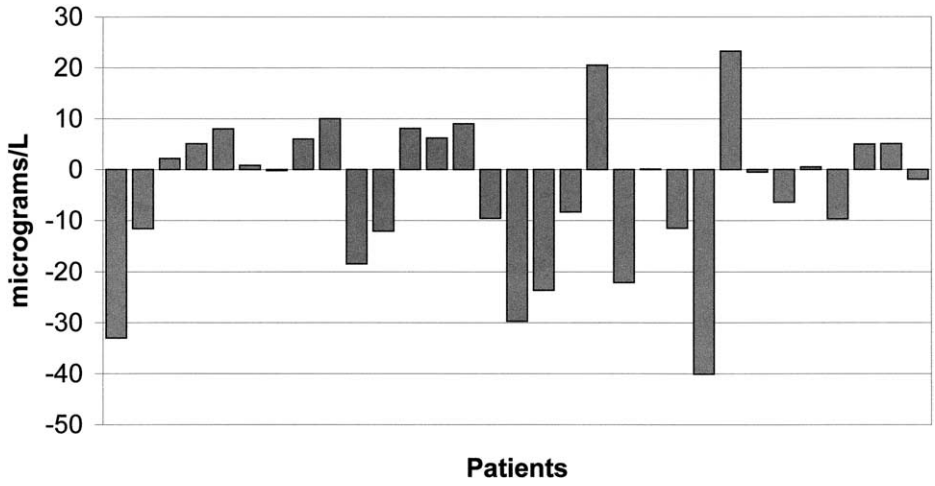

Fig. 3. Changes in serum pepsinogen I levels 1 year postoperatively for each patient in the control group. No obvious pattern was observed.

PGI disappears after total gastrectomy and is low or even absent in pernicious anemia[9,17] due to the severe atrophy of the mucosa secondary to autoimmune mechanisms. However, the low PGI levels in our RYGBP patients do not seem to be correlated with immunologic gastritis inasmuch as the H,K-ATPase titers remained unchanged. Chronic gastritis, intestinal metaplasia, and gastric carcinoma are all characterized by low levels of PGI.[18] In Japan measurements of serum pepsinogen have been used as a screening test to detect persons with extensive atrophic gastritis, who have a high risk of developing gastric cancer.[19,20] The accuracy is as reliable as routine photofluorography,[21] which carries the risks associated with x-ray exposure, and some even believe that small or flat lesions can be detected more accurately.[22] The pepsinogen method has many advantages including its suitability for combination with other screening methods; in addition, it is simple to perform and inexpensive.[22]

Nowadays *H. pylori* is proposed to be the main cause of chronic gastritis, duodenal ulcers, MALT lymphoma, and gastric carcinoma.[23–25] None of our nine *H. pylori*–positive patients showed serologic evidence of spontaneous cure from the infection. Moreover, no additional patients were infected during the 4-year period. Unfortunately our sample is too small and the observation time too short to determine whether patients with gastric and duodenal bypass, for example after RYGBP, are protected against *H. pylori* infection.

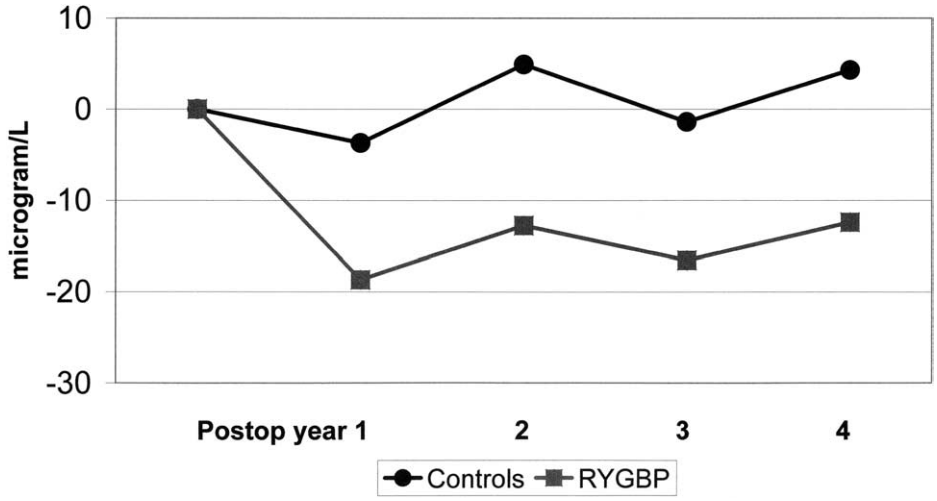

Fig. 4. Changes in mean serum pepsinogen I levels 1 to 4 years after RYGBP or gastric restriction (control group). The decrease in pepsinogen levels for the RYGBP patients was highly significant compared to the control group ($P < 0.0001$). This decrease occurred as early as 1 year postoperatively and was persistent throughout the study.

The parietal cell autoantibody (H,K-ATPase antibody) is related to autoimmune atrophic gastritis and several other autoimmune diseases, for example, thyroiditis and insulin-dependent diabetes mellitus.[26] Inflamed gastric mucosa of the fundus and corpus region can lead to an increased titer of H,K-ATPase antibodies. Our data suggest that none of the patients developed gastritis of this type in the excluded stomach after gastric bypass because the H,K-ATPase antibody levels remained unchanged.

It is well known from prospective, randomized studies that gastric bypass is followed by a better weight result in comparison with simple gastric restriction. In our study at least two selection mechanisms may have introduced bias in the proper evaluation of the weight reduction induced by the two surgical principles. First, only patients who complied with our follow-up program were available for inclusion. Second, patients with poor weight loss after gastric restriction were usually converted to gastric bypass and therefore were not included in the present study.

How can the low PGI values found in our RYGBP patients be interpreted, and what are the implications for patients who have had or are thinking of undergoing a gastric bypass? We have two explanations for the low PGI levels. First, it is possible that the environment in the excluded stomach favors development of chronic atrophic gastritis. Theoretically such epithelial changes could have premalignant potential, similar to the situation in the gastric remnant after subtotal Billroth II gastrectomy where an increased risk for adenocarcinoma has been proposed.[27] The question remains whether atrophic gastritis in this setting leads to malignancy. However, if future studies prove that such a relationship exists, an increased awareness of the state of the gastric mucosa and readiness for invasive investigation would be warranted for the safety of patients undergoing RYGBP.

Second, the absence of food stimulation in the excluded stomach and duodenum contributes to a substantial change in upper gastrointestinal physiology. The normal regulatory system is affected, and this could set the mucosa in the excluded stomach in a resting state. Pepsinogen secretion is reduced in hibernating animals, after vagotomy, and with diminished blood supply.[13] The fact that the PGI values are fully reduced as early as 1 year after RYGBP strengthens this interpretation, whereas a dysplastic process would be expected to demonstrate a more progressive year-by-year pattern. Even if we believe that mucosal inactivity is responsible for the reduction in PGI, we cannot exclude the possibility of genuine atrophy; hence the environment in the excluded stomach should be studied further.

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Benign Nonampullary Duodenal Neoplasms

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Benign duodenal neoplasms (BDNs) are uncommon, and their optimal management remains undefined. We analyzed all cases of BDN treated at our institution during a 10-year period (January 1990 through January 2000). Data are expressed as median (range). Sixty-two patients were treated for BDNs. The results of histologic examination of their lesions were as follows: 36 adenomas, eight Brunner's gland tumors, 10 inflammatory polyps, two hamartomas, and six others. Forty-seven patients were treated nonoperatively, and 15 patients underwent surgery. Lesion characteristics leading to surgical intervention included large polyp diameter and submucosal penetration detected on endoscopic ultrasound imaging. There were no treatment-related deaths. Major morbidity occurred in 2% of patients who underwent endoscopic resection and in 33% of patients who underwent surgery ($P = 0.002$). Among patients treated for adenomas, seven (19.4%) had a recurrence at a median of 12 (4 to 48) months. Most BDNs can be managed with minimal morbidity using endoscopic techniques. Systematic follow-up of patients treated for adenomas is required. (J GASTROINTEST SURG 2003;7:536–541.) © 2003 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Benign duodenal neoplasms

The first reported series of benign duodenal neoplasms (BDNs) was published in 1917.[1] Our institution's interest in BDNs originated with the report by Botsford and Seibel,[2] of the Peter Bent Brigham Hospital, who in 1947 wrote, "the diagnosis of the lesions is usually obscure, and until the physician entertains the possibility, it will remain obscure." For the subsequent 25 years, only symptomatic lesions were detected, and their treatment was limited to surgical excision.[2–9] With advances in endoscopic techniques during the 1970s, asymptomatic BDNs began to be detected and endoscopic resection became a viable treatment modality.[10–13]

BDNs are uncommon; their prevalence during routine esophagoduodenoscopy (EGD) was reported in one prospective series to range from 0.3% to 4.6%.[14] Further, published data on these lesions have been limited to case reports or small case series.[15–27] As a result, their natural history is poorly understood, and optimal management algorithms have not been defined. Therefore the purpose of this study was to analyze the entire spectrum of patients with BDNs, excluding ampullary neoplasms, treated at our center during the past decade in order to make rational management recommendations. This study represents the largest single-center experience with BDNs yet reported.

PATIENTS AND METHODS

We reviewed the medical charts and computerized medical records of all patients diagnosed as having benign small bowel neoplasms at Brigham and Women's Hospital from January 1, 1990 through January 1, 2000. The protocol was approved by the Brigham and Women's Hospital committee for the protection of human subjects.

Subsequent analysis was confined to inpatients and outpatients with the International Classification

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of Disease-9 (ICD-9) code for benign neoplasms of the duodenum (code 211.2) (excluding ampullary lesions [polyps involving the ampulla of Vater identified endoscopically] and gastrointestinal stromal tumors [as these lesions have malignant potential]) using a computer-assisted hospitalization analysis for the study of efficacy (CHASE) management system.

The hospital records of these patients were reviewed for demographic data as well as for the following information: (1) medical history (familial adenomatous polyposis); (2) results of diagnostic tests (upper gastrointestinal series, EGD, computed tomography (CT), and endoscopic ultrasound imaging (EUS); (3) histologic findings, polyp size (estimated endoscopically), and location (first, second, or third portion of the duodenum); (4) surgical (polypectomy, segmental resection, pancreaticoduodenectomy) or endoscopic management; and (5) treatment-related outcomes.

Statistical Analysis

Comparison of continuous variables between two groups was performed using the Wilcoxon matched-pairs test. Comparison of continuous variables between more than two groups was performed using the Tukey HSD analysis of variance. Categorical data were compared using Fisher's exact test. A two-tailed P value of 0.05 or less was considered statistically significant. Data are expressed as median (range).

RESULTS

Patient Demographics

This series contained 62 patients with BDNs. The median age of these patients was 62 (24 to 92) years. There were 33 male patients (53%), and five patients (8%) had a history of familial adenomatous polyposis.

Clinical Presentation

Symptoms prompting evaluation that led to the diagnosis of BDN consisted of abdominal pain in nine patients (15%) and upper gastrointestinal bleeding in 10 (17%). The majority of the patients in the study were asymptomatic, and their BDNs were detected as incidental findings.

Lesion Characteristics

The median diameter of all BDNs in this study was 10 (2 to 150) mm. The diameter of the lesions was less than 10 mm in 32 patients, between 11 and 20 mm in 10 patients, between 21 and 30 mm in nine patients, and greater than 31 mm in 11 patients. Twenty-four patients had polyps located in the first portion of the duodenum, 26 in the second portion, and 12 in the third portion.

There were 36 patients with adenomas, eight with Brunner's gland tumors, 10 with inflammatory polyps, and two with hamartomas. One patient each had one of the following lesions: lipoma, leiomyoma, ectopic pancreatic tissue, lymphangioma, carcinoid tumor, and neurofibroma. Adenomas were most frequently observed in the second portion of the duodenum; Brunner's gland tumors and inflammatory polyps were most frequently found in the first portion of the duodenum.

Diagnosis

All patients in this series underwent EGD. Fourteen patients had an upper gastrointestinal series, which revealed a polyp in eight cases, for an overall sensitivity of 57%. The sensitivity of upper gastrointestinal series in detecting polyps was higher for lesions greater than 23 mm in diameter than for smaller polyps (6/6 [100%] vs. 2/8 [25%]; $P = 0.001$). Thirteen patients underwent CT scanning, which revealed a polyp in seven cases, for an overall sensitivity of 54%. A statistically significant correlation between polyp size and probability of detection on CT scanning was not evident.

Endoscopic Ultrasound Imaging

Eleven patients underwent EUS. In general, the indication for EUS was a large polyp for which lesion depth might have had an impact on whether endoscopic and surgical resection would be elected. Six patients were found to have lesions confined to the mucosa. Of these patients, four underwent endoscopic polypectomy and two were referred for surgical resection. The patients referred for surgery had polyps that the endoscopist considered too large (40 mm and 32 mm) to be amenable to endoscopic polypectomy.

Five patients were found to have polyps with submucosal involvement. Of these patients, two underwent surgical resection, two underwent an endoscopic tunnel biopsy and were subsequently referred for surgical excision, and one underwent endoscopic polypectomy alone (this patient's polyp was less than 10 mm in diameter and was amenable to complete endoscopic resection).

Depth of lesion penetration detected on EUS varied with polyp size. Sixty-seven percent of BDNs greater than 2 cm in diameter displayed submucosal involvement, whereas only 20% of those less than 2 cm in diameter displayed submucosal involvement.

Management

Endoscopic Management. Forty-seven patients were managed endoscopically, without surgical resection, including all of the study patients with Brunner's gland tumors and inflammatory polyps. Thirty-seven of these patients underwent endoscopic polypectomy, whereas 10 of these patients underwent endoscopic biopsy of the lesion without subsequent polypectomy. Of the patients who underwent biopsy alone, nine were not advised to undergo further therapy based on the following patient characteristics and pathologic findings: one had metastatic bladder carcinoma not involving the duodenum; one was elderly (96 years of age); one had a mesothelioma; one had neurofibromatosis; and five had inflammatory polyps. In addition, one patient was advised to undergo surgical resection but refused.

Surgical Management. Fifteen patients underwent surgical resection (6 had a transduodenal polypectomy, 6 had a segmental duodenal resection of the third and fourth portions of the duodenum with a primary duodenojejunostomy, and 3 had a pancreaticoduodenectomy). Relative to patients who underwent nonsurgical management, the surgical patients had a greater median polyp diameter (35 [15 to 150] mm vs. 8 [2 to 40) mm; $P = 0.001$), and a greater percentage of them had adenomas (12/15 [80%] vs. 24/47 [51%]; $P = 0.04$) and lesions located in the third portion of the duodenum (7/15 [47%] vs. 5/47 [11%]; $P = 0.005$).

Treatment-Related Morbidity. There were no treatment-related deaths in this series. Major treatment-related complications, defined as bleeding, need for reoperation, pancreatic ductal leak, and anastomotic dehiscence, occurred with a significantly lower incidence in patients managed nonoperatively (endoscopic therapy alone) than those managed with surgical resection (1/47 [2%] vs. 5/15 [33%]; $P = 0.002$).

The single treatment-related complication in the nonoperatively managed group occurred in a patient who developed bleeding at the polypectomy site; successful hemostasis was achieved during repeat EGD in this patient. Patients who underwent pancreaticoduodenectomy had a higher incidence of treatment-related complications (3/3 [100%] vs. 2/12 [17%]; $P = 0.02$) and a longer mean length of hospital stay (50 [41 to 61] days vs. 9 [6 to 14] days; $P = 0.0001$) than patients who underwent less extensive surgical procedures.

Recurrence. Follow-up EGD data were available for 21 (58%) of the study patients who were treated for adenomas. Median time to first follow-up EGD after initial therapy was 12 (1 to 72) months. Seven patients were observed to develop a recurrence of their adenomas, with a median time to recurrence after initial therapy of 12 (4 to 48) months. Four of the patients who developed a recurrence initially had been treated with endoscopic polypectomy; their median time to recurrence was 8 (4 to 40) months. Three of the patients who developed a recurrence were treated surgically (1 had a pylorus-preserving pancreaticoduodenectomy [recurrence at 48 months] and two had a transduodenal polypectomy [both recurred at 12 months]). The site of recurrence was at the polypectomy site for patients treated endoscopically, in the doudenal remnant for the patient who had undergone pylorus-preserving pancreaticoduodenectomy, and in the duodenum distant from the polypectomy site for the patients who had undergone transduodenal polypectomy.

Familial Polyposis. Eleven patients (18%) had multiple polyps. Five of these patients had familial adenomatous polyposis. Three of the patients were managed nonoperatively. One patient had five distinct polyps in the duodenum; the three largest (5, 7, and 8 mm in diameter) were removed endoscopically, and each was found to be a hamartoma. The second patient had diffuse nodularity of the first portion of the duodenum. A single adenoma (15 mm) was removed endoscopically; recurrence was detected 7 months afterward. The third patient had numerous small polyps carpeting the first portion of the duodenum. A single dominant adenoma (15 mm) in the second portion of the duodenum was removed endosopically; this patient was recurrence free at 36 months' follow-up.

Two patients with familial adenomatous polyposis had surgical procedures. One patient had three adenomas (32, 50, and 90 mm), one of which was causing obstructive symptoms. This patient underwent pancreaticoduodenectomy; a recurrence was detected 48 months afterward. The second patient had numerous adenomas involving an area of more than 150 mm centered in the second portion of the duodenum. This patient also underwent a pancreaticoduodenectomy; no follow-up information is available for this patient.

Based on our center's experience, we propose a management algorithm (Fig. 1). After a diagnosis is made on the basis of EGD, the patient is referred for either endoscopic polypectomy if the polyp measures less than 1 cm in diameter or surgical excision if the polyp measures more than 2 cm. Patients who have polyps with a diameter of 1 to 2 cm undergo endoscopic ultrasonography in order to evaluate the depth of penetration. Patients are referred for endoscopic polypectomy if their polyps are confined to the mucosa or for surgical excision if the polyps demonstrate submucosal involvement.

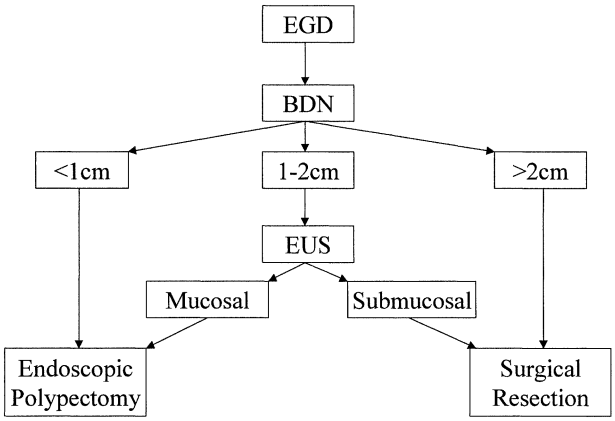

Fig. 1. Algorithm for management of benign duodenal neoplasm (BDN). EGD = esophagoduodenoscopy; EUS = endoscopic ultrasound; Mucosa = mucosal endoscopic ultrasound location; Submucosal = submucosal endoscopic ultrasound location.

DISCUSSION

In our series, adenomas were the most frequently detected BDNs. Inflammatory polyps and Brunner's gland tumors were the next most frequently detected; other lesions were rare. Adenomas had a predilection for being located in the second portion of the duodenum, whereas inflammatory polyps and Brunner's gland tumors had a predilection for being located in the first portion of the duodenum. The relative incidence of the lesions and their site predilection are consistent with data in previously reported series of BDNs.[14,15]

Diagnosis was based on EGD in all study patients. CT scanning and upper gastrointestinal contrast examinations were associated with poor sensitivities, except in the detection of the largest lesions. EUS was introduced into our center during the period of this study. More experience with this diagnostic adjunct will be required before its accuracy and utility in the management of BDNs can be conclusively delineated. Its possible role is proposed in the algorithm described below.

Most BDNs can be managed with endoscopic therapy with minimal morbidity. Small non-neoplastic, asymptomatic lesions, such as Brunner gland tumors and inflammatory polyps, are of no clinical significance and can be left alone once the histology is confirmed on endoscopic biopsy. Small adenomas and symptomatic lesions may be treated with endoscopic polypectomy; the morbidity rate for this procedure was only 3% in this series.

Patients with lesions not believed to be amenable to endoscopic therapy were referred for surgical resection. Three distinct surgical procedures were used in this series: (1) transduodenal polypectomy; (2) segmental (sleeve) duodenal resection; and (3) pancreaticoduodenectomy. Major morbidity occurred in 100% of patients undergoing pancreaticoduodenectomy and in 17% of patients undergoing the surgical procedures of lesser magnitude. The high morbidity rate associated with the few pancreaticoduodenectomies included in this series, albeit not representative of the entire group of patients undergoing this procedure at our center during the study period, is higher than those reported in large contemporary

Table 1. Characteristics of benign duodenal neoplasm according to histologic findings

	Adenoma (n = 36)	Brunner's gland (n = 8)	Inflammatory polyp (n = 10)	Other* (n = 8)
Age (yr)	63 (range 31–92)	57 (range 44–69)	67 (range 24–84)	63 (range 29–80)
Male	18 (50%)	6 (75%)	5 (50%)	4 (50%)
Endoscopic treatment	24 (67%)	8 (100%)	10 (100%)	5 (63%)
Surgery	12 (33%)	0 (0%)	0 (0%)	3 (37%)
Size (mm)	15 (3–150)	5.5 (3–10)	13.5 (4–40)	21 (8–65)
EUS	6 (17%)	1 (13%)	3 (30%)	1 (13%)
Mucosal EUS location	3 (8%)	1 (13%)	2 (20%)	0 (0%)
Submucosal EUS location	3 (8%)	0 (0%)	1 (10%)	1 (13%)
First portion duodenal location	9 (25%)	8 (100%)†	6 (60%)	1 (13%)
Second portion duodenal location	21 (58%)‡	0 (0%)	2 (20%)	3 (37%)
Third portion duodenal location	6 (17%)	0 (0%)	2 (20%)	4 (50%)

EUS = endoscopic ultrasound
*Two hamartomas, one lipoma, one leiomyoma, one ectopic pancreatic tissue, one lymphangioma, one carcinoid tumor, and one neurofibroma.
†$P < 0.05$ vs. adenoma and other.
‡$P < 0.05$ vs. Brunner's gland.
§$P < 0.05$ vs inflammatory polyp and other.

series of this operation.[28–30] Soft pancreatic parenchymal texture (a reported risk factor for the development of pancreatic anastomotic leaks),[31] as is usually found in patients with BDNs who do not have chronic pancreatitis or the desmoplastic reaction associated with periampullary cancers, may have contributed to this high morbidity rate. Indeed, all of the patients who underwent pancreaticoduodenectomy had complications related to pancreaticojejunal anastomotic dehiscence. Criteria for selecting among these procedures are outlined below; pancreaticoduodenectomy should be avoided in patients with BDNs in the absence of specific indications.

Our proposed treatment algorithm is depicted in Fig. 1. We believe that most BDNs less than 1 cm in diameter should be treated using endoscopic polypectomy. Most lesions greater than 2 cm in diameter are best treated by surgical resection. This recommendation is based on our finding that most BDNs greater than 2 cm in diameter display submucosal involvement on EUS. For the subset of lesions measuring between 1 and 2 cm in diameter, EUS may ultimately offer its greatest utility in helping to guide the management of individual patients. Lesions in this size range that are seen to be limited to the mucosa on EUS should be treated with endoscopic polypectomy, whereas those with submucosal penetration should be surgically resected.

The surgical procedure of choice should be segmental duodenal resection or transduodenal polypectomy, when feasible. Lesions located in the first portion of the duodenum are particularly well suited to transduodenal polypectomy, because the duodenum can be closed with a pyloroplasty, thereby avoiding luminal narrowing, even after a generous polypectomy. Segmental duodenal resection should be undertaken if local excision with simple closure of the resulting defect would induce luminal narrowing, as is usually the case for lesions located in the third or fourth portion of the duodenum. Lesions in the second portion of the duodenum, particularly those near the ampulla of Vater, may require pancreaticoduodenectomy. Other options, such as duodenum-preserving ampullectomy, have been described for such lesions, but they are technically difficult to perform and are associated with high complication rates; none were used in this series.[32]

This algorithm represents generalized recommendations. Caveats related to such factors as available endoscopic and surgical expertise and patient-related comorbid conditions should be considered when determining the management of individual patients. For positive margins after endoscopic polypectomy of lesions less than 2 cm in diameter, surgical excision should be considered. In this series, follow-up EGD data were available for 21 (58%) of the study patients who were treated for adenomas. A recurrence was discovered in seven (19.4%) of these patients at a median of 12 (4 to 48) months after their therapeutic procedures. Careful follow-up of patients treated for BDNs is therefore warranted. Although further study will be required to identify the optimal follow-up protocol, we currently recommend follow-up EGD at 6 months after the therapeutic procedure and yearly thereafter in the absence of recurrence.

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Surgical Management of Pancreaticocutaneous Fistula

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Although enteric drainage of the fistula tract is a widely accepted treatment for pancreaticocutaneous fistula, few data have been published on the outcome of this procedure. We conducted a retrospective chart review of 30 patients with pancreaticocutaneous fistula who underwent surgical management at a single institution over a 13-year period. The operative morbidity rate was 30%. Overall the incidence of recurrent ductal leaks requiring further intervention was 23%. Six of seven patients who had a recurrence had an ongoing inflammatory pathology, and three of seven had pancreas divisum. Recurrence was most likely when cystenterostomy was used. Enteric drainage of pancreaticocutaneous fistulas is not always curative. Fistulojejunostomy gives a better outcome than cystenterostomy. Recurrence may be expected in patients with continuing inflammatory ductal pathology. (J GASTROINTEST SURG 2003;7:542–546.) © 2003 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Pancreatic fistula, surgical procedures, operative, outcome assessment

Pancreaticocutaneous fistula results when pancreatic duct disruption occurs and the skin is breeched so that pancreatic juice leaks out onto the skin. It is reported in up to 38% of patients undergoing pancreatic resections, the incidence varying according to the definition used;[1–9] and following 28% of celiotomies for pancreaticoduodenal trauma.[10] It is also a frequent consequence of debridement for necrotizing pancreatitis and percutaneous drainage of communicating pseudocysts.[11,12] With increased use of percutaneous drainage for peripancreatic fluid collections, this complication is being seen with increasing frequency.

Approximately 70% to 90% of these fistulas close spontaneously with conservative management,[2,13] but those with unfavorable anatomy, such as downstream stenosis and main duct disruption, usually require operative management.[14]

Enteric drainage of the fistula provides effective treatment, and several options are available. Fistulojejunostomy is usually the procedure of choice where there is a well-formed fistula tract.[15] but where a mature residual pseudocyst is present, cyst enterostomy is occasionally advocated.[16,17] At present, there is little data on the morbidity and outcome of these procedures. We, therefore, conducted a retrospective study of the outcome in 30 patients who underwent enteric drainage of pancreaticocutaneous fistulas at our institution.

PATIENTS AND METHODS

Study Group

Thirty patients underwent enteric drainage of pancreaticocutaneous fistulas during the 13-year period from January 1989 to December 2001. Charts were reviewed for clinical data. Patients who were discharged after apparently successful percutaneous pseudocyst drainage and returned with persistent drainage were included. Those who had undergone same-admission enteric drainage for unsuccessful percutaneous drainage were excluded. The charts of patients who suffered from recurrent, symptomatic, ductal leaks were critically examined to identify preventable contributing factors.

Surgical Methods

Fistulojejunostomy was the preferred treatment. The technique of fistulojejunostomy is well described elsewhere.[15] Briefly, the fistula tract is identified and traced as close to the pancreatic bed as is safe.

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It is then divided and a hand-sewn anastomosis with a Roux-en-Y jejunal loop is performed. In patients with a residual mature pseudocyst, enteric drainage of the cyst was performed either as the primary drainage procedure or in addition to a fistulojejunostomy. Patients who had a distal fistula but no adequate fistula tract were treated by distal pancreatectomy with Roux drainage. Those with a more proximal fistula and an inadequate fistula tract, or those judged to have ductal disease requiring decompression on its own merits, were treated with pancreaticojejunostomy.

Feeding Protocol

Patients whose clinical evaluation suggested impaired nutrition were equipped with feeding jejunostomies either at the time of fistula surgery or at prior procedure. Postoperatively, enteric feedings were started on postoperative day 3 and continued until adequate oral intake could be established. Oral intake was begun when there was evidence that bowel function had returned. Delay in establishing feedings was defined as the need to stop oral or enteric intake because of nausea, vomiting, or abdominal discomfort.

RESULTS

The study group included 21 men (70%) and nine women (30%) with a median age of 52 years (range 16 to 74 years).

Etiology

Thirteen fistulas resulted from surgical debridement of acute pancreatitis, 13 from percutaneous drainage of a communicating pseudocyst, three from pancreatic resection, and one from remote previous cyst enteric drainage.

Type of Fistula

Twenty-nine patients had simple fistulas, one patient had a complex pancreaticocolocutaneous fistula, and patient required colonic diversion.

Duration

The median fistula duration prior to surgical intervention was 135.5 days (range 25 days to 18 months).

Type of Surgery

The procedures included fistulojejunostomy (n = 18), pancreaticojejunostomy (n = 5), cyst enteric drainage (n = 5), fistulogastrostomy (n = 1), and distal pancreatectomy with Roux drainage (n = 1).

Secondary Procedures

Fifteen patients had 21 additional procedures performed at the time of fistula surgery. These included feeding jejunostomy (n = 10), gastric drainage procedures (n = 4), cholecystectomy (n = 2), cystgastrostomy (n = 1), repair duodenum after percutaneous drain penetration (n = 1), closure colostomy (n = 1), choledochoenterostomy (n = 1), and pancreatic duct sphincteroplasty (n = 1). An additional four patients had laparoscopic feeding jejunostomy tubes placed at a prior procedure.

Recurrences

Recurrent symptomatic disease requiring further intervention occurred in seven patients (23%). Five patients had recurrent pseudocysts and two had recurrent pancreaticocutaneous fistulas. Recurrences were found at a median of 7.5 months (range 3 to 32 months). A total of 11 additional procedures were required. These included six reoperations, two percutaneous drainages, two endoscopic drainages, and one percutaneous aspiration.

Table 1 compares the underlying pancreatic disease and the type of surgery performed in patients who had a recurrence vs. those who did not. The median fistula duration before the first operation was 103 days (range 50 to 325 days) in patients with recurrent fistulas compared to 151 days (range 25 days to 18 months) in those without. The three patients with a diagnosis of "relapsing pancreatitis" all had early onset of disease with documented recurrent attacks of pancreatitis and no metabolic or biliary precipitating factors. One patient subsequently had histologically confirmed pancreatic carcinoma, another presented after 2 years with a pancreatic head mass, biliary dilatation, and suspicious pancreatic cytology, but was then lost to follow up.

Endoscopic retrograde pancreatography (ERP) results were available for six of these seven patients. One patient had a stricture in the head of the pancreas, which prevented imaging of the upstream duct, and the fistula site had been demonstrated in five. Three patients were shown to have pancreas divisum. ERP results were available for 20 of the 23 patients who did not have a recurrence, and pancreas divisum was found in two of these patients.

Table 1. Disease and type of surgery in recurrent pancreatic leakage

Recurrence (n = 7)	No recurrence (n = 23)
Underlying disease	
Relapsing pancreatitis (n = 2)	Biliary pancreatitis (n = 10)
Occult pancreatic cancer (n = 2)*	Pancreatic trauma (n = 3)
Chronic alcoholic pancreatitis (n = 2)	Post resection (n = 3)
Biliary pancreatitis (n = 1)	Acute idiopathic pancreatitis (n = 3)
	Acute alcoholic pancreatitis (n = 2)
	Chronic alcoholic pancreatitis (n = 1)
	Relapsing pancreatitis (n = 1)
Operation	
Fistulojejunostomy (n = 3)	Fistulojejunostomy (n = 15)
Cyst enterostomy (n = 3)	Pancreaticojejunostomy (n = 4)
Pancreaticojejunostomy (n = 1)	Cyst enterostomy (n = 2)
	Fistulogastrostomy (n = 1)
	Distal pancreatectomy + Roux drainage (n = 1)

*One confirmed, one probable.

Other Complications

There were no deaths. The median postoperative stay was 8 days (range 4 to 55 days). Nine patients (30%) suffered a total of 13 other postoperative complications. These included superficial wound infections (n = 4), difficulty in instituting enteral feeding (n = 4), intraperitoneal abscess (n = 2), intestinal obstruction (n = 2), and gastroenterostomy stomal ulceration (n = 1). One patient with intestinal obstruction required adhesiolysis. Three additional patients developed biliary obstruction at 6, 31, and 38 months postoperatively.

DISCUSSION

Data on morbidity and outcomes after surgical treatment of pancreaticocutaneous fistula are suprisingly difficult to find. Enteric drainage of pancreaticocutaneous fistula by fistulogastrostomy was first reported nearly 100 years ago,[18] and fistuloenterostomy remains a safe, widely accepted procedure. It has the advantage that formal pancreatic exposure, which may be hazardous in inflammatory conditions, is not required.

The report by Bassi et al.[11] indicated a uniformly good outcome in 17 patients undergoing fistulojejunostomy for pancreaticocutaneous fistula. There were four postoperative complications (23%) including one persistent fistula, which closed on postoperative day 29. Ihse et al.[19] reported on six patients who underwent enteric drainage for external pancreatic fistula; one of them had a persistent fistula for 28 days. None of the patients in these two studies had recurrent disease. This contrasts sharply with our findings of recurrent symptomatic disease in 23% of patients undergoing enteric drainage.

Reporting on a series of 26 patients with medically and surgically treated internal pancreatic fistulas, Sankaran and Walt[20] found recurrences in 10 (53%) of 19 patients who did not have preoperative ductal imaging compared with 0 of 7 who did have preoperative imaging. In the present study, most patients underwent preoperative ERP, and demonstration of the site of the leak did not prevent recurrence in five of seven patients. The finding of pancreas divisum in 17% of patients overall and three of seven who had a recurrence is interesting when compared to a population incidence of 3% to 10%[21] but is of uncertain significance. Although it is conceivable that the anomaly might increase ductal pressure and prevent spontaneous resolution of the fistula, surgical treatment would still be expected to offer a "path of least resistance," and divisum would not be expected to contribute to recurrence. However, a small case series of refractory pancreatic pseudocysts complicating pancreas divisum has been previously reported.[22]

The median duration of fistula was shorter in patients who had a recurrence; however, the numbers are small. The "youngest" fistula in the group with recurrences was still of 50 days' duration. Four patients in the group with no recurrences had fistulas less than 50 days old, so it is unlikely that this was a contributing factor.

The patients in this series underwent a variety of procedures. Looked at differently, the data in Table 1 show that recurrences were noted in 3 (16%) of 19 who underwent fistuloenterostomy, one (20%) of five who had a pancreaticojejunostomy, and three (60%) of five who had cyst enterostomy. Although the numbers are too small to imply statistical significance, it appears that cyst enterostomy is not a very good operation for pancreaticocutaneous fistula. A possible explanation for this is that collapse of the pseudocyst

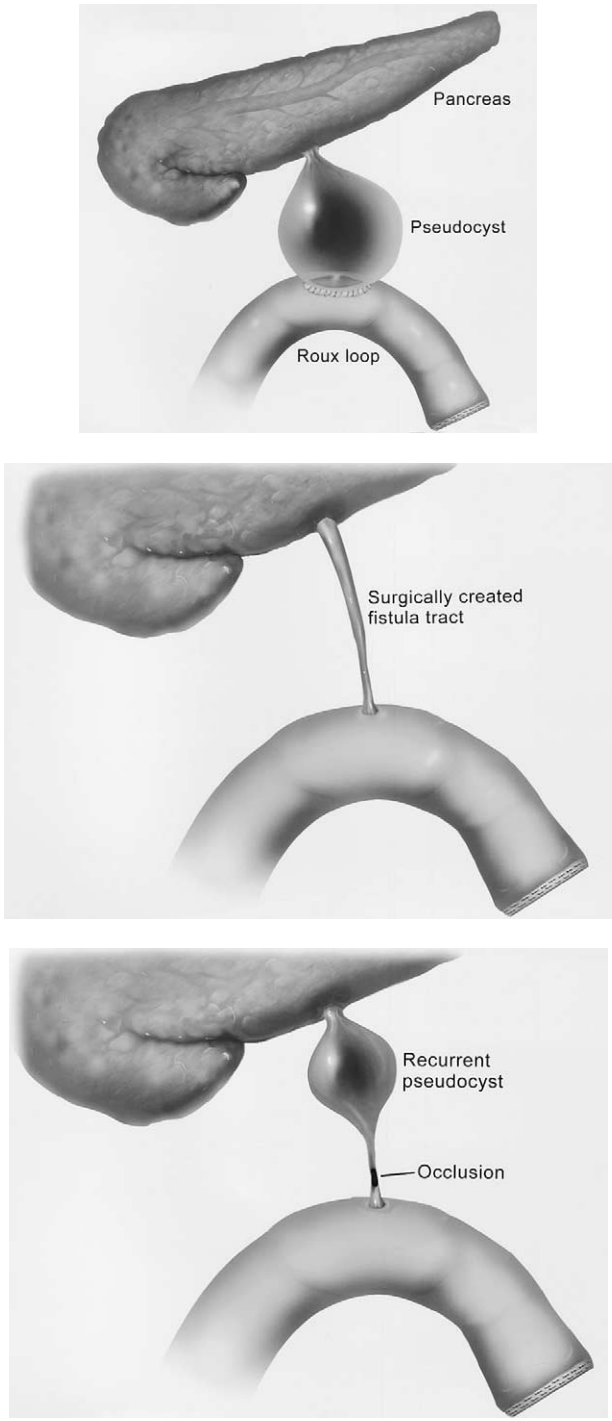

Fig. 1. Possible mechanism for recurrence after cyst enteric drainage. **A**, Cyst enterostomy for established fistula. **B**, Cyst collapses leaving long fistula tract. **C**, Fistula tract occludes leading to recurrent cyst or cutaneous fistula.

leaves a long fistula tract, which is at risk of reocclusion (Fig. 1). Although the recurrence rate for cyst enterostomy performed for uncomplicated pseudocyst is only 5% to 10%,[23,24] these are not patients with an equivalent natural history. There is a tendency toward spontaneous resolution even in large pseudocysts,[25] indicating that many of these patients do not have ongoing ductal leakage.

Table 1 shows that six of seven patients suffering a recurrence had an ongoing inflammatory process in the pancreas. Conversely, patients who had a single, acute episode of pancreatitis with correctable underlying pathology did well. The single patient who had acute necrotizing biliary pancreatitis and a recurrent cyst responded well to endoscopic drainage. Although new ductal leaks cannot be distinguished from incomplete drainage of the primary leak, it is intuitive that if the underlying fistulating process has not been addressed, the patient will be at risk for further ductal disruption.

The 30% rate of postoperative morbidity is high, but perhaps this is not surprising. In most patients, the fistula resulted from an episode of acute pancreatitis or from a postoperative leak; 13 patients (43%) had undergone a pancreatic necrosectomy. They are, therefore, a group of patients with a hostile abdomen in whom an enteric anastomosis carries increased risk. In addition, these patients are frequently nutritionally impaired. This is reflected in the perceived need for feeding jejunostomy in 14 (47%).

CONCLUSION

Enteric drainage of pancreaticocutaneous fistula is a procedure that can be associated with high morbidity, and it is not always curative. In this series, morbidity occurred in 30% and recurrent disease in 23% of cases. The best outcome was found with fistuloenterostomy, but 60% of patients treated with cystenterostomy had a recurrence. Patients with an ongoing pancreatic inflammatory process are probably at risk for symptomatic recurrence.

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Histologic Findings of Gallbladder Mucosa in 87 Patients With Morbid Obesity Without Gallstones Compared to 87 Control Subjects

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Obesity is an important risk factor for the development of gallstones. The purpose of this study was to determine histologic alterations in the gallbladder mucosa and the prevalence of gallstone disease in patients with severe and morbid obesity compared to histologic findings in the gallbladder mucosa of control subjects. Two groups were studied: 125 severely obese patients (38 with and 87 without gallstones) and 87 control subjects. Ultrasonography was performed in all of them before surgery. During surgery, cholecystectomy was performed in 87 obese patients with a "normal" gallbladder and in all 87 control subjects. Specimens were immediately sent for histologic analysis. The prevalence of gallstones was twice as high among obese women compared to obese men ($P < 0.001$). Normal gallbladder mucosa was found in 28.7% of obese women compared to 34.2% of control women ($P > 0.59$). Findings were similar among the men. The most frequent histologic abnormality in the gallbladder mucosa among obese women was cholesterolosis (37%), followed by chronic cholecystitis and cholesterolosis (18%), with frequencies of 23% and 12%, respectively, in control women ($P > 0.1$). Among men, a similar proportion of histologic abnormalities was seen in obese men and control subjects. In our population of obese patients compared to control subjects, a similarly high proportion of histologic abnormalities of the gallbladder mucosa was found in the absence of stones. These findings could have been attributed to the fact that the Chilean population has a high incidence of gallstones. (J GASTROINTEST SURG 2003;7:547–551). © 2003 The Society for Surgery of the Alimentary Tract. Inc.

KEY WORDS: Morbid obesity, cholecystectomy, gallbladder mucosa

Obesity is an important risk factor in the formation of gallstones.[1–6] High serum levels of cholesterol and triglycerides also seem to be an important factor during lithogenesis.[1,7] Histologic studies after routine cholecystectomy in morbidly obese patients have shown that up to 95% of these patients have histologic abnormalities of the gallbladder mucosa without the presence of gallstones.[8,9] We conducted a prospective study to determine the presence of histologic abnormalities in the gallbladder mucosa in a group of patients with severe and morbid obesity compared to control subjects.

MATERIAL AND METHODS

Patients

Two groups were included in this prospective study, which was begun in January 2000 and ended in January 2002. A total of 125 obese patients were divided into the following groups: severe obesity (body mass index [BMI] <39.9 kg/m^2); morbid obesity (BMI 40 to 49.9 kg/m^2); and hyperobesity (BMI $\geq$ 50 kg/m^2). There were 108 women and 17 men whose mean age was 40.8 years (range 16 to 70 years).

Another group of 87 patients (74 women and 13 men) whose mean age was 47 years (range 16 to 79 years) served as control subjects. These were patients with severe reflux esophagitis and Barrett's esophagus or gastric cancer who were referred for surgery, in whom cholecystectomy is routinely performed because of the high prevalence of the development of gallstones reported after vagotomy and partial or total gastrectomy.[11,12] This high incidence of gallstones is attributed to the physiologic changes that occur after vagotomy rather than to the disease itself. These control subjects had a BMI ranging from 15 to 30 kg/m^2 with a mean of 25.8 kg/m^2.

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Ultrasonography

In all of those included in the present investigation (control subjects and obese patients), abdominal ultrasonography was performed 7 to 10 days before surgery to evaluate the characteristics of the gallbladder and common bile duct. All studies were performed by the same radiologist who used an Aloka 1200 real-time imaging system.

Surgical Procedure

Immediately after laparotomy and careful operative exploration of the abdomen, cholecystectomy was performed by ligating the cystic artery with linen or double clips. The cystic duct was ligated by double ligature with Vicryl 3-0 sutures or double clips. The hepatic bed was coagulated and no drains were left in place.

Histologic Analysis

Immediately after cholecystectomy, all resected gallbladders were submerged in 10% formalin solution and sent for histologic evaluation. All of the gallbladders arrived in adequate condition for pathologic analysis with no evidence of autolysis. The histologic appearance of the gallbladder mucosa was categorized as follows:

1. Normal
2. Chronic cholecystitis. Some mononuclear infiltration and fibrosis with relatively normal or atrophic epithelium or some hyperplasia and metaplasia (intestinal or pyloric); the gallbladder wall may show fibrosis, muscle hypertrophy, and Rokitansky-Aschoff sinuses.
3. Cholesterolosis. Collections of lipid-filled foamy cells in the tips of the cells.
4. A combination of chronic cholecystitis plus cholesterolosis.

Statistical Analysis

The chi-square test and Fisher's exact test were used to calculate statistical significance. $P < 0.05$ was considered as significant.

RESULTS

Table 1 shows the prevalence of gallstones in patients with obesity as determined by BMI. Among the 38 patients with gallstones (30.4%), 35 were women who had a mean age of 43.7 years (range 16 to 66 years) and a mean BMI of 43.3 kg/m^2. The other three patients were men who had a mean age of 40 years (range 33 to 46 years) and a mean BMI of 52.6 kg/m^2. The prevalence of gallstone disease was twice as high in the women ($P < 0.001$). However, there was no significant difference in the incidence of gallstones according to BMI ($P > 0.7$). Table 2 shows the histologic findings in the gallbladder mucosa in 73 women with morbid obesity but no gallstones compared to a similar number of control subjects. These 73 obese women had a mean age of 37.3 years (range 19 to 70 years) and a BMI of 43.4 kg/m^2. The control group had a mean age of 45.5 years (range 19 to 76 years) and a BMI of 24.5 kg/m^2. Normal gallbladder mucosa was found in 28.7% of obese women compared to 34.2% of the control group, which was not significant ($P > 0.59$). When groups were compared according to BMI, no differences were noted. Histologic abnormalities of the gallbladder mucosa showed a similar prevalence in obese women compared to control subjects independent of BMI. Table 3 presents the histologic findings in the gallbladder mucosa in 14 morbidly obese men compared to 14 control subjects. The 14 obese men had a mean age of 35.6 years (range 16 to 54 years) and a mean BMI of 47.1 kg/m^2. The control group had a mean age of 48.5 years (range 23 to 60 years) and a BMI of 27.5 kg/m^2. All obese patients had a BMI that was higher than 40 kg/m^2. Both groups had a similar proportion of normal findings and histologic abnormalities and significant differences were noted according to BMI.

DISCUSSION

The results of the present study suggest that (1) gallstones are present in a significant proportion of obese patients and (2) histologic abnormalities of the gallbladder mucosa are frequently present in obese patients without gallstones as well as in control subjects. It has been shown that obesity is a significant risk factor in the development of gallstones.[1–6] Freeman et al.[2] reported that 37% of morbidly obese patients have gallstones, which is similar to our findings (30.4%). In a study of 477 obese patients, Thilt et al.[3] found that 39.1% had gallstones, which is four times higher than in the nonobese population. Orie[5] reported that up to 45% of morbidly obese patients have gallstones, whereas Shiffman et al.[6] pointed out that 14% of the obese patients had previous cholecystectomy, and 21% had gallstones at the time of bariatric surgery. What is the explanation for this condition? On one hand, it is known that obese patients have higher serum levels of cholesterol and triglycerides, which favors a higher excretion of cholesterol through

Table 1. Gallstone disease in patients with obesity according to body mass index (N = 125)

BMI (kg/m²)	Men	Women	Total
<39.9 (n = 31)	0	10/31 (32.2%)	10 (32.2%)
40–49.9 (n = 71)	1/11 (9%)	20/60 (35%)	21 (29.6%)
≥50 (n = 23)	2/6 (33%)	5/17 (29.3%)	7 (30.4%)
TOTAL	3/17 (17.6%)	35/108 (32.4%)	38 (30.4%)

the hepatic bile.[1,7] On the other hand, several studies directly evaluating the composition of hepatic and gallbladder bile in morbidly obese patients have shown a supersaturation of bile with cholesterol, promoting the precipitation of microcrystals of cholesterol. Freeman et al.[2] in a comparison of 11 obese and 11 nonobese patients, found that all obese subjects had hepatic and gallbladder bile saturation outside the micelar zone, compared to only 1 of 11 control subjects. Worobitz et al.[4] showed that the saturation index of gallbladder bile among obese patients was 1.62 compared to 0.92 among nonobese subjects. Similar findings were reported by Shiffman et al.[6] In experimental studies in animals that developed obesity quite easily with diet, St. George and Shaffer[7] described a significant increase in cholesterol saturation from gallbladder bile compared to nonobese control animals, with a significant increase in serum cholesterol and the presence of microvesicular steatosis in the liver parenchyma. Besides all of these biochemical alterations, Vezima et al.[10] described an increase in gallbladder volume and a decrease in gallbladder emptying in obese patients compared to control subjects. Mean gallbladder volume was 41 ml among obese patients and 17 ml among control subjects ($P < 0.01$). Gallbladder emptying measured by ^{99}Tc was significantly slower ($P < 0.05$). These biochemical abnormalities are probably related to the histologic abnormalities in the gallbladder mucosa that are frequently found in morbidly obese patients in the absence of gallstones (i.e., "prestone findings"). Mooney and Carter,[8] among 51 patients undergoing bariatric surgery and routine cholecystectomy, found that 30% had stones, 30% had cholesterolosis, and 8% had chronic cholecystitis, whereas 27% had a normal gallbladder mucosa, which is very close to our 28.7% of obese women with normal histologic findings. Calhoun[9] performed 92 routine cholecystectomies in obese patients. Among them, 95% had histologic evidence of gallbladder disease—that is, chronic cholecystitis, cholesterolosis, a combination of the two, and gallstones. In our study we found a high incidence of histologic abnormalities in the gallbladder mucosa in the absence of stones, which was independent of the BMI. However, what is disturbing is the fact that a similarly high proportion of nonobese control subjects have histologic evidence of gallbladder disease. We previously reported that 10 (24%) of 42 normal men and 21 (40%) of 53 normal women had abnormal histologic findings in the gallbladder mucosa.[13] The only difference between these two studies is that in the former study only a small 5 to 8 mm sample was obtained from the wall of the gallbladder, whereas in the latter the whole gallbladder was resected; therefore it is possible that the histologic analysis of the gallbladder mucosa was very different in the two studies. The same pathologist participated in both studies and the study populations were quite similar. We have not found any previous reports of histologic examination of the gallbladder mucosa in control subjects.

In Chile, there is a high incidence of gallstones.[14] Two previous studies from our unit concerning bile composition in control subjects have shown that the lithogenic index is significantly higher in normal Chilean women because of an increase in the canalicular secretion of cholesterol.[15,16] In addition, patients with cholesterolosis in the absence of stones have bile that is supersaturated with

Table 2. Histologic findings in gallbladder mucosa of 73 morbidly obese women without gallstones compared to 73 control women

	Obese patients (BMI)					
Gallbladder histology	<39.9 (n = 21)	40–49.9 (n = 40)	≥50 (n = 12)	Total (n = 73)	Control subjects (n = 73)	*P* value
Normal	9 (42.8%)	7 (17.5%)	5 (41.6%)	21 (28.7)	25 (34.2%)	>0.59
Chronic cholecystitis	6	3	3	12 (16.4%)	22 (30.1%)	>0.07
Cholesterolosis	4 (19%)	21 (52.2%)	2 (16.6%)	27 (36.9%)	17 (23.3%)	>0.1
Chronic cholecystitis + cholesterolosis	2	9	2	13 (17.8%)	9 (12.3%)	>0.48

Table 3. Histologic findings in gallbladder mucosa of 14 morbidly obese men compared to 14 control men

Gallbladder histology	Morbidly obese patients (BMI) 40–49.9 (kg/m^2)	≥50 (kg/m^2)	Total (n = 14)	Control subjects (n = 14)	*P* value
Normal	3	2	5 (35.7%)	2 (14.3%)	>0.19
Chronic cholecystitis	2	1	3 (21.4%)	4 (28.6%)	>0.5
Cholesterolosis	3	0	3 (21.4%)	5 (35.7%)	>0.48
Chronic cholecystitis + cholesterolosis	2	1	3 (21.4%)	3 (21.4%)	>0.67

cholesterol.[16] Another study from our group analyzed the composition of bile in control subjects, patients with cholesterolosis, and patients with gallstones, and showed similar concentrations of bile salts and phospholipids in all groups.[17] However, the cholesterol concentration was significantly higher in the latter two groups. Therefore we postulated that supersaturated hepatic and gallbladder bile in control subjects could induce some histologic changes in the gallbladder mucosa prior to the macroscopic appearance of gallstones. This is only a hypothesis, and we have no objective evidence to support such an idea. Ultrasound studies are very useful for the detection of gallstones, but obviously cannot be used to diagnose histologic alterations in the gallbladder mucosa. In our study, the correlation with gallstones findings was 100%. Oria[5] retrospectively reviewed the correlation between ultrasound and histopathologic findings with regard to gallstones in 3084 obese patients. He reported a discrepancy in only 1.1% of the cases with false negative results due to the presence of very small soft stones or cholesterolosis.

Because of the high frequency of gallstones and the increased prevalence of abnormal histologic findings in the gallbladder mucosa, several investigators have proposed the use of prophylactic or routine cholecystectomy among morbidly obese patients undergoing bariatric surgery. In addition, a high incidence of stones formation after bariatric surgery has been reported.[4,6] Shiffman et al.[6] reported a 10% incidence of symptomatic gallstones 2 years after surgery, whereas Worobitz et al[4] described the development of gallstones in 43% of the operated patients followed for more than 3 months. Other investigators such as Mooney and Carter,[8] Calhoun and Willbanks[9] Fakhry and Herbst,[19] and Bajardi et al.[20] have also emphasized the necessity of performing prophylactic cholecystectomy during bariatric surgery. Besides avoiding the risks of complications of biliary disease after surgery, the difficulties, side effects, and risk of a second operation are avoided, not to mention the unnecessary expense of this second operation.[6,9,11,12] In our 87 patients who had prophylactic cholecystectomy, the duration of this operation was 8 to 10 minutes, and no complications were seen in any patient. In light of all of this background information, we strongly recommend a prophylactic cholecystectomy for all morbidly obese patients undergoing surgery.

An alternative to cholecystectomy has been the use of ursodeoxichohic acid early after surgery. Worobitz et al. evaluated 13 obese patients treated with ursodeoxichohic acid, 100 mg/day. Three patients did not tolerate the drug, leaving 10 patients who completed the 3-month treatment protocol. None of them developed gallstones compared to 6 of 14 patients treated with placebo. However, the high cost, collateral effects, and the appearance of stones after the drug is discontinued make this treatment impractical. It seems much easier to perform routine cholecystectomy during the initial bariatric surgery.

In summary, morbidly obese patients not only have a high frequency of gallstones, but also a high proportion of abnormal histologic findings in the gallbladder mucosa and a high probability of developing stones after bariatric surgery, which makes routine prophylactic cholecystectomy advisable during bariatric surgery.

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Laparoscopic vs. Open Biliopancreatic Diversion With Duodenal Switch: A Comparative Study

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Biliopancreatic diversion with duodenal switch (BPD-DS) is a well-known emerging open procedure that appears to be as effective as other bariatric operations and has been shown to provide excellent long-term weight loss. Therefore we looked at the safety and efficacy of the laparoscopic BPD-DS procedure compared to open BPD-DS in superobese patients (body mass index >60). A retrospective study of 54 superobese patients (body mass index >60) was carried out from July 1999 to June 2001: laparoscopic BPD-DS in 26 patients and open BPD-DS in 28 patients. Median preoperative body weight was 189.8 kg (range 155.1 to 271.2 kg) in the laparoscopic BPD-DS group and 196.5 kg (range 160.3 to 298.9 kg) in the open BPD-DS group. Median body mass index was 66.9 kg/m^2 in the laparoscopic group and 68.9 kg/m^2 in the open group. The two groups were compared by means of the unpaired *t* test, which yielded the following results: Major morbidity occurred in six patients (23%) in the laparoscopic BPD-DS group and in five patients (17%) in the open BPD-DS group ($P = 0.63$). There were two deaths in the laparoscopic BPD-DS group (7.6% mortality) and one death (3.5% mortality) in the open BPD-DS group ($P = 0.51$). Preoperative comorbidity was improved in eight patients in the laparoscopic BPD-DS group and two patients in the open BPD-DS group ($P < 0.02$). Laparoscopic BPD-DS is a technically feasible procedure that results in effective weight loss similar to the open procedure. However, both open and laparoscopic BPD-DS procedures are associated with appreciable morbidity and mortality in the superobese population. Additional studies are needed to determine the best surgical treatment for superobesity. (J GASTROINTEST SURG 2003;7:552–557.) © 2003 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Biliopancreatic diversion with duodenal switch, superobese

Technological advances in minimally invasive surgery have enabled surgeons to perform bariatric surgery using laparoscopic techniques.[1–3] Laparoscopic biliopancreatic diversion with duodenal switch (BPD-DS) is a technically challenging operation that requires extensive surgical dissection, transection and restoration of intestinal continuity, and advanced laparoscopic suturing and stapling skills.

BPD-DS has been shown to have the best result of any bariatric procedure in the superobese population, in terms of magnitude and duration of weight loss.[4–7] Therefore, since July 1999, we have been offering BPD-DS to superobese patients. However, to date, there has been no study comparing the results of laparoscopic and open BPD-DS in the management of morbid obesity. The purpose of this study was to compare surgical outcomes in patients who underwent laparoscopic BPD-DS vs. open BPD-DS for the treatment of superobesity (body mass index >60).

PATIENTS AND METHODS

Between July 1999 and June 2001, a total of 54 superobese patients (BMI >60) underwent BPD-DS. Twenty-six patients underwent laparoscopic BPD-DS and 28 patients underwent conventional open BPD-DS. Each of these operations was performed by one of four surgeons who had already passed the learning curve for both procedures. A retrospective

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chart review was performed to collect data. Patients were stratified by sex, age, body weight, and BMI. Preoperative evaluation was extensive and included a nutrition consultation, a psychiatric evaluation, routine upper endoscopy, and medical clearance. Pulmonary function tests, sleep studies, and cardiac workup were individualized according to the comorbid conditions. There were 28 female patients and 26 male patients whose ages ranged from 24 to 59 years (median 42 years). Median preoperative body weight was 189.8 kg (range 155.1 to 271.2 kg) for the laparoscopic group and 196.5 kg (range 160.3 to 298.9 kg) for the open group. Median BMI was 66.9 kg/m^2 (range 60 to 88.8 kg/m^2) in the laparoscopic group and 68.9 kg/m^2 (range 60 to 103.1 kg/m^2) in the open group. There were no significant differences with regard to age, sex, and BMI between the two groups (Table 1). Improvements in clinical outcome, operative outcome, morbidity, mortality, and comorbidity after operation were evaluated. All data are expressed as median ± standard deviation, and the two groups were compared using an unpaired Student's *t* test.

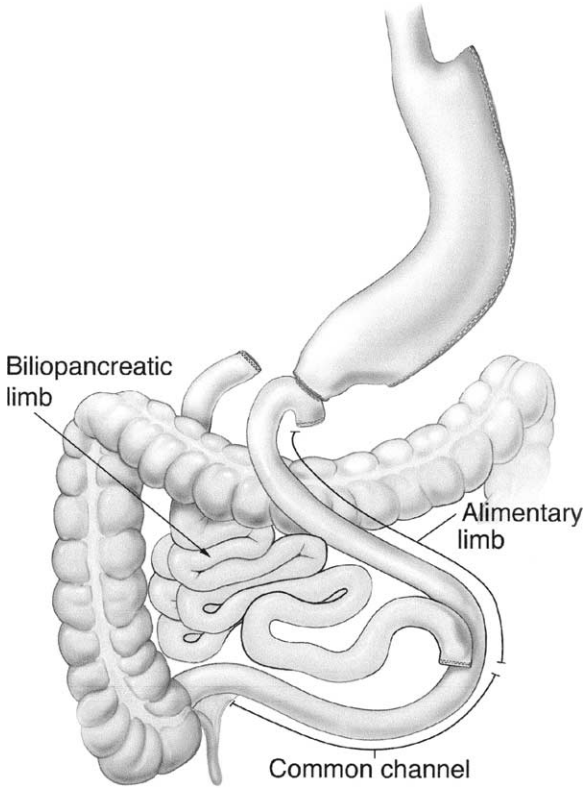

Fig. 1. Biliopancreatic diversion with duodenal switch. Different limbs with an astecolic end to side duodeno-ileostomy and side to side ileo-ileostomy.

Surgical Technique

Laparoscopic BPD-DS was performed as previously described[4] (Fig. 1). Briefly, after placement of appropriate monitoring devices and pneumatic compression boots, patients underwent general anesthesia and endotracheal intubation. All procedures were performed with the patient in the French position (legs abducted with the surgeon standing between the patient's legs). The peritoneal cavity was then insufflated with CO_2 to a pneumoperitoneum of 15 mm Hg. Seven trocars were usually required for each procedure, but up to nine were sometimes used. Extra-long trocars were occasionally needed in patients who had a thicker abdominal wall. The trocars were placed as previously described.[4] The laparoscopic BPD-DS involved several steps including sleeve gastrectomy, division of the duodenum, creation of a duodenoileostomy, measurement of the common channel, and a distal ileoenteric anastomosis. The duodenum was usually divided 2 cm distal to the pylorus with a linear stapler. A 60 F bougie was passed into the stomach and aligned along the lesser curvature. A sleeve gastrectomy was created using sequential firing of a linear stapler parallel to the bougie. The remaining gastric tube measured approximately 150 to 200 ml and was anastomosed to the distal 250 cm

Table 1. Demographic data from 54 patients undergoing BPD-DS

Demographic variable	Laparoscopic BPD-DS (n = 26)	Open BPD-DS (n = 28)	*P* value
Median age ± SD (yr)	42 ± 8 (range, 31–60)	42 ± 8 (range, 24–58)	NS
Sex ratio (F:M)	15:11	13:15	NS
Median weight ± SD (kg)	189.8 ± 31.7 (range, 155.1–271.2)	196.5 ± 29.1 (range, 160.3–298.9)	NS
BMI (kg/m^2) ± SD	66.9 ± 7.5 (range, 60–88.8)	68.8 ± 10.1 (range, 60–103.1)	NS

BPD-DS = biliopancreatic diversion with duodenal switch. NS = not significant.

of divided ileum to form the alimentary limb. The flip-top anvil of a 25 mm circular end-to-end stapler (CEEA; U.S. Surgical Corp., Norwalk, CT) was advanced into and through the proximal duodenal stump using a modified nasogastric tube–anvil apparatus (end of the flip-top anvil, which is connected to a nasogastric tube by a polypropylene suture). An antecolic end-to-side duodenoileostomy was created by passing the circular stapler transabdominally, advancing it into the lumen of the distal ileum, and attaching it to the anvil residing in the gastroduodenal pouch. A plastic camera drape was secured around the circular stapler as a wound protector during the removal of the contaminated device. A methylene blue test was performed after every duodenoileostomy anastomosis to confirm the integrity of all staple lines. The size of the gastric tube was determined by the volume of methylene blue required to distend the pouch. The duodenum, jejunum, and proximal ileum were excluded from digestive continuity to form the biliopancreatic limb. The biliopancreatic limb was anastomosed to the distal 75 or 100 cm of the alimentary limb to form a short absorptive common channel. Fascial closure of all trocar sites larger than 5 mm was accomplished with a suture-passing device.

Open BPD-DS was performed through an upper midline incision. A 150 to 200 ml sleeve gastrectomy was created with application of the stapler, and biliopancreatic diversion was performed using the same techniques as those used in the laparoscopic group.

RESULTS

Clinical data from the two groups are presented in Table 2. The median duration of surgery was not significantly different between the two groups ($P = 0.11$). There was no difference in estimated blood loss or hospital stay between the two groups.

Perioperative complications after laparoscopic and open BPD-DS are shown in Table 3. There was no significant difference in the number of complications between the two groups. There were two deaths (7.6% mortality) in the laparoscopic group and one (3.5% mortality) in the open group (see Table 3).

Twenty-six patients in the laparoscopic group were available for follow-up at 6 months, 24 patients at 9 months, and 20 patients at 12 months. Twenty-seven patients in the open group were available for follow-up at 6 months, 22 patients at 9 months, and 20 patients at 12 months. The mean follow-up was 18.5 months (range 6 to 23 months) in the laparoscopic group and 10.1 months (range 4 to 19 months) in the open group. The two groups had similar preoperative comorbid conditions (see Table 2). The comorbidity was improved postoperatively in eight patients in the laparoscopic group and two patients in the open group (Table 4). Most of them were improved by decreasing their previous drug dosage. This improvement was significantly greater in the laparoscopic group compared to the open group ($P < 0.02$). The median excess body weight losses in the laparoscopic and open BPD-DS groups are shown in Table 5. Median excess body weight was 127 ± 28 kg in the laparoscopic group and 137 ± 28 kg in the open group. Median excess body weight loss after 12 months was 76.7 ± 19.7 kg in the laparoscopic group and 56.8 ± 26.3 in the open group. There was no significant difference in the median weight loss between the two groups.

Table 2. Comparison of clinical data and preoperative comorbid conditions in patients undergoing laparoscopic and open BPD-DS

Results	Laparoscopic BPD-DS	Open BPD-DS	*P* value
Median operative time (min)	210 ± 68 (range, 145–403)	259 ± 60 (range, 180–400)	NS
Median estimated blood loss (ml)	100 ± 130 (range, 50–500)	300 ± 285 (range, 125–1000)	NS
Median length of hospital stay (days)	4 ± 41 (range, 3–200)	5 ± 47 (range, 3–225)	NS
Comorbidity (% of patients)			
Hypertension	57.6	42.8	
Arthritis	26.9	28.5	
Asthma	19.2	21.4	
Diabetes	26.9	32.1	
Sleep apnea	46.1	46.4	

Abbreviations as in Table 1.

Table 3. Operative complications and deaths in patients undergoing laparoscopic and open BPD-DS

	Laparoscopic BPD-DS	Open BPD-DS	*P* value
Complications			
Major			
Subphrenic abscess	1	0	
Anastomotic leak	1	0	
Respiratory failure	1	1	
Wound disruption	0	1	
Severe wound infection	0	2	
Minor			
Low extremity edema	1	0	
Wound infection	1	0	
Incisional hernia	1	0	
Urinary tract infection	0	1	
TOTAL	6 (23%)	5 (17%)	NS
Cause of death			
Respiratory failure	1	0	
Necrotizing pancreatitis	0	1	
Anastomotic leak	1	0	
TOTAL	2 (7.6%)	1 (3.5%)	NS

Abbreviations as in Table 1.

DISCUSSION

Superobesity is associated with serious comorbidity. A number of surgical procedures are used in the treatment of morbid obesity, including procedures that are purely restrictive, a combination of malabsorptive and restrictive procdures, and primarily malabsorptive procedures. The purely gastric restrictive procedures, including vertical banded gastroplasty and laparoscopic adjustable silicone gastric banding, do not provide adequate weight loss in patients with severe obesity.[8]

The Roux-en-Y gastric bypass has become the "gold standard" for morbid obesity surgery in North America. However, the long-term results of gastric bypass have been less than optimal in the superobese patients.[4,9–12] Sugerman et al.[13] found that when less than 40% excess weight loss was used as the definition for failure, Roux-en-Y gastric bypass was ineffective in up to 19% of superobese patients and, in fact, 31% remained more than 200% above their initial body weight.

Table 4. Postoperative improvement in preoperative comorbidity among patients after laparoscopic and open BPD-DS

Comorbidity	Laparoscopic BPD-DS (% improved) (n = 26)	Open BPD-DS (% improved) (n = 28)
Hypertension	20	8.3
Arthritis	14	—
Asthma	20	17
Diabetes	71	—
Sleep apnea	25	—

The biliopancreatic diversion was introduced in 1976. This procedure is a hybrid of gastric restriction and intestinal malabsorption. Biliopancreatic diversion is also known as the Scopinaro procedure; it was named for Dr. Nicola Scopinaro who was not only its creator but also its greatest advocate. The initial series of these operations was reported in 1979,[14] but Scopinaro et al.[15] have modified the procedure over time. The current operation consists of a partial horizontal gastrectomy with closure of the duodenal stump, gastrojejunostomy with a long Roux limb, and anastomosis of the long biliopancreatic limb to the Roux limb, 50 cm from the ileocecal valve, creating an extremely short common channel. In a recent publication, Scopinaro et al.[15] reported on their 23 years of experience encompassing 2316 patients. The initial excess weight loss (IEWL) at 1 year in this series was approximately 70% and was essentially maintained for 20 years.

In an effort to reduce the side effects of biliopancreatic diversion, such as marginal ulceration and malabsorption of iron, protein, and calcium, the procedure was modified by a number of investigators.[4,6,7] Duodenal switch combined with biliopancreatic diversion was first introduced by Marceau et al.[17] in 1993, and has been rapidly gaining in popularity in the United States and Canada. Marceau's procedure

Table 5. Excess body weight loss after laparoscopic and open BPD-DS

Characteristics	Laparoscopic BPD-DS	Open BPD-DS	*P* value
3 mo weight loss (kg)			
Median ± SD	35.6 ± 15.6	32.2 ± 14.7	NS
Range	15.4 ± 77.2	9.9–60.8	
6 mo weight loss (kg)			
Median ± SD	56.9 ± 20.4	44.3 ± 5.7	NS
Range	32.6–91.7	42.6–56.2	
9 mo weight loss (kg)			
Median ± SD	68.1 ± 26.5	48.7 ± 4.1	NS
Range	42.0–102.6	58.5–68.7	
12 mo weight loss (kg)			
Median ± SD	76.7 ± 19.7	56.8 ± 26.3	NS
Range	68.8–112.9	32.2–94.8	
Change in BMI after 12 mo			
Median ± SD	37.3 ± 5.6	48.2 ± 6.3	NS
Range	31.2–43.4	40.7–54	

Abbreviations as in Table 1.

deviated from the one introduced by Scopinaro in that it involved construction of a lesser curvature gastric tube by a vertical two-thirds resection of the stomach rather than performing a horizontal gastrectomy, preserving the pylorus, anastomosing the enteric limb to the proximal duodenum, and cross-stapling the distal duodenum without dividing it. Unfortunately, the initial patients rapidly displayed failure of the duodenal staple line and weight gain, because the duodenum, unlike the stomach, does not tolerate cross-stapling. Having converted to duodenal division before anastomosing the enteric limb to the proximal duodenum, Marceau et al.[18] recently reviewed 11 years of experience with 467 patients. Their IEWL was 84% at 18 months.

Hess and Hess[6] popularized the duodenal switch in the United States. Their technique is comparable to that of Marceau et al., with a 150 to 200 ml residual stomach and an end-to-end anastomosis of the enteric limb to the postpyloric duodenum. In their report on 440 patients over a 10-year time span, they noted an IEWL of 80% at 18 months with the use of a common channel of 50 to 100 cm. Hess and Hess varied the length of their common channel from 50 to 75 to 100 cm, as a function of each individual patient's weight, and they also altered the length of the enteric limb. The IEWL percentage over time was not too different with these various combinations, but the 50 cm common channel combined with a 300 cm enteric limb had nearly a 100% IEWL at 108 months.[14] The BPD-DS has provided one of the greatest maintained weight losses of any bariatric procedure.[6,14]

Advances in laparoscopic skills and instrumentation have enabled surgeons to perform the BPD-DS procedure laparoscopically.[2] As with other laparoscopic operations, the objectives of the laparoscopic approach are to reduce postoperative pain and complications, decrease the length of hospital stay, and allow the patient an earlier return to normal activity.[4] Our results also demonstrate that the laparoscopic group offers minimal advantages with regard to the perioperative clinical state over the open group. However, the laparoscopic technique offers better exposure of the gastroesophageal region, avoids a large abdominal incision, reduces abdominal wall trauma from the retraction device, and is responsible for a reduction in postoperative adhesion formation.[1] In particular, the large abdominal incision in open BPD-DS can result in a high risk of postoperative wound seroma, infection, and incisional hernia complications.[1,19] In our case, one patient in the open group had a wound disruption postoperatively and required reoperation. Laparoscopy avoids a long abdominal incision and is expected to decrease such complications. The follow-up period in our study was too short to fully evaluate the incidence of late complications. One patient in the laparoscopic group had an anastomotic leak and one patient had a late incisional hernia; and in the open group, two patients had severe wound infections requiring operative debridement.

When major morbidity and mortality are studied, a higher rate of complications is noted in patients with a BMI greater than 65 compared to those with BMI of less than 65 (8.3% vs. 38%), and the exist-

ence of serious comorbid conditions in superobese patients certainly correlates with a higher surgical risk.[4] Morbidity and mortality were high in our study in comparison to the general morbid obesity group (BMI <60).[20] However, our preliminary results in the laparoscopic group are acceptable, considering that superobese patients have a higher risk of complications and especially because the procedure itself is technically complex and difficult. It must be noted that this report was not a prospective randomized comparison so it does have certain limitations.

Laparoscopic BPD-DS is technically challenging and is associated with a steep learning curve. Our study demonstrates the safety and efficacy of laparoscopic BPD-DS in the superobese patient population. Additional long-term studies are needed to determine the best treatment for superobese patients.

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Laparoscopic Colectomy in Obese and Nonobese Patients

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Obese patients carry a higher risk of wound complications and cardiopulmonary complications along with a higher incidence of comorbidity, all of which have the potential to affect outcome after a variety of surgical procedures. The data regarding outcomes after laparoscopic colectomy in obese and nonobese patients are limited. The purpose of this report was to compare the outcome of laparoscopic bowel resection in obese and nonobese patients. All patients prospectively entered into a laparoscopic bowel resection database from March 1999 to December 2001, who underwent a segmental colectomy for any pathologic condition, were analyzed. Patients with a body mass index above 30 were defined as obese, and patients with a body mass index below 30 were defined as nonobese. Data collected included age, sex, duration of operation, body mass index, American Society of Anesthesiologists score, operative procedure, diagnosis, complications relating to length of hospital stay, mortality, and readmission within 30 days of discharge. Statistical analysis consisted of Student's *t* test and chi-square analysis where appropriate, with significance set at $P < 0.05$. A total of 260 patients were evaluated (201 [77.3%] in the nonobese group and 59 [22.7%] in the obese group). There were no significant differences between the two groups with respect to age, sex, operative procedure, length of hospital stay, or readmission rates. The obese group had significantly more conversions to an open procedure (23.7% vs. 10.9%), a longer operative duration (109 minutes vs. 94 minutes), a higher morbidity rate (22% vs. 13%) and a higher anastomotic leakage rate (5.1% vs. 1.2%). This large experience with laparoscopic colectomy for a variety of conditions demonstrates that despite higher conversion rates, an increased risk of pulmonary complications, and anastomotic leakage rates in obese laparoscopic patients that parallel those of open surgery, laparoscopic colectomy can be performed safely in both obese and nonobese patients with the similar benefit of a shorter hospital stay in both groups. (J GASTROINTEST SURG 2003;7:558–561.) © 2003 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Laparoscopic colectomy, obesity

Laparoscopic-assisted surgical techniques have been applied to virtually all forms of intestinal pathology and have demonstrated significant benefits related to decreased pain, ileus reduction, and shortened recovery periods. Because laparoscopic colectomy requires mobilization of relatively large lengths of mesentery and the appropriate management of major vascular pedicles, it appears plausible that body habitus might play a role in the ability to safely complete the procedure laparoscopically. Obesity is increasing in prevalence and was estimated to affect almost 50% of the United States population in the year 2000.[1] Obese patients carry a higher risk of wound complications and cardiopulmonary complications along with a higher incidence of comorbid conditions, all of which have the potential to affect outcome after a variety of surgical procedures.[2–5]

An evaluation of laparoscopic colectomy for sigmoid diverticular disease revealed similar outcomes for obese, overweight, and normal-weight persons.[6] However, other reports have suggested that obesity is a key risk factor in conversion rates and possibly adversely affects the outcome of laparoscopic colectomy.[7–10] The purpose of this report was to compare the outcome of laparoscopic bowel resection in obese and nonobese patients.

PATIENTS AND METHODS

All patients prospectively entered into a laparoscopic bowel resection database from March 1999 to

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December 2001 were eligible for this study. Inclusion criteria encompassed segmental colectomy for any pathologic condition including curative cancer resection. Patients undergoing stoma procedures, total or subtotal colectomy, stricturoplasty, or excision of peritoneal lesions were excluded. Patients with a body mass index (BMI) of 30 or more were defined as obese, and patients with a BMI of less than 30 were considered nonobese.[11] Data collected included age, sex, duration of operation, BMI, American Society of Anesthesiologists score, operative procedure, diagnosis, length of hospital stay (LOS), complications, mortality, and readmission within 30 days of discharge. Statistical analysis consisted of Student's *t* test and chi-square analysis where appropriate, with significance set at $P < 0.05$.

RESULTS

During the study period, 260 patients were found to fulfill the inclusion criteria. The distribution between the two groups was 201 patients (77.3%) in the nonobese group and 59 (22.7%) in the obese group. There were no significant differences between the two groups with respect to age, sex, operative procedure, LOS, or readmission rates. There were no operative deaths or wound infections in either group. A slight predominance of Crohn's disease was noted in the nonobese group; however, there were no other significant differences in underlying pathology requiring resection (Table 1). Similarly, the distribution of types of colonic resections and the distribution of right-sided and left-sided anastomoses were similar between the groups (see Table 1). A similar percentage of patients with Crohn's disease in both groups underwent synchronous small bowel resection in conjunction with a partial colectomy (see Table 1). The nonobese group had significantly fewer conversions, a shorter operative duration, lower minor and total morbidity rates, and a lower anastomotic leakage rate (Table 2). The incidence of major complications was similar between the two groups. However, three patients in the nonobese group developed postoperative angina pectoris, all of whom had known cardiac disease and responded to oral nitrates, and two patients with deep venous thrombophlebitis required systemic anticoagulation. The need for reintervention for either small bowel obstruction (laparotomy with lysis of adhesions) or abdominal abscess (all image-guided drainage procedures) was similar in both groups (see Table 2). Conversely, the incidence of anastomotic leakage was significantly higher in the obese group, and all patients required reoperation with proximal fecal diversion (see Table 2). Readmissions for postoperative small bowel obstruction were similar in the two groups.

Table 1. Comparison of data collected in obese and nonobese patients*

	Obese (N = 59)	Nonobese (N = 201)
Sex ratio (M/F)	26/33	97/104
Age (yr)	51 ± 13	52 ± 18
ASA distribution (1–4)	3/34/20/2	6/130/59/6
Diagnosis		
Diverticular disease	26 (44%)	82 (41%)
Neoplasia	20 (34%)	50 (25%)
Crohns	3 (5%)	36 (18%)†
Endometriosis	5 (9%)	15 (8%)
Other	5 (9%)	18 (9%)
Operations		
Left/Sigmoid colectomy	42 (71%)	129 (64%)
Right colectomy	14 (24%)	62 (31%)
Small bowel resection	3 (5%)	10 (5%)
OR time (min)	109 ± 36	94 ± 39†
Conversion	14 (24%)	22 (11%)†
BMI	34 ± 4	24 ± 3†
LOS (days)	4 ± 4	4 ± 3
Readmission	5 (9%)	18 (9%)

*Sex distribution, mean age, American Society of Anesthesiologists score (ASA), diagnoses, operations, duration of operation (OR time), conversion to open resection, body mass index (BMI), length of hospital stay (LOS), and readmission within 30 days. Small bowel resection refers to additional small bowel resections required in addition to a partial colectomy.
†$P < 0.05$ Student's *t* test.

DISCUSSION

The influence of obesity on the outcome of colorectal surgical procedures remains unclear, with data both supporting and refuting the concept that obesity is an independent influence on morbidity and mortality after open colectomy.[1,2,12] Obesity in patients requiring laparotomy has been variably reported as a risk factor for increased wound complications, deep venous thrombophlebitis, need for blood transfusion, and anastomotic leakage for left-sided anastomoses.[1–4,12] A recent report from Benoist et al.[12] found little difference in outcome after right or left colectomy between obese and nonobese patients, although their definition of obese was BMI above 27 compared to the BMI of 30 that was used in our report. Similarly, Blee et al.,[1] reporting on patients requiring open colectomy for cancer, found no differences in complications among patients with the following BMIs: less than 25, 25 to 29, and 30 or

Table 2. Incidence and distribution of conversions, complications, and mortality in obese and nonobese patients

	Obese (N = 59)	Nonobese (N = 201)
Minor Complications	10 (17%)	13 (7%)
Atelectasis	4 (7%)	0
Ileus	3 (5%)	3 (2%)
Urinary retention	2 (3%)	2 (1%)
Port site hematoma	1 (2%)	2 (1%)
Diarrhea	1 (2%)	3 (2%)
Other	0	3 (2%)
Major complications	6 (9%)	16 (8%)
Anastomotic leaks	3 (5%)	4 (1%)*
Abdominal abscess	2 (3%)	6 (3%)
Small bowel obstruction	1 (2%)	4 (1%)
Deep venous thrombosis	0	2 (1%)
Angina	0	3 (2%)
Total complications	13 (22%)†	27 (13%)*†

Reintervention was required for patients with either small bowel obstruction (lysis of adhesions) and abdominal abscess (image-guided drainage). All anastomotic leaks required laparotomy and proximal fecal diversion.

*$P < 0.05$ chi square analysis.

†Several patients had multiple complications.

above. Interestingly, pulmonary complications are widely held to be a significant risk in obese patients, but this risk has not been reported in recent series of colectomy patients.[1,2,12]

Laparoscopic bowel resection has been associated with a number of important benefits including decreases in perioperative stress response, pulmonary complications, duration of hospital stay and rehabilitation, anterior hernia, and small bowel obstruction.[7,8,13]

Although it may be difficult to quantify the clinical significance of some findings, it is clear that by almost any measure the perioperative stress response commonly associated with laparotomy is markedly decreased by laparoscopic techniques.[14] Measurements of interleukin (IL)-6 and serum elastase, both indicators of the systemic response to surgical stress and predictors of morbidity, have consistently shown reductions in laparoscopic colectomy compared to open procedures.[14,15] Conversely, evaluation of the components of the neurohumoral axis (norepinephrine and cortisol) and IL-1 and tumor necrosis factor-alpha have not demonstrated distinctly different patterns of secretion with open or laparoscopic bowel resection.[14,16] A standard technique for laparoscopic colectomy has demonstrated an improvement in outcome.[17] We have recently used the POSSUM scoring system as a means of comparing operative stress and demonstrated much lower than predicted morbidity and mortality in patients undergoing laparoscopic procedures.[18] Data regarding the effects of obesity on complications after laparoscopic colectomy are limited; however, obesity is commonly mentioned as a risk factor for conversion to an open procedure.[7–9] A report by Teuch et al.[2] described similar conversion rates (approximately 14%) and morbidity rates for obese and nonobese patients requiring laparoscopic colectomy for sigmoid diverticular disease. Pikarsky et al.[19] reported on 31 patients with a BMI above 30 and found a conversion rate of 39% and a prolonged hospital stay of 9.5 days (vs. 6.9 for nonobese patients). These adverse outcomes were likely influenced by the high conversion rate and the reported longer ileus in the obese patients.[19] The current study divided patients into only two groups: obese (BMI $\geq$30) and nonobese (BMI $<$30), as compared to the commonly used three groups. This may have accounted for the fact that we identified a higher but statistically insignificantly increased risk of pulmonary complications in the obese group (6.8% vs. none in the nonobese group). Interestingly, only one case of atelectasis occurred in a converted obese patient, indicating that even a patient whose operation is completed laparoscopically has some risk of postoperative pulmonary complications. The data also suggest that laparoscopic bowel resection is more complicated in obese patients, as we experienced somewhat longer operative times (109 minutes vs. 94 minutes) and a significantly higher risk of conversion (23.7% vs. 10.9%) in obese patients. Finally, the risk of anastomotic leakage was significantly increased in the obese patients, and all leaks occurred in colorectal anastomoses in that group. A higher anastomotic leakage rate has been reported previously with open colectomy, particularly with left-sided colonic and colorectal anastomoses.[12] There is no reason to suspect that patients who undergo laparoscopic colonic anastomoses would be at greater risk for leakage because the anastomotic techniques are identical when a circular stapler is used. This higher risk rate may be due to the fact that adipose tissue secretes a variety of proinflammatory cytokines that may be further activated by surgical stress.[20,21]

CONCLUSION

This large experience with laparoscopic colectomy for a variety of conditions demonstrates that conversion rates are likely to be higher in obese patients and operative times may be somewhat longer. In addition, the incidence of pulmonary complications, anastomotic leaks, and postoperative ileus are

more frequent in obese patients. However, laparoscopic colectomy can be performed safely in both obese and nonobese patients with a similar benefit of a shorter hospital stay in both groups.

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Home Total Parenteral Nutrition: An Alternative to Early Surgery for Complicated Inflammatory Bowel Disease

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This paper examines the safety and feasibility of providing short-term, in-home total parenteral nutrition (TPN) for patients with inflammatory bowel disease (IBD) for whom the alternative is prolonged hospitalization or early surgery. The records of all patients with IBD who were receiving temporary home TPN between June 1996 and July 2000 were reviewed. A quality-of-life phone interview was conducted at the time of review. Fifteen patients (11 men and 4 women) were identified whose average age was 35 years. The underlying diagnosis was Crohn's disease in 10 and ulcerative colitis in five. The indications for home TPN were complex internal fistulas and resolving sepsis in two, postoperative septic complications (anastomotic leak/enterocutaneous fistula) in five, high-output proximal stomas in four, prolonged ileus/partial obstruction in three, and spontaneous enterocutaneous fistula in one. The average duration of home TPN was 75 days (range 7 to 240 days). Two patients (13%) failed home TPN (1 with uncontrolled sepsis; 1 with dehydration) and were readmitted to the hospital. Home TPN was discontinued in one patient whose enterocutaneous fistula failed to heal with nonoperative treatment. Home TPN was successful in 12 patients (80%): eight (53%) who underwent planned definitive surgery and four (27%) whose conditions resolved without surgery. Complications of home TPN were line sepsis and pulmonary aspergillosis in one patient. All patients preferred home TPN to further hospitalization and reported good or excellent quality of life at home. Home TPN is a safe alternative to prolonged hospitalization or early surgery in patients with complicated IBD. (J GASTROINTEST SURG 2003;7:562–566.) © 2003 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: TPN, surgery, IBD

A small number of patients with inflammatory bowel disease (IBD) develop significant intra-abdominal complications (because of the disease or after surgical therapy) resulting in intestinal failure. In some instances, surgery is performed earlier than is judged to be optimal because of pressure from the patient and for economic reasons. However, within the first few weeks after surgery, reoperating for septic complications poses significant dangers to the patient. Postoperative adhesions are most difficult to manage, and the chance of inadvertent enterotomy, mesenteric damage, or other surgical misadventure is high. Alternatively, patients can receive total parenteral nutrition (TPN), recognizing that some of these patients may require further surgery. Delaying surgery for 3 to 6 months or more may make a difficult procedure easier, and sometimes surgery may even be avoided. Traditionally, if surgery is delayed, patients have had to remain in the hospital while they receive this nutritional support. This report examines the safety and feasibility of providing short-term, home TPN for patients with IBD for whom the alternative is prolonged hospitalization or early surgery.

METHODS

Patients with IBD who were receiving temporary in-home TPN from the Mount Sinai Hospital pharmacy between June 1996 and August 2000 were

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identified from a registry of all patients receiving TPN at home. Pharmacy and office records, as well as hospital charts, were examined. Patients with malignancies or short gut syndrome, and patients receiving TPN during treatment for an acute flareup of disease were excluded from the study. Only patients with IBD in whom TPN was prescribed to delay or possibly obviate (e.g., fistula closure) the need for surgery were included. Demographic data and information related to underlying illness, indication for TPN, duration of TPN, nutritional status, and final outcome were recorded. All patients also completed a telephone questionnaire to assess patient satisfaction, quality of life, and problems encountered with home TPN (Appendix I).

Before patients were discharged from the hospital, they were assessed by a gastrointestinal surgeon and a TPN physician to determine their suitability for home TPN. Patients were deemed suitable for discharge if they had no evidence of undrained or uncontrolled sepsis, no major fluid or electrolyte disturbances, and if suitable long-term intravenous access was available. Home TPN was dispensed from the hospital pharmacy under the supervision of a pharmacist, a dietitian, and a physician (A.H.S.). Solutions and supplies were provided by Caremark pharmacies in Ontario. All costs were borne by the Ontario Health Insurance Program. TPN was delivered to patients' homes by the visiting home nursing service. TPN was administered over a 12- to 16-hour period during the night in all patients so that patients were free from the pump for 8 to 12 hours per day. Home nurses initially visited all patients twice daily. Six of the 15 patients learned to connect and disconnect themselves from the pump independently within 2 weeks of discharge from the hospital. Home nurses visited these patients once or twice a week and were available to assist with problems. Two patients were able to disconnect from the pump and required only once daily home nursing visits to commence the infusion. Seven patients continued to have twice daily home nursing visits until TPN was discontinued. Electrolytes were measured weekly in all patients. Trace elements and nutritional indexes were evaluated monthly. The physician responsible for the home TPN program (A.H.S.) reviewed the results of all blood tests.

RESULTS

Fifteen patients (11 men and 4 women) were identified with an average age of 35 ± 11.8 years (range 22 to 55 years). The underlying diagnosis was Crohn's disease in 10 and ulcerative colitis in five patients.

The indications for TPN varied. Twelve patients received home TPN after undergoing surgery during that admission. Eight patients had elective procedures, whereas four underwent emergency surgery. Five developed septic complications postoperatively (anastomotic leak/abscess/enterocutaneous fistula), four had high-output proximal stomas, and three had prolonged ileus/partial obstruction. Of the three patients who had not undergone surgery recently, two patients with Crohn's disease received preoperative home TPN for complex internal fistulas and resolving sepsis after percutaneous drainage of abscesses. One patient with Crohn's disease received home TPN for a spontaneous abscess and enterocutaneous fistula to an old surgical wound.

TPN was given to seven patients with the intention of performing delayed surgery. Five patients were given a trial of nonoperative management, with a plan to perform surgery if fistulas failed to heal. Three patients with obstructive symptoms were managed with TPN until their symptoms resolved and they were able to tolerate oral feeding.

The average duration of TPN before discharge was 19.6 ± 10.8 days (range 7 to 47 days), and for home TPN the duration was 75 ± 59.6 days (range 7 to 240 days). Fourteen patients received TPN via a peripheral intravenous central catheter (PICC), whereas one patient with problematic venous access required a Hickman catheter. Three patients with high-output stomas received intravenous fluid therapy in addition to the prescribed TPN.

Two patients (13.6%) failed home TPN after 40 and 7 days, respectively (one with uncontrolled sepsis and one with dehydration from an extremely high-output stoma) and were readmitted to the hospital. One of these patients required emergency surgery and loop ileostomy for a leak from a pouch–anal anastomosis. The other patient received TPN for an additional 43 days in the hospital before her stoma was closed. A third patient was briefly readmitted with fever and abdominal pain but improved with intravenous antibiotics. Home TPN was subsequently discontinued in this patient whose enterocutaneous fistula failed to heal with nonoperative treatment. Although this patient continues to have a low-output fistula with a normal diet, she has refused definitive surgery. Thus home TPN was successful in 12 patients (81%). Eight patients (54%) underwent planned definitive surgery after a mean 102 days of home TPN. Four patients (27%) with obstructive symptoms (n = 3) or enterocutaneous fistula (n = 1) recovered without the need for surgery (mean duration of TPN 54 days).

All patients undergoing planned definitive surgery had an intestinal resection and anastomosis without

covering the stoma. Seven of these eight patients had an uncomplicated postoperative course, whereas the other patient developed a major secondary hemorrhage and PICC line infection.

No patient developed deterioration in any of the nutritional indexes (weight, hemoglobin, transferrin, albumin, lymphocyte count) used to monitor therapy. The mean weight gain for patients on home TPN was 3.3 kg. Mean albumin level at discharge was 32.6 g/dl and 34 g/dl when TPN was discontinued. Complications of home TPN were line sepsis and pulmonary aspergillosis in one patient. Problems were infrequent at home. Three patients encountered persistent problems with pump alarms, whereas one other patient had a malfunctioning pump.

Nine patients (60%) reported that they were quite or a little anxious before discharge, whereas six patients (40%) were not at all anxious. After a week at home, 13 patients (87%) were not at all anxious, whereas two patients (13%) remained a little anxious. Patient anxiety was related to concerns about the level of expertise among community nurses (33%), whom to call with problems (33%), and PICC line safety (13%). One patient was concerned about feeling less secure than he had in the hospital.

All patients reported that they preferred receiving TPN at home to further hospitalization. Patients reported less stress on their families (47%), fewer financial concerns (13%), familiar and comfortable surroundings (75%), greater independence (27%), and being with their families (27%) as the main advantages of the home TPN program. Eight (73%) of 11 working patients were able to return to work while receiving home TPN. Five (83%) of six patients were able to resume their studies. Patients were also able to resume household duties (93%), shopping (93%), and social activities (87%). Two patients (13%) returned to sporting activities. All patients reported good or excellent quality of life with home TPN.

DISCUSSION

Outpatient TPN has potential advantages for both patients and health care providers. The feasibility and safety of its use has been demonstrated in patients requiring permanent home TPN for intestinal failure.[1] However, the use of short-term outpatient TPN as an alternative to early surgery has not previously been documented.

In the first few weeks after surgery, reoperating for septic or obstructive complications poses significant dangers to the patient. Postoperative adhesions are most difficult to manage in this early phase, and the chance of an inadvertant enterotomy, mesenteric damage, or other surgical complications is high. In addition, bringing out a defunctioning stoma and closing the abdominal wall may tax even the most experienced surgeon. Patients who have uncontrolled fistulas with gross abdominal contamination or systemic signs of instability require immediate operation. For those with controlled leaks, or fistulas, there are considerable advantages to managing them with percutaneous drainage, antibiotics, local control of the fistula, and nutritional support, with deferral of surgery for 3 to 6 months when surgical conditions are more favorable. The delay may allow for definitive surgery without the need for a stoma or possibly even obviate the need for further surgery in a small number of patients in whom fistula healing occurs. A second group of postoperative patients, where there is often pressure to reoperate, are those patients who experience a significant delay before the gastrointestinal tract begins to function again. In these patients there is usually no one site of obstruction, and surgery can be unrewarding and often puts the patient at risk for further complications. Thus observation with nutritional support is often the best management. However, the delay in surgery may have significant economic consequences to the patient and/or system, as well as psychosocial consequences for the patient. Thus there is often pressure on the surgeon to reoperate earlier than the optimal time, which puts the patient at risk for more intra-abdominal complications. Instituting home TPN may avert the pressure to perform surgery at a suboptimal time and result in improved outcome.

Our series included five patients with anastomotic leaks (presenting as an abscess or enterocutaneous fistula) and three patients who had a prolonged ileus/bowel obstruction for which a nonoperative strategy was adopted. Clearly this is a select group of patients. All of those with fistulas were treated with antibiotics, bowel rest, and nutritional support plus three had percutaneous drainage prior to discharge. The patients with a prolonged ileus were in the hospital for an average of 15 postoperative days before discharge. All had a favorable outcome with only one requiring rehospitalization and surgery earlier than planned. One patient with a fistula avoided surgery, as did all of those who had a prolonged ileus.

The presence of spontaneous internal fistulas in Crohn's disease is not in itself an indication for surgery. If surgery is indicated, most patients can be operated on within a week or two after percutaneous drainage of intra-abdominal abscesses. The patients in this series again were a select group and had complex disease. One patient with multiple enteroenteral and enterocolic fistulas presented with a large abscess in the left flank. Percutaneous drainage, antibi-

otic therapy, and TPN allowed the inflammation to subside and a single-stage operation to be performed. In a second patient with complex foregut fistulas treatment with infliximab had failed, and this patient required preoperative TPN to improve his nutritional status (weight gain 8 kg; albumin increased from 19 to 38 g/dl). In both patients, surgery was delayed to allow the inflammation to subside and to improve their nutritional status.

Two patients in this series presented with perforations of the proximal small intestine secondary to Crohn's disease, whereas another patient had a perforation secondary to a closed loop obstruction. Because of the gross abdominal contamination, resection, end stoma, and mucous fistula were performed. The stoma was constructed between 40 and 60 cm from the ligament of Treitz and the output ranged from 2500 to 5000 ml/day so these patients were unable to maintain their nutritional status with oral intake. These patients were young and active and ideally suited to outpatient TPN. In addition to the TPN, they all required extra intravenous fluids because of the excessive stoma losses. Despite concerns about electrolyte imbalance, dehydration, and fluid overload, only one patient could not be handled in the outpatient setting.

To achieve optimal results, there must be a committed team that includes a physician, a pharmacist, and a nutritionist, as well as a reliable and a well-motivated patient and family. However, unlike for those patients starting on permanent TPN, extensive training is not required. In this series, all patients lived in the metropolitan Toronto area where temporary home TPN is administered by visiting home care nurses who do not have any specialized training in the administration of TPN. Also, generally only a few days were required to organize home care nursing and to train patients and their families in the care of the line and the administration of the TPN.

Although most patients experienced some anxiety before discharge, this generally disappeared soon after discharge. Furthermore, many patients learned to mange their TPN independently, although regular visits by the home care nurse continued. Most patients were able to return to their normal activities including work and school. The psychological benefits to the patient and his or her family should not be underestimated, and the patients' enthusiastic assessments attest to this.

The infrequency of complications of short-term home TPN attests to the safety of this program. Line sepsis, venous thromboembolism, air embolism, and electrolyte and fluid imbalances are potential problems that have been reported in other series of permanent home TPN.[2] The reported complication rates with PICC lines, which are our preferred means of vascular access for short-term outpatient therapy, are lower than those associated with central venous catheters or implantable venous lines and may account for the low complication rates in this series. Our infection rate in this series was consistent with those in other published reports.[2]

In addition to the benefits to the patient, administration of TPN in the home setting results in economic benefits because TPN is a major contributor to the overall cost of hospitalization in patients with IBD. Bernstein et al.[3] reported that 27.1% of the cost of treating patients with IBD at a Canadian tertiary hospital was incurred by those requiring TPN, even though they comprised only 9.5% of all admitted IBD patients. Cohen et al.[4] reported that in their series, 27% of patients hospitalized with IBD required TPN, and the length of stay and costs for these patients were, respectively, 2.9 and 3.9 times greater than those for patients not requiring TPN. Not only does providing TPN in the outpatient setting alleviate some of the costs incurred by the health care system, it leads to decreased societal costs since many patients are able to return to work.

CONCLUSION

Although permanent home TPN is a recognized treatment modality for patients with Crohn's disease who have extensive disease or have undergone multiple resections, the utility of short-term home TPN has not been reported previously in the context of complicated IBD. Our results show that patients with IBD requiring short-term TPN can be managed on an outpatient basis with acceptable rates of complications and readmissions. In addition, deferral of surgery results in excellent outcome in a cohort of patients with complex disease. There are economic benefits of home TPN to the health care system, while the patient benefits from reduced stress on the family, increased independence, and the ability to return to normal activities including work and study.

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Appendix 1—TPN Questionnaire

We are currently evaluating the efficacy of our home TPN program at Mount Sinai Hospital. Our patients' feelings about this program are extremely important to us. This questionnaire is intended to assess patients' attitudes toward the home TPN service.

1. How did you feel when it was suggested you could go home and continue with outpatient TPN?

Extremely anxious-----Quite anxious-----A little anxious-----Not anxious at all

2. How did you feel after the first week or so of home TPN?

Extremely anxious-----Quite anxious-----A little anxious-----Not anxious at all

3. What concerns did you have going home on TPN?

. . . . . .
. . . . . .

4. What (if any) problems did you encounter with home TPN?

. . . . . .
. . . . . .

5. Were you satisfied with the visiting home nursing service?
   - How often did they visit?
   - Did they always start and stop TPN?
   - Did family members learn to start/stop TPN?

6. Were you satisfied with the contact you had with the Mount Sinai Hospital TPN team after discharge?

. . . . . .
. . . . . .

7. What did you like about having TPN at home?

. . . . . .
. . . . . .

8. Given the choice, would you rather have TPN at home or in hospital?

9. In what ways could the home TPN program be improved?

. . . . . .
. . . . . .

10. Were you able to return to any normal activities while on home TPN?

Work?	Y/N
Study?	Y/N
Shopping?	Y/N
Housework?	Y/N
Social activities?	Y/N
Sport?	Y/N

11. How would you rate your overall quality of life while on home TPN?

Extremely poor----------Poor----------Fair----------Good----------Excellent

Outcome of Patients Undergoing Ileal Pouch–Anal Anastomosis for Left-Sided Chronic Ulcerative Colitis

I. Hassan, M.D., A.F. Horgan, M.B., B.Ch., S. Nivatvongs, M.D., J. Harrington, M.A., D.R. Larson, M.S.

Chronic ulcerative colitis is not a uniform disease entity because the clinical pattern and disease characteristics differ on the basis of the anatomic location of the inflammation. The aim of this study was to compare the preoperative characteristics, postoperative complications, and long-term functional outcome of ileal pouch–anal anastomosis (IPAA) in patients with left-sided colitis to those same characteristics in patients with pancolitis. Between 1990 and 1996, a total of 565 patients underwent IPAA for chronic ulcerative colitis at our institution. Of these, 111 patients were determined to have left-sided involvement, whereas 283 patients had pancolitis. The mean age at surgery was greater in the patients with left-sided colitis (37 years vs. 34 years, $P = 0.01$), and the mean duration of disease (8.7 years vs. 7.7 years, $P = 0.05$) tended toward a significant difference between the left-sided colitis and pancolitis groups. The complication rates were similar with the exception of small bowel obstructions, for which there was a higher incidence in the group with left-sided colitis (27% vs. 13%, $P = 0.002$) at 5 years. The incidence of pouchitis (43% vs. 39%) at 5 years was comparable. Long-term functional results and quality-of-life assessment did not show any significant differences between the two groups. We were unable to detect any correlation between the extent of colon involvement and the subsequent incidence of pouchitis, long-term pouch function, and quality of life. Patients with left-sided colitis were older, had a relatively longer duration of disease, and were at increased risk for postoperative small bowel obstruction as compared to patients with pancolitis. (J GASTROINTEST SURG 2003;7:567–571). © 2003 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Chronic ulcerative colitis, ileal pouch–anal anastomosis, pancolitis, left-sided colitis, complications, functional results

The spectrum of chronic ulcerative colitis ranges from ulcerative proctitis to pancolitis. Although approximately half of the patients diagnosed as having chronic ulcerative colitis will eventually develop pancolitis, the remainder will only have variable extents of colonic inflammation.[1] Various histologic, metabolic, and immunolgic differences have been reported in patients with differing extents of colon involvement.[1–3] Furthermore, the clinical behavior of limited proctocolitis has been seen to differ from pancolitis in that proctocolitis has a lower risk of malignancy, a decreased incidence of systemic complications, and lower colectomy rates.[1,2,4] As result of these differences, it has been suggested that the variable extent of colonic involvement may not just be a manifestation of one disease, but instead limited colitis is a separate disease entity.[1]

Previous studies have shown that the underlying disease process determines the clinical outcome and postoperative functional results of patients undergoing ileal pouch–anal anastomosis (IPAA).[5–7] Better clinical and functional results have been seen in patients with familial adenomatous polyposis,[5] whereas a poorer outcome has been noted in patients with indeterminate colitis[7] or Crohns colitis,[6] as compared to patients with chronic ulcerative colitis. If indeed, based on the extent of colitis, there are distinct subtypes of patients with ulcerative colitis, this difference may potentially affect subsequent pouch function and outcome. However, only a few studies have looked at how the preoperative extent of colon involvement in patients undergoing IPAA affects the postoperative functional and clinical results.[8,9] The purpose of the present study was to see if there was

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any difference in the preoperative characteristics and postoperative clinical course of patients with limited colitis vs. pancolitis.

MATERIAL AND METHODS

Between January 1990 and December 1996, a total of 565 patients underwent an IPAA procedure for chronic ulcerative colitis at the Mayo Clinic in Rochester, Minnesota. We excluded 124 patients for the following reasons: 51 had undergone a previous subtotal colectomy elsewhere; 17 had a coexisting cancer; 10 patients subsequently underwent a liver transplant for end-stage liver disease resulting from primary sclerosing cholangitis; 15 were less than 16 years of age; and 31 patients lacked follow-up or adequate data. The pathology specimens of the remaining 441 patients were reviewed. Forty-seven patients were excluded because of unclear proximal margins. The final cohort of 394 patients, based on macroscopic and/or microscopic examination of the postoperative specimens, was divided into the following three categories: (1) pancolitis = complete involvement of the rectum and the colon including the cecum (283 patients); (2) extended left colitis = proximal extent of colitis up to the hepatic flexure (77 patients); and (3) limited left colitis = proximal extent of colitis up to the splenic flexure (34 patients). For the purposes of analysis and discussion, patients with extended left colitis and limited left colitis were considered as one group and will be referred to in subsequent sections as patients with left-sided colitis.

The type of pouch constructed was a J-shaped pouch in 384 patients (98%) and a diverting loop ileostomy in 388 patients (98.5%). Preoperative, postoperative, and follow up information on all patients undergoing IPAA was entered into a centralized database. Postoperative data included complications such as pelvic infections, intestinal obstructions, and pouch failure. Follow-up information included stool frequency, degree of fecal continence, questions related to quality of life, and occurrence of pouchitis. Pouchitis was diagnosed on the basis of signs and symptoms of increasing diarrhea, abdominal cramps, endoscopy and, if necessary, biopsy of the pouch. Follow-up for all patients was initiated 6 months after closure of the temporary ileostomy and was carried out yearly thereafter, and included return visits to the clinic and written and/or telephone questionnaires. Additional information was obtained by reviewing hospital records and follow-up letters.

Comparisons of proportions of events were carried out by means of chi-square or Fisher's exact tests. Comparisons of the distribution of ordinal variables, such as fecal incontinence, were made with rank-sum tests. Comparisons of the distribution of continuous variables (such as age or number of stools) were made with two-sample *t* tests, or with rank-sum tests when necessary. The cumulative probability of postoperative complications was estimated using the method of Kaplan and Meier, with comparisons between the two cohorts being made using log-rank tests. All significance tests were two sided, and *P* values less than 0.05 were considered statistically significant. All analyses were performed using SAS version 8.2 software (SAS Institute Inc., Cary, NC).

RESULTS

Preoperative Patient Characteristics

The male-to-female ratio, mean age at diagnosis, and mean duration of follow-up in the two groups were similar (Table 1). The average duration of disease was longer and the mean age at operation was greater in patients with left-sided colitis (patients with limited and extended left-sided colitis) compared to patients with pancolitis (see Table 1). The frequency of bloody stools and abdominal pain preoperatively was higher in patients with left-sided colitis compared to patients with pancolitis (Table 2), whereas the number of hospitalizations and the incidence of preoperative steroid use during the year prior to surgery did not differ (see Table 2). The average number of preoperative stools, average preoperative dose of steroids, and mean preoperative hemoglobin concentration were similar for the two groups (Table 3). However, the mean preoperative albumin concentrations were significantly higher in the group with left-sided colitis as compared to the group with pancolitis (see Table 3).

Postoperative Complications

The cumulative probability of various postoperative complications at 5 years in the two groups was

Table 1. Demographics of patients with left-sided colitis and pancolitis undergoing IPAA

	Left-sided colitis (n = 111)	Pancolitis (n = 283)
Sex ratio (M:F)	1:1.1	1.2:1
Mean age at diagnosis (yr)	29	27
Mean duration of disease (yr)	8.7*	7.7
Mean age at surgery (yr)	37†	34
Mean follow-up (yr)	5.6	5.7

*$P = 0.05$.
†$P = 0.01$.

Table 2. Preoperative characteristics of patients with left-sided colitis and pancolitis undergoing IPAA

	Left-sided colitis (n = 111)	Pancolitis (n = 283)
Blood in stools	91 (83%)*	195 (69%)
Pain/discomfort	84 (76%)*	166 (59%)
Current steroid use	89 (81%)	208 (74%)
Hospitalizations within the past 1 year	43 (39%)	119 (43%)

*$P < 0.05$.

similar, with the exception of small bowel obstruction, which was significantly higher in the patients with left-sided colitis compared to those with pancolitis (Table 4). The cumulative probability of pouchitis at 5 years was not significantly different between the two groups.

Functional Results and Quality-of-Life Data

The various questions pertaining to functional outcome and quality of life in the two groups are shown in Tables 5 and 6. There were no significant differences between the two groups with regard to functional results and overall quality of life after an IPAA.

The preoperative characteristics, postoperative complications, and functional outcomes were similar between the group of 47 patients excluded because of unclear proximal margins and the study cohort reported here (data not shown).

DISCUSSION

Natural history and epidemiologic studies on the clinical course of chronic ulcerative colitis have shown that approximately half of the patients develop inflammation of the entire colon.[10] Recently Loftus et al.[11] reviewed the incidence and prevalence of ulcerative colitis in Olmsted County, Rochester, Minnesota, between 1940 and 1993, and found that among all of the patients followed, 47% had pancolitis or extensive involvement and 53% had limited involvement of the colon. This variation in the extent of colonic involvement has been associated with differences in the clinical course and subsequent outcome of patients with chronic ulcerative colitis. In our present series, preoperative patient demographics, postoperative complications, and functional results for the entire group were comparable to our previous experience[12] and those of others.[13,14] Yet when the cohort of patients was divided on the basis of the extent of colonic involvement, certain differences were seen.

The average age at diagnosis and surgery and the duration of disease in the overall cohort were similar to the series reported by Fazio et al.[13] among patients with ulcerative colitis who underwent an IPAA. However, based on the extent of the colitis, the patients in our series with left-sided colitis had a longer duration of disease and were older at the time of surgery compared to patients with pancolitis. This observation was also made by Farmer et al.[10] who reported a difference in the age at operation and the duration of disease in a large cohort of patients with chronic ulcerative colitis who had differing extents of disease involvement and were followed for an extended period of time.

Patients with left-sided colitis had the same average number of stools per day and hospitalizations in the year prior to surgery but had more clinical symptoms preoperatively, as shown by the higher incidence of bloody stools and abdominal pain, compared to patients with pancolitis. This contrasted with the fact that patients with left-sided colitis had higher preoperative albumin levels but a similar inci-

Table 3. Preoperative characteristics of patients with left-sided colitis and pancolitis undergoing IPAA

	Left-sided colitis (n = 111)	Pancolitis (n = 283)
Mean No. of stools preoperatively	8.5	10
Preoperative steroid dosage (mg)	34	33.5
Albumin (mg/dl)	3.8*	3.7
Hemoglobin (gm/dl)	12.6	12.4

*$P < 0.05$.

Table 4. Cumulative 5-year probability of postoperative complications in patients with left-sided colitis and pancolitis undergoing IPAA

Complication rate at 5-years	Left-sided colitis (n = 111)	Pancolitis (n = 283)
Any complication	49%	37%
Small bowel obstruction	27%*	13%
Pouch failure	1%	1%
Pouchitis	43%	39%
Intra-abdominal abscess	6%	5%
Anal fistula	5.5%	1.5%
Anastomotic anal stricture	17%	22%

*$P = 0.002$.

dence of preoperative steroid use and a similar mean hemoglobin concentration. These preoperative laboratory values, in general, corresponded to the data reported by Ziv et al.[15] in a review of 692 patients who underwent an IPAA for chronic ulcerative colitis. These results suggest that patients with limited colitis initially have a milder clinical course with a slower evolution of symptoms and are therefore managed nonoperatively for longer periods. However, over time, the disease severity progresses to the point where these patients actually become more symptomatic than patients with pancolitis, but because of the slower disease progression they are not as debilitated.

The overall long-term postoperative complication rates between the groups were not different, with the exception of the incidence of small bowel obstruction. The occurrence of small bowel obstruction was inversely related to the extent of colon involved, with a higher incidence noted in patients with left-sided colitis as compared to patients with pancolitis (the highest incidence was seen in patients with limited left colitis, followed by patients with extended left colitis, and then pancolitis). Although when looked at as a group, the cumulative probability of small bowel obstructions was 17% at 5 years, which is comparable to our previously reported data.[16] It is possible that a longer duration of preoperative disease and more advanced age of the patients at the time of surgery were contributing factors. Techniques to decrease adhesion formation, such as placement of Seprafilm Adhesion Barrier (Genzyme Corp., Cambridge, MA), were not used during our study period; however, with their increasing availability and use it will be important to consider this factor in future trials with these products.

There was no difference in the cumulative probability of pouchitis at 5 years in the two groups. Several reports have postulated that chronic inflammation in the proximal colon extends into the terminal ileum, creating a "backwash ileitis," thus predisposing the surgically created ileal pouch to subsequent episodes of inflammation or pouchitis.[4] Our observation that the incidence of pouchitis is the same, irrespective of the proximal extent of inflammation, would suggest that extension of inflammation from the proximal colon to the terminal ileum is unlikely to be the causative factor in the pathogenesis of pouchitis.

Table 5. Comparison of functional outcome in patients with left-sided colitis and pancolitis after IPAA

	Left-sided colitis* (n = 111)	Pancolitis* (n = 283)
Incontinence		
Daytime		
None or occasional	91%	92%
Frequent/major	9%	8%
Night time		
None or occasional	84%	83%
Frequent/major	16%	18%
Mean No. of stools	7.7	8.0
Day	5.9	6.1
Night	1.8	1.9
Medication usage	55%	47%

*No significant difference between categories.

Table 6. Comparison of quality of life in patients with left-sided colitis and pancolitis after IPAA

	Left-sided colitis* (n = 111)	Pancolitis* (n = 283)
Domestic activity		
Improved	38%	38%
Unaffected	52%	54%
Restricted	10%	8%
Travel		
Improved	48%	47%
Unaffected	29%	21%
Restricted	23%	32%
Social activity		
Improved	48%	43%
Unaffected	27%	28%
Restricted	25%	29%
Sexual activity		
Improved	23%	26%
Unaffected	52%	54%
Restricted	25%	20%
Professional work		
Affected	11%	15%
Not affected	89%	85%

*No significant differences between categories.

Furthermore, because the incidence of pouchitis is lower in our patients undergoing IPAA for familial adenomatous polyposis,[5] it is unlikely that technical factors or the postoperative physiologic changes that occur in the pouch are themselves responsible for the development of pouchitis. A possible explanation has been that the underlying pathogenic factors responsible for the inflammatory process in the colon may subsequently be reactivated, precipitating a similar inflammatory response in the small bowel mucosa of the pouch, presenting as pouchitis.[17]

The functional outcomes between the two groups were comparable, demonstrating that the extent of colonic involvement does not affect postoperative pouch function or quality of life. These findings were also observed in two previous studies by Samarasekera et al.[8] and Brunnel et al.[9] who looked at postoperative pouch function and quality of life in patients with limited colitis.

CONCLUSION

Despite the evidence in the literature demonstrating various clinical, biochemical, and histologic differences between patients with differing extents of disease involvement, we believe that this variability represents a spectrum of presentations for the same disease. However, within the cohort of patients with left-sided colitis, there is a subset with a clinical course similar to that of patients with pancolitis, who eventually need surgery because of intractable symptoms. This difference in the preoperative extent of disease involvement does not affect the postoperative clinical or functional outcome and the incidence of pouchitis. These data should allow physicians caring for patients with limited disease to confidently offer IPAA as a therapeutic option when refractory disease develops.

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Neuronal Adrenergic and Muscular Cholinergic Contractile Hypersensitivity in Canine Jejunum After Extrinsic Denervation

*Bruno M. Balsiger, M.D., Chong-Liang He, M.D., Nicholas J. Zyromski, M.D., Michael G. Sarr, M.D.**

Extrinsic denervation may be responsible for motor dysfunction after small bowel transplantation. The aim of this study was to examine the role of extrinsic innervation of canine jejunum on contractile activity. An in vitro dose response of cholinergic and adrenergic agonists was evaluated in canine jejunal strips of circular muscle at 0, 2, and 8 weeks in a control group and after jejunoileal extrinsic denervation (EX DEN). Neurons in circular muscle were quantitated by means of immunohistochemical techniques. Adrenergic and cholinergic responses did not differ at any time in the control group. However, at 2 and 8 weeks, extrinsic denervation caused an increased sensitivity to the procontractile effects of the cholinergic agonist bethanechol at the level of the smooth muscle cells, and increased sensitivity to the inhibitory effects of the adrenergic agent norepinephrine mediated at the level of the enteric nervous system. Immunohistochemical analysis showed a reduction in all neurons and a complete lack of adrenergic fibers in the EX DEN group after 2 and 8 weeks. Extrinsic denervation induces enteric neuronal cholinergic and adrenergic smooth muscle hypersensitivity in canine jejunal circular muscle. (J GASTROINTEST SURG 2003;7:572–582). © 2003 The Society for Surgery of the Alimentary Tract, Inc.

KEY WORDS: Motility, smooth muscle contractions, denervation, contractility, cholinergic nerves, adrenergic nerves, denervation hypersensitivity, small intestine

Gut transplantation remains the next frontier in human organ transplantation.[1–3] However, despite great advances in our ability to suppress the immune response, our knowledge of the effects of transplantation on enteric function remains incomplete. Diarrhea is a significant problem after clinical small bowel transplantation[4] and may be related, in large part, to the transplantation procedure itself. Probably, this is largely the result of obligate extrinsic denervation of the graft, as we and others have shown.[5,6] Indeed, models of autotransplantation or in situ complete extrinsic denervation of the jejunoileum in dogs, devoid of any immune phenomena, are associated with severe diarrhea.[7] Other disorders of gastrointestinal motor function, such as intestinal pseudoobstruction and diabetic enteropathy, are related to neuropathies of extrinsic nerves entering the bowel or the intrinsic (enteric) nervous system of the gut.

The current study was designed to investigate the effects of chronic extrinsic denervation on the contractile properties of jejunal circular smooth muscle in vitro. We used a previously well-characterized and well-validated large animal model of complete in situ neural isolation of the jejunoileum in dogs.[7] This preparation extrinsically denervates the entire jejunoileum but avoids the confounding effects of im-

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mune phenomena or ischemia/reperfusion injury necessitated by a complete transplantation procedure. Our aim was to determine whether selective chronic extrinsic denervation of the small bowel alters the contractile response of jejunal circular smooth muscle to classical cholinergic and adrenergic agonists early (2 weeks) and later (8 weeks) after extrinsic denervation. This design also allowed us to investigate whether any adaptive changes occurred over the 8-week postdenervation period. Our hypothesis, based on our previous work in a small animal (rat) model,[8] was that extrinsic denervation would induce an adrenergic hypersensitivity but would not alter the response to cholinergic agonists. We specifically chose a dog model because of the much closer similarities in motor patterns between dogs and humans than between rats and humans.

METHODS

Preparation of Animals

Procedures and subsequent animal care were approved by and performed according to guidelines set forth by the Mayo Animal Care and Use Committee and the National Institutes of Health. Thirteen healthy female mongrel dogs, weighing 15 to 25 kg, were anesthetized by means of intravenous methohexital sodium (12.5 mg/kg), and anesthesia was maintained with inhaled 1.5% halothane. Dogs were assigned randomly to one of two groups: an extrinsic denervation (EX DEN) group and a control group. Dogs in the EX DEN group (n = 7) underwent our model of in situ jejunoileal neural isolation, as described in depth previously.[7] In brief, all connections (neural, lymphatic, connective tissue, intestinal wall, etc.) to the entire jejunoileum were transected except for the superior mesenteric artery and vein, which were stripped of investing adventitia for 2 cm under optical magnification. The proximal jejunum and distal ileum were transected and reanastomosed to complete the in situ neural isolation of the jejunoileum. This model has been validated as a preparation of extrinsic denervation by demonstrating lack of tissue catecholamines, a marker of extrinsic innervation.[9] Dogs in the control group (n = 6) underwent a proximal jejunal and distal ileal transection with end-to-end reanastomosis. This control group served as operated control subjects to compare the effects of anesthesia, celiotomy, and disruption of enteric myoneural continuity between the jejunoileum and the remainder of the gut necessitated in the EX DEN group. All extrinsic innervation to the bowel wall, however, was carefully preserved in this control group; any extrinsic nerves traveling within the bowel wall would, of course, be disrupted at the sites of jejunal and ileal transection and reanastomosis.

Tissue Harvest

At 0 weeks (the time of the initial operation) and 2 weeks and 8 weeks later, a biopsy sample of the proximal jejunum was obtained (all biopsy specimens were within a 20 cm segment distal to the site of jejunal transection/reanastomosis). At the 2-week time point, a noncircumferential transmural biopsy sample was obtained from the antimesenteric surface, and the enterotomy was closed transversely. This technique allowed adequate tissue for study but did not completely interrupt myoneural continuity across the biopsy site. A 20×10 mm biopsy specimen was pinned flat, mucosal side up, in chilled modified Krebs-Ringer's bicarbonate solution. The mucous and luminal contents were carefully removed with forceps. After sharp removal of the mucosa, multiple 10×2 mm transmural strips were cut in the orientation of the circular muscle for contractile studies, and the remaining tissue was preserved for immunohistochemical analysis.

Recording of Intestinal Motility

Jejunal muscle strips were transferred to eight separate 10 ml tissue chambers filled with modified Krebs-Ringer's bicarbonate solution maintained at 37.5° C and bubbled continuously with 95% O_2 and 5% CO_2. The muscle strips were suspended vertically in the axis of the circular muscle between a fixed point in the chamber and a noncompliant force transducer (Kulite Semiconductors Products, Inc., Leona, NJ) to measure isometric force from circular muscle contraction. Because the muscle strips were suspended in the orientation of the circular muscle, the contribution of longitudinal muscular contraction to measured contractile activity is believed to be negligible. Contractile activity was monitored simultaneously on a strip chart recorder (Grass 7D Polygraph; Grass Instrument Co., Quincy, MA) and converted to digital signals by a computerized data acquisition system (Biopac Systems, Inc., Goleta, CA). The digital signals were displayed and stored on a personal computer (Reason Pentium 90; Reason Technology, Inc., Minneapolis, MN) for both on-line and subsequent analyses using specialized software (AcqKnowledge; Biopac Systems, Inc.).

Tension-Length Experiment and Measurement of Spontaneous Contractile Activity

After a 45- to 60-minute equilibration in the tissue chambers with repetitive bath washout every 15

minutes, each strip was stretched incrementally at 8- to 10-minute intervals to its "optimal length," defined as the length beyond which further stretching did not increase the amplitude or the frequency of spontaneous contractile activity. After reaching this optimal length, the muscle strips were allowed to equilibrate for 10 minutes, and spontaneous baseline contractile activity was measured during this period.

Dose-Response Study

After equilibration of contractile activity, increasing doses of acetylcholine and norepinephrine were administered directly into the chambers. Because of the relatively small individual variability and good reproducibility between individual muscle strips from the same dog, we studied one muscle strip from each dog under each condition. A dose-response curve was obtained with the use of the following five increasing molar doses of acetylcholine in the bath: 3×10^{-8}, 10^{-7}, 3×10^{-7}, 10^{-6}, and 3×10^{-6}. The effects of the following five increasing molar doses of norepinephrine were tested in another chamber: 3×10^{-8}, 10^{-7}, 3×10^{-7}, 10^{-6}, and 3×10^{-6}. The drugs were added cumulatively every 6 minutes. At the conclusion of these experiments, the chambers were washed three times. After spontaneous activity was again stable, we added 10^{-6} mol/L tetrodotoxin to block all neural transmission within the strip mediated by sodium channels, and thereby evaluated the effects of cholinergic and adrenergic agonists directly on muscle function independent of enteric nerves; 15 minutes later we repeated the same dose-response study. However, instead of repeating the dose-response to acetylcholine, we used the more selective muscarinic cholinergic agonist bethanechol in the same dose range. Our goal was to test only muscarinic function at the muscular level, because almost all of the cholinergic receptors expressed on the smooth muscle cells themselves are muscarinic. All muscle strips were blotted dry, and their weights were measured after completion of the experiments. Individual measurements were then normalized by tissue weight of each muscle strip. All drugs were purchased from Sigma Chemical, St. Louis, MO.

Analysis of Data

Tracings were analyzed visually, and each strip was checked for baseline activity and qualitative responses to pharmacologic agents. To quantitate responses, we measured the area under the contractile curve (integrated contractile activity) for the 5-minute baseline period by our software program and normalized these measurements by weight of the muscle strip ($g \cdot 5$ min/mg tissue weight). This measurement was determined in the drug-free state in the buffer bath solution (spontaneous baseline activity), after tetrodotoxin, and after each dose of acetylcholine, bethanechol, or norepinephrine before and after tetrodotoxin. A new spontaneous "baseline" activity was measured after the addition of tetrodotoxin to compare the effects of bethanechol and norepinephrine in the presence of tetrodotoxin. Norepinephrine resulted in a two-phase effect comprised of an initial short inhibitory response followed by a sustained procontractile response. Therefore we analyzed the first 30 seconds after application of norepinephrine doses in order to capture the inhibitory effect. Strips in which the dose of agonist did not produce either inhibition (first 30 seconds after norepinephrine; 8%) or contraction (after acetylcholine or bethanechol; 5%, or within the first 5 minutes after norepinephrine; 26%) were excluded from the respective analysis. The excluded strips were equally distributed among groups and time points.

Dose responses were displayed as estimated concentrations of excitatory concentrations (EC) or inhibitory concentrations (IC), with spontaneous baseline activity as 100%. Concentrations of drug were first converted to their negative natural log values and plotted (x axis) against the contractile response. We then calculated the concentrations that would cause either an excitatory response of 150% of baseline contractility (50% increase) defined as the EC_{150} or an inhibitory response of 50% of baseline contractility (50% inhibition) defined as the IC_{50}. Thus an IC_{50} represents net inhibition, whereas an EC_{150} represents a net procontractile response.

Analysis of variance (ANOVA) followed by individual Student's t tests were used for comparisons among multiple measurements within groups (comparison of activity after a given drug dose across groups), and t tests were used for single comparisons both within and between groups at individual time points (i.e., effect of denervation on drug EC values or effects of tetrodotoxin on baseline spontaneous activity); a Bonferroni correction was used to correct for multiple comparisons.

Immunohistocytochemical Analysis

Jejunal tissue samples were obtained from four dogs in the control group and two in the EX DEN group at 0 weeks, and from all dogs at the end of the study. Tissue samples were fixed with Zamboni's fixative (Newcomer Supply, Middleton, WI) for 4 to 6 hours at 4° C and then washed three times with 0.1 mol/L phosphate-buffered saline (PBS) solution, transferred to 30% sucrose in 0.1 mol/L PBS, and refrigerated

for up to 24 hours until sectioned. Serial longitudinal and transverse sections (40 to 150 mm thick) were cut with a Cryostat (Miles Inc., Elkhart, IN), placed in spot plates, and flooded with 0.1 mol/L PBS with 0.3% Triton X-100 (Sigma) and 5% normal donkey serum for 2 hours to permeabilize the tissue and reduce background staining. Immunohistochemical staining was performed with protein gene product 9.5 (PGP 9.5) rabbit polyclonal antibody (1:500 dilution, Biogenesis, England, UK) and tyrosine hydroxylase sheep polyclonal antibody (1:200 dilution, Chemicon International Inc., Temecula, CA). Nonimmune sera were used as negative control samples to determine background nonimmune staining. Immunoreactivity was demonstrated by incubating the tissues with primary antibodies overnight at 4° C. Bound antibodies were visualized by incubating tissues for 2 hours with secondary antibodies to rabbit or sheep immunoglobulin G (1:200 dilution; Jackson ImmunoResearch, West Grove, PA) labeled with indocarbocyanine (Cyä2)- or Lissamine Rhodamine. Double labeling was made possible by using primary antibodies raised in different species in conjunction with species-specific secondary antibodies (donkey anti-rabbit and antisheep [Jackson ImmunoResearch]) coupled to contrasting fluorophorescence (Cyä2 or Lissamine Rhodamine). After washing with PBS, the sections were mounted on slides, air dried overnight at room temperature, and then coverslipped.

Confocal Microscopy

Lissamine Rhodamine fluorescence was visualized with a Zeiss LSM 310 laser scanning confocal microscope (Carl Zeiss, Inc.) using an argon/krypton laser tuned to 568 nm for excitation; emission was taken above 590 nm. Cyä2 fluorescence was viewed with the argon/krypton laser tuned to 488 nm for excitation with emission taken between 515 and 545 nm. Digitized images of 512 × 512 pixels were obtained with the laser scanning confocal microscope. The files collected under the confocal microscope were converted to an appropriate file for analysis using the ANALYZE software package.[10]

Nerve Density Analysis

The muscular wall was divided into the following three major regions: longitudinal muscle layer, myenteric plexus, and circular muscle layer. The circular muscle layer was further arbitrarily grouped as outer third, beginning at the myenteric border, central third, and inner third terminating at the submucosal border. One cross section from each of the three layers was used to quantify the nerves in the circular muscle layer. Four randomly selected consecutive areas of images in this region were collected. The total tissue area (including nerves, smooth muscle cells, and other kinds of cells and intercellular space) and the nerve area of those consecutive images were pooled together. The overall density of nerves in the circular layer was calculated from the pooled data. All areas selected for quantitative study had no tears or holes during tissue processing procedures and were deemed subjectively to be of good quality and representative of all other areas. Because samples at the 0-weeks time point were only available in six dogs (4 control and 2 EX DEN) and because both groups of dogs at 0 weeks were comparable (i.e., the samples were obtained from the EX DEN dogs before the bowel was denervated), we calculated the mean for results in the control and EX DEN groups at the 0-weeks time point. Values for these parameters are expressed as means ± standard error of the mean. Statistical differences between various regions were tested using analysis of variance (ANOVA).

RESULTS

Overall Health of Dogs

None of the dogs died intraoperatively. One dog in the EX DEN group, however, died on postoperative day 6 after the 2-week biopsy. Data from this dog were used in the 0- and 2-week analyses only. At necropsy, the distal ileum was necrotic and dilated, suggesting a mechanical small bowel obstruction. One dog required reoperation 5 days after extrinsic denervation because of sepsis related to an anastomotic leak at the jejunojejunostomy; 15 cm of jejunum including the jejunojejunostomy was resected. The dog recovered well, and 2 weeks after reoperation, the open biopsy and the second experiment with tissue from this dog were performed.

All dogs lost weight during the initial 2 weeks postoperatively. A net weight loss continued but in a reduced manner until week 8. Although the EX DEN dogs appeared to lose more weight than the control dogs (at 2 weeks 8% ± 3% vs. 6% ± 1% and at 8 weeks 14% ± 4% vs. 6% ± 2%, respectively), these changes were not statistically significant. Associated with the weight loss in EX DEN dogs was an early watery diarrhea that lasted for approximately 2 weeks despite the fact that the dogs appeared and acted healthy and maintained an ad libitum diet. In the control group, only one dog had diarrhea for 7 days.

Spontaneous Contractile Activity

Phasic contractile activity was recorded in all experiments beginning shortly after strips were sus-

Table 1. Spontaneous contractile activity of canine jejunal circular muscle strips: Effect of 10^{-6} mol/L tetrodotoxin

Time points (wk)	No TXX		TXX*	
	Control	EX DEN	Control	EX DEN
0	2.64 ± 0.42	2.27 ± 0.40	3.09 ± 0.56	3.11 ± 0.49
2	3.32 ± 0.73	2.27 ± 0.62	4.45 ± 1.13	2.52 ± 0.60
8	2.78 ± 0.79	1.95 ± 0.51	3.48 ± 0.91	2.57 ± 0.65

Values are means ± SEM; g · 5 min/mg; n ≥6 dogs (2 muscle strips per dog).
*Values differ from no tetrodotoxin (TTX) at each time point; $P < 0.05$.

pended in the organ chambers, washed, and stretched. Muscle strips from one EX DEN dog showed only weak activity at 2 and 8 weeks postoperatively; data from this dog were included in the data set. Quantification (area under the contractile curve; 5 min · g/mg tissue weight) revealed no differences in spontaneous baseline contractile activity either within groups at the individual time points or between groups (Table 1).

Effect of Tetrodotoxin

Blockade of neurally mediated activity within the muscle strips by incubation with 10^{-6} mol/L tetrodotoxin caused an increase in overall contractile activity in all groups at all time points (see Table 1; $P < 0.05$). This increase in contractile activity involved an increase in both amplitude of phasic activity and baseline force (Fig. 1) but did not differ between groups at any time point.

Response to Cholinergic and Adrenergic Agonists

Cholinergic Agonists. Exogenous acetylcholine induced a dose-dependent increase in maximal phasic amplitude; at higher doses the baseline tone was increased, whereas the amplitude of phasic contractions tended to decrease during the initial increase in tone in both the control and EX DEN groups (Fig. 2, *A*). At time 0 weeks (before denervation) there were no differences between groups, as would be expected, because both groups at this time point had all extrinsic innervation intact. When bethanechol was evaluated in the presence of tetrodotoxin at time 0 weeks, a procontractile dose response was evident (Fig. 2, *B*) that did not differ between groups, again, as would be expected.

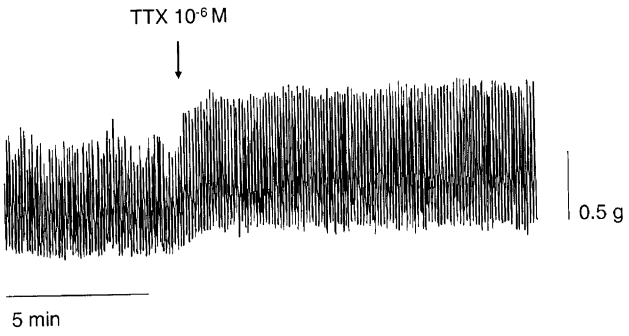

Fig. 1. Effect of tetrodotoxin (*TTX*) on spontaneous contractile activity of a representative canine jejunal circular muscle strip in a control dog at 0 weeks.

In the control group, the dose-response curves to acetylcholine and the EC_{150} evaluated at the 2-week and 8-week time points did not differ from time 0 weeks (Table 2). Despite minor changes at the lower threshold doses of bethanechol in the control group, the calculated EC_{150} values did not differ at any of the time points (see Table 2).

Different procontractile cholinergic responses were noted in the EX DEN dogs. For acetylcholine, minor changes were noted at individual concentrations, but the EC_{150} did not vary at any time point (see Table 2). However, for bethanechol in the presence of tetrodotoxin, an increase in cholinergic sensitivity was noted at both the 2-week and 8-week time points when compared as paired data in this group. Most concentrations of bethanechol, when analyzed separately, also elicited an increased contractile response. The EC_{150} for bethanechol increased from 4.8 ± 0.5 at 0 weeks to 6.4 ± 0.1 at 2 weeks and 6.2 ± 0.1 at 8 weeks (ANOVA; $P < 0.05$).

Adrenergic Agonists. The contractile responses to exogenous norepinephrine revealed a complex pattern. In 94% of the muscle strips there was a dramatic rapid inhibition of phasic activity that lasted from 30 seconds to 1 minute; in 74% of the strips this inhibition was followed by a return to normal phasic amplitude but an increase in tone (Fig. 3). When the overall 5-minute response to norepinephrine was quantitated, there were no differences either within or between groups at any time point (data not shown).

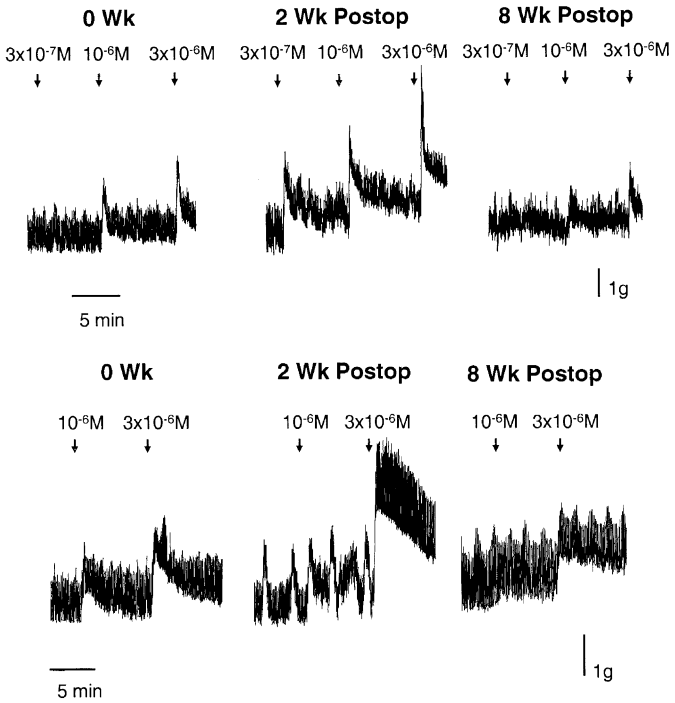

Fig. 2. Effect of cholinergic agents on spontaneous contractile activity in jejunal circular muscle of EX DEN dogs at 0, 2, and 8 weeks postoperatively. Acetylcholine (**A**) and bethanechol (**B**) in the presence of 10^{-6} mol/L tetrodotoxin.

In contrast, when we quantitated just the first 30 seconds of the inhibitory response, differences were seen between groups. In the control group, no differences were noted over the three time points with or without tetrodotoxin. However, in the EX DEN group a more marked inhibition was noted at most concentrations, and the IC50 was increased from 4.9 ± 0.2 at 0 weeks to 6.1 ± 0.1 and 6.2 ± 0.2 at 2 weeks and 8 weeks, respectively (ANOVA, $P < 0.05$; Fig. 4, Table 2). When norepinephrine was evaluated in the presence of tetrodotoxin, this adrenergic hypersensitivity to norepinephrine (i.e., a lower dose of norepinephrine required for 50% inhibition) was abolished, such that the IC_{50} at 2 weeks and 8 weeks did not differ from the IC_{50} at 0 weeks.

Immunohistochemical Analysis

When total nerve density was examined with PGP 9.5, changes were noted in both the control and EX DEN groups (Table 3 and Figs. 5 and 6). At both 2 weeks and 8 weeks, in both groups, total nerve density decreased without significant differences between groups. When adrenergic nerves were stained

Table 2. Responses to acetylcholine, bethanechol, and norepinephrine in canine jejunal circular muscle strips*

Group	Time point (wk)	Ach (EC_{150})	Be/TTX† (EC_{150})	NE (IC_{50})	NE/TXX† (IC_{50})
Control	0	6.0 ± 0.3	5.4 ± 0.7	5.5 ± 0.3	5.0 ± 0.5
	2	6.1 ± 0.1	5.3 ± 0.4	6.0 ± 0.4	5.1 ± 0.7
	8	6.2 ± 0.4	6.0 ± 0.1	5.7 ± 0.5	5.2 ± 0.3
EX DEN	0	5.3 ± 0.4	4.8 ± 0.5	4.9 ± 0.2	4.7 ± 0.9
	2	6.2 ± 0.3	6.4 ± 0.1‡	6.1 ± 0.1‡	4.8 ± 0.8
	8	6.1 ± 0.4	6.2 ± 0.1‡	6.2 ± 0.2‡	5.1 ± 0.5

*Values are negative log of drug concentrations that elicit 150% of baseline activity (EC_{150}) for acetylcholine (Ach) and bethanechol (Be) and 50% of baseline activity (IC_{50}) for norepinephrine (NE), n ≥ 4 dogs (1 muscle strip per dog). The effect of NE was measured over the first 30 seconds after administration of NE.
†In the presence of 10^{-6} mol/L tetrodotoxin (TTX).
‡Differs across the time points in same groups; ANOVA, $P < 0.05$.

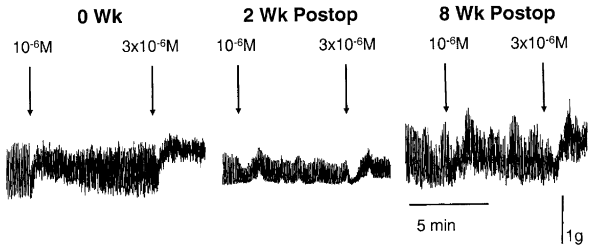

Fig. 3. Effect of norepinephrine on spontaneous contractile activity in a representative jejunal circular muscle strip from an EX DEN dog.

for tyrosine hydroxylase activity, approximately 3% of nerves stained positive at 0 weeks. Immunohistochemical staining in the control group decreased at 2 weeks and 8 weeks, respectively; as expected, no tyrosine hydroxylase activity was evident in the EX DEN group at 2 weeks and 8 weeks.

DISCUSSION

We were specifically interested in the response of canine jejunal circular smooth muscle to the classic cholinergic and adrenergic neurotransmitters before and after chronic extrinsic denervation. These motor responses were of special interest because small bowel transplantation necessitates extrinsic denervation of the small bowel involving both a complete vagotomy with its cholinergic input and a complete sympathectomy with its adrenergic input. After denervation procedures in other muscular organs, an increase in sensitivity to the appropriate neurotransmitter has been shown in skeletal muscle,[11] aortic smooth muscle,[12] and cardiac muscle.[13] This relative increase in responsiveness, termed "hypersensitivity" or "supersensitivity," is defined as the phenomenon in which the dose of a substance required to produce a given biological response becomes less than in the normal tissue.[14]

The primary findings in our study were that after chronic extrinsic denervation, spontaneous contractile activity and the increase in contractile activity after enteric neural blockade did not change in canine circular smooth muscle. In contrast, cholinergic mechanisms mediated at the level of the smooth muscle responded to chronic extrinsic denervation with a hypersensitivity. Similarly, inhibitory neural mechanisms mediated within the enteric nervous system were hypersensitive to exogenous norepinephrine, resulting in a more pronounced inhibition of contractile activity to a given dose of norepinephrine. However, spontaneous contractile activity and both the neural and muscular mechanisms responsible for the later sustained procontractile effect of norepinephrine (following the initial effect) remained unchanged by extrinsic denervation. Immunohistochemical analysis confirmed the absence of adrenergic innervation after extrinsic denervation, but otherwise a similar decrease in overall nerve density was observed in both experimental groups.

Spontaneous contractile activity of jejunal circular muscle strips was not specifically influenced by the extrinsic denervation. Using the same animal model, but studying the electrophysiology of the canine je-

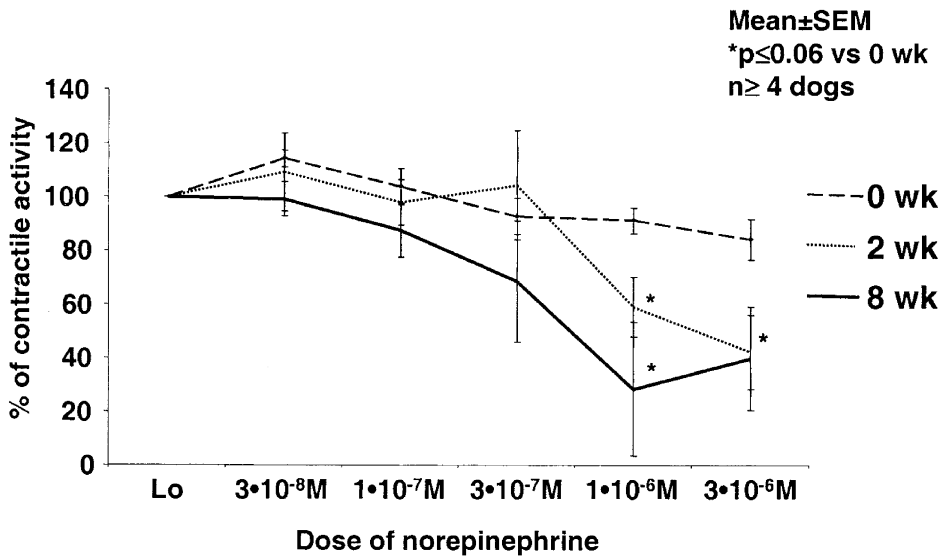

Fig. 4. Dose response of norepinephrine for the initial 30 seconds after norepinephrine administration in EX DEN canine jejunal circular muscle strips.

Table 3. Nerve density of canine circular jejunal muscle*

	PGP 9.5		Tyrosine hydroxylase	
Time points (wk)	Control	EX DEN	Control	EX DEN
0	12 ± 3		3.0 ± 0.9	
2	6 ± 2	6 ± 1	1.0 ± 0.2	0†
8	4 ± 1†	2 ± 1†	0.9 ± 0.2†	0†

*Values at 0 weeks represent pooled mean ± SEM of four dogs from the control group and two dogs from the EX DEN group; both groups should be comparable at 0 weeks; all other time points are means ± SEM; n = 6 dogs in each group.
†Differs from 0 weeks; $P \leq 0.06$.

junal circular layer, we had previously studied the effects of extrinsic denervation.[15] This study found no changes in frequency of contractions, resting membrane potential, or amplitude of the intracellular slow wave but did suggest a mild increase in the amplitude of contractions. In the rat, extrinsic denervation was associated with an increase in contractile activity in circular[16] but not in longitudinal muscle contractions in the jejunum.[17] These findings point out marked differences not only between species but also between anatomic regions within the gut wall. These anatomic differences are further reinforced by our previous findings that spontaneous activity was unaffected in rat circular or longitudinal ileal muscle[8,18] or in canine longitudinal muscle in jejunum or ileum.[19] The lack of any changes in the current study in dog jejunal circular muscle suggests that extrinsic innervation or neural input originating from the duodenum via continuity of the enteric nervous system (over a 20 cm segment) does not seem to influence spontaneous contractile activity.

In contrast, blockade of enteric neural activity with tetrodotoxin markedly increased overall contractile activity in both extrinsically innervated and denervated groups. We have obtained similar findings in rat circular jejunal muscle,[16] suggesting a tonic inhibition of myogenic contractile activity mediated by the enteric neural system. This increase in contractile activity after enteric neural blockade is also dependent on anatomic region and the muscular layer of the bowel wall because, in canine jejunal and ileal longitudinal muscle, tetrodotoxin decreased spontaneous activity,[20] whereas in rat jejunal longitudinal muscle, as well as ileal longitudinal and jejunal muscle, tetrodotoxin had no effect on spontaneous contractile activity.

Extrinsic denervation was associated with an increased cholinergic sensitivity in the presence of tetrodotoxin in our study. Because this cholinergic hypersensitivity was not observed in the absence of neural blockade with tetrodotoxin, this finding suggests an effect mediated at the level of the smooth muscle and thus independent of effects mediated in the enteric nervous system. Whether the increased cholinergic sensitivity after tetrodotoxin is mediated by a change in the number or sensitivity of cholinergic receptors on the smooth muscle, an effect on the intracellular receptor-coupled signaling mecha-

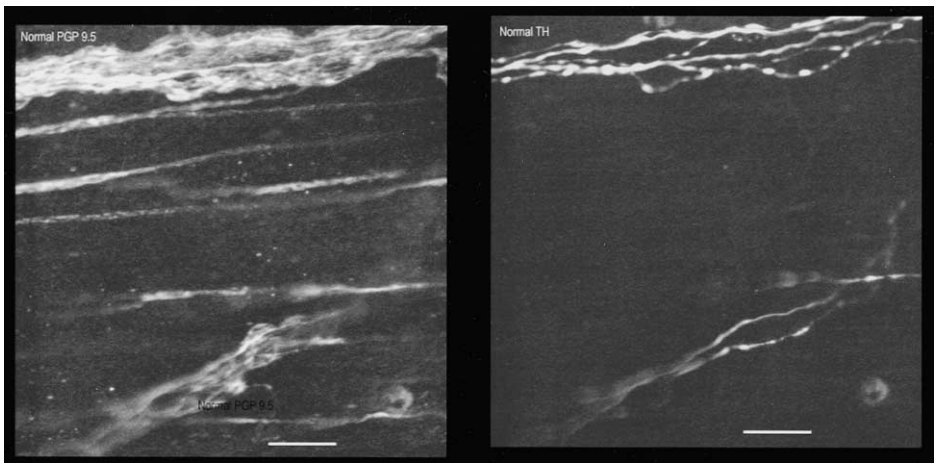

Fig. 5. Immunohistochemistry of normal neurally intact canine jejunal circular smooth muscle stained for PGP 9.5 (*left panel*) and tyrosine hydroxylase (*right panel*).

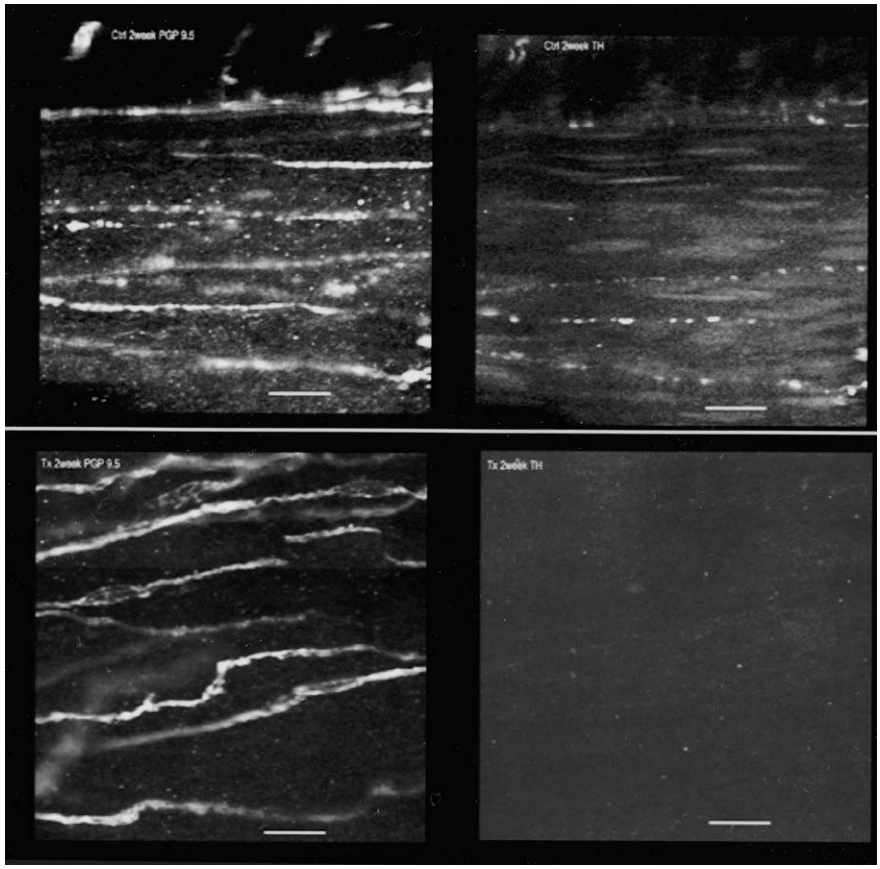

Fig. 6. Immunohistochemistry of canine jejunal circular muscle at the 2-week time point stained for PGP 9.5 in control (*upper left panel*) and EX DEN (*lower left panel*) dogs postoperatively and similarly stained for tyrosine hydroxylase in control (*upper right panel*) and EX DEN (*lower right panel*) dogs.

nism of cholinergic excitation, or the lack of an offsetting inhibitory effect mediated through the enteric nervous system counteracting the increased muscular response to pharmacologic cholinergic stimulation is unknown and cannot be further elucidated by our experimental design. Similar experimental findings of a cholinergic hypersensitivity after extrinsic denervation of the gut have not been reported. Indeed, in the rat ileal and jejunal circular and longitudinal muscles,[8,17,18] and in our recent work in canine jejunal longitudinal muscle,[20] although bethanechol induced a procontractile response, no denervation hypersensitivity was evident. Similarly, Govier et al.[21] failed to find any cholinergic denervation hypersensitivity in guinea pig ileal longitudinal smooth muscle. Also, our previous work in canine jejunal circular muscle also failed to demonstrate any hypersensitivity after extrinsic denervation to bethanechol or substance P.[15] We assume that these latter changes are related to differences in experimental design; in that experimental setup, we measured only changes in contractile amplitude, whereas our current study examined total contractile force (a combination of changes in amplitude, baseline tone, and frequency). The lack of a similar response in the rat again suggests marked species differences.

Our study also demonstrated an adrenergic hypersensitivity to extrinsic denervation. Our laboratory has previously characterized the response of rat jejunal and ileal muscle layers to extrinsic denervation; rat ileal circular and longitudinal muscle layers, but not jejunal circular or longitudinal muscle layers, show a rather dramatic adrenergic denervation hypersensitivity.[17,18] The current canine studies showed a markedly different response. First, unlike in rat intestinal smooth muscle and dog longitudinal muscle,[9] which show a prolonged inhibitory response to norepinephrine, dog jejunal circular muscle manifested a similar initial dose-dependent inhibitory response, but this inhibitory effect was followed by a procontractile response evident by both a return of phasic amplitude to normal and an increase in baseline tone. The biphasic response occurred both before and after extrinsic denervation, and thus was not likely mediated by extrinsic neural mechanisms. However, the initial adrenergic inhibitory response, unlike in rat

jejunal circular and longitudinal muscle, showed a denervation hypersensitivity; no effect was evident in the later procontractile response. Because tetrodotoxin abolished this adrenergic hypersensitivity, the increased response to norepinephrine appears to be mediated by changes not in the muscle cell (as in rat ileum) but rather by changes in the enteric nervous system. These findings in the dog are consistent with current thinking that most all extrinsic innervation modulating the non–sphincteric muscularis externa of the small bowel synapses only in the enteric nervous system[22,23] with few, if any, direct synapses at the level of the smooth muscle cells.[24,25] Frigo et al.[26] showed an adrenergic hypersensitivity in guinea pig colon after chronic sympathectomy, an effect specific for adrenergic agents involving both α-and β-adrenergic receptors at the level of both the enteric nerves as well as at the muscle layer. Once again, the differences noted between species and anatomic regions point to marked variability in the enteric and extrinsic neural modulation of gut smooth muscle contractile activity.

Because our studies were conducted at both 2 and 8 weeks after extrinsic denervation, we were able to investigate some aspects of the adaptive response (up to 8 weeks) to chronic extrinsic denervation and to disruption of enteric neural continuity to the proximal gut (control group). Spontaneous contractile activity, either in the absence or presence of tetrodotoxin, did not change over this time interval, nor did the dose responses to acetylcholine, bethanechol, or norepinephrine, either in the absence or presence of tetrodotoxin. This lack of change in responses over the 8-week interval may suggest either that adaptation has already been fully established by the 2-week time point without further change thereafter or that any further adaptation to chronic extrinsic denervation may take much longer to establish. These observations are consistent with our previous experiments in rat gut muscle, which also failed to show significant adaptive changes between the 2- and 8-week time points; interestingly, the changes that occurred as early as 2 weeks postoperatively secondary to extrinsic denervation in the rat ileum were also evident 1 year after extrinsic denervation.[27]

Finally, our observations with the use of immunohistochemical neural staining, although crude, are of interest. First, the lack of tyrosine hydroxylase activity in the EX DEN group confirms the extent of our canine model of extrinsic denervation. Second, the reduction in total nerve density (as quantitated by PGP 9.5 staining) occurred to a similar extent in both groups. Obviously this reduction was not solely a response to extrinsic denervation, because it occurred in both groups. Whether this decrease in nerve density was a reaction to disruption of enteric neural continuity of the jejunum with the more proximal duodenum (present in both groups) or it was a nonspecific effect of the anesthetic and celiotomy remains unknown, although the former seems likely.

In summary, our study showed that extrinsic denervation of the dog jejunoileum, but not simple disruption of enteric neural continuity with the duodenum, led to both cholinergic and adrenergic denervation hypersensitivity. The cholinergic hypersensitivity appeared to be mediated not at the level of the enteric nervous system but rather directly at the muscle layer, whereas the adrenergic response appeared to be mediated through the enteric nervous system. These changes in neural responses in conjunction with our observations in the rat jejunum and ileum and canine longitudinal muscle serve to reinforce the marked differences in neural modulation of gut smooth muscle contractile activity between species, between anatomic regions, and even within muscle layers of the bowel wall at any one site, and may manifest as changes in enteric motor function clinically. How these marked species differences compare to the human jejunal smooth muscle is yet to be determined.

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Erratum

The article entitled, "Apoptotic and Proliferative Indexes in Esophageal Cancer: Predictors of Response to Neoadjuvant Therapy Apoptosis and Proliferation in Esophageal Cancer," by Beardsmore DM, Verbeke CS, Davies CL, Guillou PJ, and Clork G.W.B., published in the January issue of the JOURNAL OF GASTROINTESTINAL SURGERY (2003;7:77–87) should have been entitled, "Apoptotic and Proliferative Indexes in Esophageal Cancer: Predictors of Response to Neoadjuvant Therapy."

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Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Bariatric Surgery, May 30–31, 2003; September 26–27, 2003; The University of Texas Southwestern Medical Center at Dallas. Cost: physicians ($300, lecture only; $1050, lecture and lab); UTSW and SCMIS Alumni ($250, lecture only; $950, lecture and lab); nurse ($175, lecture only; $375, lecture and lab). For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Bariatric Surgery Mini-Fellowship Program, June 22–27, 2003; August 24–29, 2003; October 26–31, 2003; The University of Texas Southwestern Medical Center at Dallas. Cost: $12,500 (team of 2 physicians and 1 nurse); $6,250 (physician); $1,000 (nurse). For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Management & Percutaneous Ablation of Small Retinal Tumors, July 25–26, 2003; The University of Texas Southwestern Medical Center at Dallas. For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

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