Who Would Have Thought It?

An Operation Proves to Be the Most Effective Therapy for Adult-Onset Diabetes Mellitus


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Objective
This report documents that the gastric bypass operation provides long-term control for obesity and diabetes.

Summary Background Data
Obesity and diabetes, both notoriously resistant to medical therapy, continue to be two of our most common and serious diseases.

Methods
Over the last 14 years, 608 morbidly obese patients underwent gastric bypass, an operation that restricts caloric intake by (1) reducing the functional stomach to approximately 30 mL, (2) delaying gastric emptying with a c. 0.8 to 1.0 cm gastric outlet, and (3) excluding foregut with a 40 to 60 cm Roux-en-Y gastrojejunostomy. Even though many of the patients were seriously ill, the operation was performed with a perioperative mortality and complication rate of 1.5% and 8.5%, respectively. Seventeen of the 608 patients (<3%) were lost to follow-up.

Results
Gastric bypass provides durable weight control. Weights fell from a preoperative mean of 304.4 lb (range, 198 to 615 lb) to 192.2 lb (range, 104 to 466) by 1 year and were maintained at 205.4 lb (range, 107 to 512 lb) at 5 years, 206.5 lb (130 to 388 lb) at 10 years, and 204.7 lb (158 to 270 lb) at 14 years.

The operation provides long-term control of non–insulin-dependent diabetes mellitus (NIDDM). In those patients with adequate follow-up, 121 of 146 patients (82.9%) with NIDDM and 150 of 152 patients (98.7%) with glucose impairment maintained normal levels of plasma glucose, glycosylated hemoglobin, and insulin. These antidiabetic effects appear to be due primarily to a reduction in caloric intake, suggesting that insulin resistance is a secondary protective effect rather than the initial lesion. In addition to the control of weight and NIDDM, gastric bypass also corrected or alleviated a number of other comorbidities of obesity, including hypertension, sleep apnea, cardiopulmonary failure, arthritis, and infertility.
Conclusions

Gastric bypass is now established as an effective and safe therapy for morbid obesity and its associated morbidities. No other therapy has produced such durable and complete control of diabetes mellitus.

Non-insulin-dependent diabetes mellitus (NIDDM), the form of diabetes that afflicts more than 90% of the 14 million diabetic Americans, is notoriously resistant to treatment. The current therapies, including insulin, diet, exercise, behavior modification, and oral agents, rarely return patients to long-term euglycemia. Further, these therapies have not been shown to reduce the incidence of the complications of diabetes, including stroke, myocardial infarction, loss of vision, renal failure, amputations, and neuropathies.

This report details our experience with the gastric bypass operation in a series of 330 of 608 (54.3%) morbidly obese patients who had either NIDDM or impaired glucose tolerance (IGT). Operative management restored and maintained normal levels of glucose, insulin, and glycosylated hemoglobin in 91% of the patients for as long as 14 years. This degree of diabetic control is far better than any reported by medical means.

METHODS

Since 1980, 608 morbidly obese patients were treated with the Greenville modification of Mason's gastric bypass operation. The operations were performed on 404 white (66.4%) and 102 African American (16.8%) women and on 87 white (14.3%) and 15 African American (2.5%) men. The average age at the time of surgery was 37.3 years (range, 14 to 64 years). Preoperative weights of the group ranged from 198 to 615 lb, with a mean of 304.4 lb. Of these 608 individuals, 364 (59.9%) were employed: two as executives or major professionals; 52 as managers, professionals, or owners of medium businesses; 46 as administrators, semiprofessionals, or small business owners; 122 as technicians or clerical/sales workers; 79 as skilled workers; 42 as semiskilled workers; and 21 as laborers. Two hundred forty-four (40.1%) were not employed. Marital status inquiries revealed that 418 (68.8%) were married, 54 (8.9%) were divorced, 25 (4.1%) were separated, 11 were (1.8%) widowed, and 100 (16.4%) had never married.

Of these 608 morbidly obese patients, 165 (27%) had NIDDM, and another 165 (27%) had IGT. Before surgery, 353 (58.1%) of the patients had hypertension.

Of the initial 608 patients who underwent surgery, 553 of the 574 living patients maintained contact over the 14 years, a follow-up rate of 96.3%. After surgery, 599 (98.5%) survived the periparative period and 574 (94.4%) are currently alive. Of these, 281 (49%) were examined in the clinic and 272 (47%) were interviewed by phone over the last year. Information was received from the family for 4 (1%) patients, and 17 patients (3%) were lost to follow-up.

Patient Selection

Patients between the ages of 14 and 65 years were accepted for evaluation for bariatric surgery if they had a body mass index (BMI, kg/m²) of ≥35 if comorbidities such as diabetes, cardiopulmonary failure, or arthritis existed or ≥40 if no comorbidities existed. Table 1 shows ideal body weights and BMIs at each height as well as the weights for these heights when BMI values are 24 (considered normal weight by some), 35, and 40. Contraindications to surgery included a history of unresolved alcohol or substance abuse in the previous 5 years, depression, an inability or unwillingness to cooperate in long-term follow-up, a lack of understanding of the operation and its consequences, an unrealistic expectation of outcome, and failure to correct the medical conditions to a degree to permit safe surgery. Strong immutable opposition from the family was a relative contraindication.

Preoperative Evaluation and Preparation

The evaluation of these patients as candidates for bariatric surgery was simplified as we gained experience. Even so, we continue to prefer a slow evaluation, that is, over 2 to 3 months, to be certain that the patient and the family are well educated about the operation and its consequences. The first visit is used for the initial evaluation, for the first screening to determine whether the patient is a candidate for bariatric surgery, for the distribution of educational materials, and, if the patient is deemed suitable, for ordering of a psychologic evaluation as well as a chest roentgenogram, upper gastrointestinal series, complete blood count, SMA-17, thyroid-stimulating hormone levels, urinalysis, electrocardio-
Table 1. IDEAL BODY WEIGHTS FOR MEN AND WOMEN WITH COMPARISONS TO
WEIGHTS WITH BMIS AT 24, 35, AND 40*

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<th>Height (cm)</th>
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BMI = body mass index.
* Based on the 1983 tables from the Metropolitan Life Insurance Company. New York, New York. Surgery is the therapy of choice for weight control when the BMI ≥35 in a patient with comorbidities such as diabetes and hypertension or when the BMI ≥40 in a patient without such comorbidities.

gram, and pregnancy test in women younger than age 50. Every patient is seen by the project psychologist, because depression and other emotional disorders are common in the morbidly obese population. The decision to proceed with bariatric surgery is made on the second visit, usually a month later, after the review of the various study outcomes and another counseling session with the patient. If the patient then requests the operation, additional consultations to evaluate and stabilize cardiac failure, pickwickian syndrome, sleep apnea, anemia, or pulmonary function are requested if needed. Morbidly obese patients who select surgical therapy have often exhausted all other treatment options. They must be regarded as chronically ill individuals with complex medical problems, often burdened with 50 to 100 lb of excess water, chronic malnutrition, and complex social conflicts. Insurance approval, occasionally difficult to obtain, is also requested at this visit. The third visit occurs within a week before surgery, at which time the operation, risks, alternatives, and benefits are again reviewed and the preadmission hospital workup is completed.

Preoperative Preparation

Serious health problems need to be stabilized before surgery. Skin lesions need to clear as much as possible, and chronic problems, such as asthma, chronic pulmonary infections, diabetes, and hypertension need to be stabilized; if the patient is receiving medications, these need to be reviewed and adjusted to appropriate levels. Patients are generally admitted on the morning of surgery. Complicated cases, however, such as those involv-
The dissection peritoneum that is entered through the Omnipor transabdominal incision in patients with cardiorespiratory failure, may require several days of preparation in the hospital to bring them to an optimal preoperative status. A cephalosporin is given intravenously for prophylaxis the morning of surgery and for 2 days thereafter.

Special equipment must be available for the care of the morbidly obese. The clinics require seats, couches, examining tables, and wheelchairs designed for individuals who may weigh over 600 lb. In addition, sturdy beds, strong gurneys, and X-ray that can accommodate these patients are required in the hospital.

**Description of the Operation**

A diagram of the operation is shown in Figure 1. The abdomen is entered through a high midline incision, and exposure is provided by a mechanical retractor, such as the Omni models (Omni-trak, St. Paul, MN). If the exploration demonstrates no contraindications, the upper stomach is isolated by inserting the index finger gently into the angle at the cardia to the left of the esophagus. At this point, there is a weak, thin area of the posterior peritoneum that is easily entered by the dissecting finger. The dissection is gently continued behind the esophagus and cardia and the finger brought out, not at the right side of the esophagus but between the ascending branches of the left gastric artery, 2.5 to 3.0 cm below the esophagogastric junction. A No. 36 Malecot catheter, from which the bulbous end has been cut, is used to pull a TA90 stapling instrument through the passage. A proximal pouch measuring 4 cm in width and 1.5 cm in height, approximately the size of a thumb, is then prepared by firing the staples. Two additional layers of similar TA90 staples are then superimposed and fired over the first set. A figure-of-eight suture is placed at each end of the staple line to close the ends securely and to serve as guy sutures. To prepare the Roux-en-Y, the jejunum is divided 40 to 60 cm from the ligament of Treitz with the GIA stapling instrument (Ethicon, Somerville, NJ) and then threaded through the mesocolon and the lesser sac and taken back out by the bare area of the greater curvature. The proximal end of the distal jejunum is then sutured to the gastric pouch. The anastomosis is sewn to fit loosely around a 0.8-cm Salem SUMP tube (Sherwood Medical Co., St. Louis, MO) in two layers with continuous polypropylene. The Roux-en-Y enterostomy is then completed by joining the proximal jejunum end-to-side to the distal jejunum 60 cm below the gastroenterostomy with GIA and TA55 stapling devices. It is important to ensure that the intestine is not constricted in its passage through the lesser sac, that the Roux loop is attached to the mesocolon with three sutures to prevent an internal hernia, and that the enterostomy is not bleeding from the internal staple line before applying the TA55. The abdomen is closed with a running double-stranded 0 PDS absorbable suture (Ethicon, Somerville, NJ). The skin is stapled. The operation can usually be performed in 60 to 75 minutes; blood loss rarely exceeds 300 mL. The first 519 gastric partitions were done with a four-row TA90 stapling device. Since then, to avoid further staple line failures, we have either divided the stomach or used the triple superimposed layers of double-row TA90 staples. Except for the different approaches for partition, the operations were identical and can therefore be evaluated as one cohort.

**Postoperative Care**

The postoperative care of bariatric patients demands close attention. The first 24 hours are particularly critical because of the great seriousness of a leak or intra-abdominal infection in these individuals. If the pulse remains over 120, if there is a rise in temperature over 39 C., or if the patient looks ill despite normal vital signs, emergency exploration and additional types of antibiotics may be needed. In such cases, swallow of a small amount of a
water-soluble radiopaque agent followed by barium may be helpful to detect an anastomotic leak. (Such tests are not always reliable; we have several patients with leaks who, on the first examination, demonstrated normal passage of barium without extravasation.) Neglect of a perforation or intra-abdominal infection is associated with a high mortality rate. If there is doubt, it is best to proceed with surgery; an unnecessary exploration is a lot safer than a missed perforation.

Patients usually spend the first night on an intermediate unit with nurses who are familiar with bariatric care. Patients are kept on nothing-by-mouth status until they pass flatus, usually on the 3rd day, begun on half-strength Ensure Plus (30 mL four times daily) with water (30 mL every hour) on the 4th day, and full-strength Ensure Plus with water, in the same doses, on the 5th or 6th day, when they are sent home. After discharge, the patients are maintained on full fluids for 2 weeks and then cautiously progress to a full diet by the end of 6 weeks. Most patients gradually return to their previous diet in terms of variety but with a marked reduction in quantity, because they fill up quickly and because the gastric pouch empties slowly. Most patients cannot tolerate simple carbohydrates, such as candy, because of the dumping induced by the gastroenterostomy. Meats may present difficulties: we start slowly with fish, then progress to chicken, and finally, after some months, introduce red meat. By the end of 3 months, most patients eat a limited but well-balanced diet. Considerable counseling may be needed during the initial adjustment to the operation so that the patients understand that the emesis after overeating and the dumping after the ingestion of candy are desirable side effects of the operation and that these symptoms can be avoided by adherence to the dietary limitations.

The most common early complications seen in the clinic are wound abscesses, and these, as might be expected, occur most commonly in the diabetic patients. The wound infections generally present as red bulges that drain spontaneously or that can be drained through a small 1- to 2-cm opening of the incision. It is not necessary to open the whole wound or significant lengths of the incision; such interventions may lead to long-term wound care and delays in healing. Late subphrenic abscesses can usually be drained percutaneously with interventional radiologic techniques.

Long-Term Follow-up

Patients generally do remarkably well and are delighted with their new body image, their freedom from diabetes, and their new life. Daily long-term intake of liquid or chewable total mineral and vitamin product is essential; 600 μg/day of B₁₂ is the recommended minimum dose.¹ Omission of this may lead to severe anemia, Wernicke-Korsakoff syndrome, or other neuropathies. Weight gain exceeding 12% above the lowest postoperative weight is generally the result of staple line breakdown, pouch or anastomotic dilatation, or compulsive snacking. Abdominal pain is most commonly due to cholecystitis, although some patients may develop marginal ulcers that clear quickly with histamine blockers and, when indicated, with therapy for Helicobacter pylori. Recurrent vomiting usually signals overeating but may be due to stenosis of the gastrojejunostomy. Such strictures can almost always be relieved with one or two dilatations of the anastomosis. Finally, these patients require considerable emotional support from their referring physician, the surgical staff, and their families. We have found monthly support groups useful.

Revision of Failed Bariatric Procedures

All bariatric procedures have a failure rate, ranging from 80% or more for horizontal gastroplasties to about 5% to 10% for the vertical banded gastroplasties and gastric bypasses. Most of the failures are due to failed staple

Figure 2. Revision of a failed gastric bypass. The pouch is restored to the original 20- to 30-cm size by dividing the stomach and resecting the previous staple line en bloc with the gastroenterostomy. A new anastomosis is then constructed to restore the 8-10-mm gastric outlet. The formation of a fistula between the two gastric segments can be minimized by overswinging the two staple lines and interposing a tongue of omentum.
lines, stenosis of the gastric outlets, distended gastric pouches, or dilated gastrojejunostomies. Revision of these failures is technically challenging and associated with a high complication and second failure rate. Our most useful approach has been to (1) define the stomach and the alimentary limb, (2) expose the pouch and previous anastomosis, (3) resect the old staple line and the gastroenterostomy, and (4) reanastomose the jejunal limb to the now-divided gastric pouch (Fig. 2).

RESULTS

Control of Disease

The operation produced significant and durable weight loss. Table 2 demonstrates that the mean preoperative weight of 304.4 lb (range, 198 to 615 lb) drops to 192.2 lb (range, 104 to 466 lb) by the 1st year, a decrease of 112 lb. Usually there is some additional loss by 18 months, followed by a remarkable stability of weight for almost a decade and a half: 205.4 lb (range, 107 to 512 lb) at 5 years, 206.2 lb (range, 130 to 388 lb) at 10 years, and 204.7 lb (range, 158 to 270 lb) at 14 years. Not only has the mean weight of these patients at 14 years dropped 100 lb below their operative weights, but also, the maximum weights have diminished even more significantly, from 615 lb to 270 lb. An average maximum weight loss of 70% of excess body weight occurred approximately 2 years after surgery. At the end of 5 years, mean weight loss was 58% of excess body weight; after 10 years, 55%; and after 14 years, 49%. Similarly, the mean BMI levels fell from 49.7 to 31.5, 33.7, 34.7, and 34.9 at 1, 5, 10, and 14 years, respectively. The durability of the weight loss is graphically illustrated in Figure 3.

Gastric bypass effectively reduced the proportion of body fat. Measurements of body composition with hydrodensitometry (underwater immersion weighing) in 220 randomly selected patients demonstrated that the percentage of fat in females fell from a preoperative mean of 50.92% to 38.46% and in males from 46.70% to 31.93%.

Even more striking is the control of adult-onset diabetes. Before surgery, 165 of 608 patients (27%) had NIDDM and another 165 patients (27%) had IGT, however, a full set of data was not available for 19 of the 608 patients for technical reasons. Adequate follow-up data are available on 298 glucose-intolerant patients following surgery, 146 of 165 (88.5%) with NIDDM and 152 of 165 (92.1%) with IGT. Of these 298 patients, 271 (91%) have maintained normal values of fasting blood glucose and glycosylated hemoglobin, whereas 27 (9%) continue to be diabetic. Among these 27 diabetic patients, 25 originally presented with NIDDM and 2 with IGT. As of September 12, 1994, the date of the last annual summary, 121 of 146 patients (82.9%) who presented with NIDDM maintained normal values of blood glucose and glycosylated hemoglobin.

The 165 patients with IGT were followed until death

### Table 2. Weight Loss in 608 Morbidly Obese Patients after the Gastric Bypass over 14 Years with 97% Follow-Up

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<th>Mean Weights (lb) (range)</th>
<th>% Excess Weight Loss (range)</th>
<th>Body Mass Index</th>
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<td>Preoperation 304.4 (198-615) 0.0 49.7 (33.9-101.6)</td>
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<tr>
<td>1 yr 192.2 (104-466) 68.9 (10.3-124) 31.5 (19.1-69.3)</td>
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<td>5 yr 205.4 (107-512) 57.7 (-14.6-115.9) 33.7 (19.6-7.16)</td>
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<td>10 yr 206.2 (130-388) 54.7 (-0.9-103.1) 34.7 (22.5-64.7)</td>
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<td>14 yr 204.7 (158-270) 49.2 (7.2-80.9) 34.9 (25.9-54.6)</td>
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or until September 12, 1994, for an average of 7.6 years after gastric bypass surgery, for a total of 1254 patient years of follow-up. Two patients (1.2%) who presented with IGT progressed to NIDDM; of the others available for study, 150 of 152 (98.7%) reverted to euglycemia. (Compared with a similar IGT population who did not undergo surgery, between 43 and 75 would have been expected to progress to NIDDM² within the same time frame [95% confidence interval].)

The normalization of glucose metabolism occurred with surprising speed, even before there was significant weight loss. Figure 4 demonstrates the response in patient 1, whose blood sugar levels were almost uncontrollable, with a fasting blood glucose of 495 mg/dL, despite administration of 90 U of insulin on the day before surgery. By the 6th postoperative day, she no longer required insulin, and by the end of the first month, her fasting blood glucose fell to 155 mg/dL. Within 3 months, her fasting blood glucose and glycosylated hemoglobin levels returned to normal. Figure 5 compares the changes in glucose and insulin levels in three groups: morbidly obese patients with NIDDM, morbidly obese non-NIDDM patients, and lean control subjects. The rapid fall in glucose levels in the patients with NIDDM contrasts sharply with the mild elevation of both of these indices in the nondiabetic group after surgery, thus fasting alone may not account for the euglycemia in the NIDDM and IGT groups. The differences in insulin levels among the three groups are also shown.

A review of the 27 failed operations in which the patients did not return to euglycemia revealed that 10 of these failures were due to staple line breakdowns, that is, technical failures prevented their correction. When the 17 nonresponders with intact operations, that is, without staple line breakdowns or anastomotic dilatation, were compared with those patients with full control of diabetic indices, the data showed that the patients who failed to revert to full euglycemia were older (48.0 vs. 40.7 years; p < 0.01) and their diabetes was of longer duration (4.6 vs. 1.6 years; p < 0.04) than those with successful control of glucose and insulin levels.

It is also of interest that the gastric bypass can overcorrect the hyperglycemia. We have documented 43 episodes of hypoglycemia in 35 patients, 6 of whom were from the NIDDM cohort, 1 from those with insulin-dependent diabetes mellitus, 8 from those who presented with IGT, and 20 from those with normal oral glucose tolerance curves. Postgastric bypass hypoglycemia can
be troublesome, with blood glucose levels as low as 27 mg/dL. We have treated these without therapeutic intervention, urging these patients to carry sugar, and most were self-limited, with corrections occurring usually within 1 year.

Before surgery, 353 of the 608 patients (58.1%) had hypertension. After surgery, this rate has been reduced to 14%. In addition to these improvements, patients almost always demonstrated improvement of cardiopulmonary function, clearance of sleep apnea, cessation of snoring, control of asthma, clearance of peptic reflux, fewer limitations of physical activity from arthritis, and restoration of fertility. Mental health evaluations revealed marked overall improvement in mood and mental health indicators during the first 2 years after surgery. These gains, however, eroded by the 3rd year, with a return to their previous mood status, perhaps because some of their personal dreams in terms of mates or socioeconomic success were unrealized.

**Complications**

Complications diminished with increasing experience and rose with the severity of the comorbidities. For the whole series, including some patients with daunting risks, perioperative mortality was 9 of 608 (1.5%), with 5 dying of sepsis, 3 of pulmonary embolism, and 1 of an unknown cause (perhaps dysrhythmias) shortly after discharge. Perioperative morbidity, that is, during the first 30 days, included the following complications: minor wound infections, 8.7%; wound seromas, 5.8%; severe wound infections, 3.0%; anastomotic stenosis, 3.0%; splenic tears, 2.5%; and subphrenic abscesses, 2.5%. Hospital readmissions were required for 8.2% of the patients, and 2.8% of the patients needed reoperations during the early postoperative period. The total mortality over the 14 years was 34 of 608, with 9 perioperative and 25 late deaths. The latter were divided into two groups, 13 from emotionally related causes and 12 due to "more natural" causes. The emotionally related deaths involved three suicides, three cases of cirrhosis due to a return to drinking, one case of bulimia, one case of pernicious anemia due to a refusal to take vitamin B₁₂, one case of alcoholic hepatitis, and four, perhaps more questionable, cases of auto accidents. (Even though we have begun a regular support group, there have been three such deaths in the 3 years since its commencement.) The other late "natural" deaths included four of cardiac causes, two of cancer, and one each of atherosclerosis, pneumonia, acquired immunodeficiency syndrome, peritonitis, pulmonary embolus, and sepsis from a later operation.

The most frequent late complications were B₁₂ deficiency (40%), anemia (39%), hospital readmission (38.1%), incisional hernia (23.9%), depression (23.4%), staple line failure (15.1%), gastritis (13.2%), cholelithiasis (11.4%), and bile reflux (8.7%). Dumping syndrome developed in 70.6% of the patients, but although this syndrome is sometimes listed as a complication, it is easily controlled by the avoidance of sweets and is actually a desired side effect.

**DISCUSSION**

The importance of our findings is not that gastric bypass can control diabetes in the morbidly obese, but that NIDDM, previously considered a progressive and inexcusable disease, can be controlled for as long as 14 years.

What is the explanation for this remarkable control? We can immediately rule out several of the traditional approaches used in the treatment of NIDDM: exercise, sulfonylureas, and insulin. None of these play a role in the operative correction of diabetes. Morbidly obese patients do not exercise immediately after surgery, sulfonylureas are never given after the operation, and insulin, even when required initially for the 1st few postoperative days, is rarely needed after the 1st week. The reason for success must be associated with one of the changes induced by surgery:

1. Limitation of total caloric intake.
2. Decrease of carbohydrates in the diet (sweets cause dumping).
3. Exclusion of food from the hormonally active antrum, duodenum, and proximal jejunum by the bypass.
4. Delayed transit time from the stomach to the small bowel because of the small gastric outlet.
5. Presentation of the midjejunum with undigested food directly from the stomach.

There are several observations that offer clues in sorting out the role of each of these changes:

1. The correction of NIDDM occurs within days, long before significant weight loss has occurred and long before there is a significant reduction in the mass of adipocytes.
2. The correction of NIDDM is durable even though most of these patients remain obese. (Although the morbid obesity is almost always "cured," most patients do not return to an ideal body weight, but remain, on the average, 50% above their ideal body weight.)
3. The operation prevents the progression of IGT to NIDDM in 97.8% of the patients and, instead, returns them to euglycemia.
4. The correction of the NIDDM is less likely in pa-
tients who are older (48.0 vs. 40.7 years; p < 0.01) and who have had the disease longer (4.6 vs. 1.6 years; p < 0.04), probably due to a lower cell reserve.

5. In the three morbidly obese patients with NIDDM who underwent the vertical banded gastroplasty, an operation that also limits food intake but does not bypass any section of the foregut, the diabetes was also corrected.

6. In a unique patient who had a sham operation, the NIDDM also resolved rapidly when the patient was given the same postoperative diet as the patients who were treated with the gastric bypass. (The patient, a 48-year-old morbidly obese man with NIDDM, was scheduled for a gastric bypass but during surgery was found to have a stomach full of food. We did not, therefore, proceed with the procedure but closed his incision and then requested that he stay on the identical postoperative regimen as if he had undergone the bypass. His levels of blood glucose fell rapidly, similar to the correction seen in the gastric bypass patients, but rose again to preoperative levels as soon as he was unable to maintain the diet. 4 weeks after the procedure.)

Accordingly, based on these observations, it is reasonable to conclude that the gastric bypass controls NIDDM through the reduction of caloric intake. Whether the realignment of intestinal flow with the exclusion of the antrum, duodenum, and proximal jejunum as well as the presentation of undigested food to the midjejunum plays an additional role is not known, because we lack a definitive comparison between the effects of the gastric bypass and the gastroplasty. The observation by Sugerman's group that gut hormone changes are more profound with the bypass than with the vertical banded gastroplasty suggests that such a comparison may demonstrate additional effects of the bypass on glucose metabolism.

The relationship between obesity, that is, the increased intake of food, and diabetes and the improvement of diabetes with weight control was noted even in the earliest descriptions of the disease. Most patients older than age 50 with NIDDM are overweight. However, dietary control of NIDDM has generally been disappointing. Although diets can improve glucose metabolism in the obese, the improvement usually represents only a partial and usually brief return to euglycemia, even when patients appear to comply. In the study of the effect of diet on diabetes by Doar et al., 118 obese patients with newly diagnosed NIDDM were subjected to a rigorous diet that produced a significant weight loss of 5.1 ± 4.0 kg within 2 months. Even so, the average reduction in the fasting plasma glucose was only from approximately 250 to 170 mg/dL, and random blood glucose levels were below 140 mg/dL in only 59% of the group. Although these values reflect improvement, the reversal of NIDDM is not nearly so complete as it is after the gastric bypass.

Our studies of insulin resistance at the cellular level also support the theory that NIDDM is the result of obesity, that is, increased food intake. Because muscle is the site of utilization of approximately 80% of the glucose ingested in a meal, we studied the mechanism(s) causing insulin resistance in rectus abdominis muscle of lean and obese patients undergoing abdominal surgery. Very thin muscle fiber strips were incubated in vitro to make metabolic measurements, including rates of glucose transport, glycogen synthesis, and glycolysis. With this preparation, we demonstrated that insulin stimulation of glucose transport, which is the limiting step in glucose utilization, is depressed in muscle of morbidly obese patients with or without diabetes. The degree of insulin resistance is correlated with the degree of obesity up to a body mass index of approximately 30,8 after which there is little further change.

If NIDDM can be controlled so completely by the reduction of caloric intake followed by a rapid decrease in insulin levels and insulin resistance long before there is any significant reduction in the mass of adipose tissue, it is also reasonable to conclude that the lesion of NIDDM must be related to food intake and the signaling mechanisms stimulated by that food. If that hypothesis is true, it follows that the increased insulin resistance of NIDDM may not be the cause, but rather, an effect of the disease. What are these signaling mechanisms? The gastrointestinal tract, on contact with food and especially with carbohydrates, stimulates insulin secretion through the release of endocrine transmitters, also known as incretins. The incretin effect denotes the phenomenon that glucose elicits a higher β-cell secretory response when administered through the gut as compared with the intravenous route. Incretizing hormones, then, are endocrine insulinotropic factors released from the gut in response to glucose (or, less strictly, nutrient) ingestion. Two gut peptides have been identified as incretins: glucagon-like peptide-1 (7 to 36) amide (glucagon-like insulinotropic peptide) and glucose-dependent insulinotropic polypeptide (gastric inhibitory peptide). None of the other peptides from the gut, that is, cholecystokinin, gastrin, or secretin, are thought to be involved in the regulation of insulin in humans.) There may be other incretins that are unidentified. For further information, refer to Creutzfeldt and Nauck.

The errors in signaling probably are not confined to the gut. Further evidence of a broader faulty glucose metabolism signaling system is our finding that decreased
tissue content of glucose transport protein is not the cause for this decrease in transport. In addition, the glucose transport effector system operates normally in insulin-resistant muscle of obese individuals if an appropriate signal is generated. These results suggest that the defect causing insulin resistance is in the insulin signaling system of muscle. To confirm this conclusion, we have shown that the tyrosine kinase activity of the insulin receptor is decreased in morbidly obese individuals with or without diabetes and that this change in receptor kinase activity is the most likely cause of the decreased phosphorylation of insulin receptor substrate-1 and activation of phosphatidylinositol 3-kinase in obese muscle.

Our clinical observations do not support the belief that the islets are sick in the early stages of NIDDM. In fact, as shown in Figure 6, the islets in the morbidly obese patients with NIDDM are initially normal and are able to produce three times as much insulin as those of healthy control subjects before finally failing under the continued stimulation, perhaps due to accumulation of amylin faster than it can be cleared.

The lesion of NIDDM, however, is not based on high food intake alone. Genetics clearly plays an important, but still undefined, role. One third of our morbidly obese patients have normal glucose metabolism, despite massive obesity. These patients appear to have a different distribution of fat as well, with a greater tendency to be pear-shaped than apple-shaped, that is, the patients without diabetes have a gynecoid appearance, with the fat distributed to hips and breasts, rather than the android conformation, with a large concentration of abdominal fat. Most of our patients with NIDDM have strong family histories of diabetes.

Differences in the characteristics and genetic expressions of the adipocytes from the NIDDM and non-NIDDM morbidly obese patients are being studied in several centers, including ours. We have conducted studies that revealed differences in the physical, chemical, and biologic properties of plasma lipoproteins in insulin-resistant patients compared with that of insulin-responsive subjects. Plasma low-density lipoprotein (LDL) molecules of insulin-resistant patients tended to be smaller and more dense than LDL of control patients. These changes in the physical properties of LDL could be attributed to changes in the chemical composition of LDL, which included a decrease in the cholesterol ester content and an increase in the protein content of these particles. The changes in the physical and chemical properties of the lipoproteins appear to affect the biologic function of LDL, as is evident from our studies. We have shown that cells that depend on exogenous cholesterol for growth and proliferation did not grow as fast when cultured in the presence of LDL of insulin-resistant patients, compared with cells grown in the presence of LDL.
of control patients. We confirmed these findings with a comparison of the properties of LDL in morbidly obese patients with NIDDM before and after gastric bypass surgery.

**Study Limitations**

There are several limitations to our study and our hypothesis. First, the claim that NIDDM is controlled by the gastric bypass needs to be supported with evidence that the complications of diabetes are also avoided. We are encouraged by our finding in these patients that LDL reverted to a more normal pattern with respect to physical, chemical, and biologic properties. There is also some evidence in patients with NIDDM that the level of glycemic control is a major predictor of the early development of proliferative retinopathy and that hyperinsulinemia is a factor in the progression of coronary artery disease. (Whether these conclusions can be extrapolated to patients with NIDDM remain unclear.) Even so, although it is true that none of our 608 patients have suffered renal failure, progressed to blindness, or required an amputation, our group is too small in terms of statistical power for us to claim that the gastric bypass prevents diabetic system failures.

The second limitation is the lack of assays of glucose-dependent insulinotropic polypeptide and glucagon-like insulinotropic peptide to support the hypothesis (1) that these incretin levels are high in the morbidly obese, (2) that high incretin levels can cause exhaustion of the islets, and (3) that these levels fall after bariatric procedures. We have recently sent specimens, drawn from NIDDM subjects before and after bariatric surgery, for analysis to Gutniak in Vällingby, Sweden, but the results are not yet available. Even that study is limited by the fact that there may be other incretins, perhaps even more powerful, that have not been identified.

The third limitation is the lack of a prospective, rigorous comparison between the gastric bypass and one of the gastric banding procedures in terms of the efficacy of diabetic control. Kuzmak’s adjustable gastric banding procedure would be an excellent choice for such a study.

**CONCLUSION**

Non–insulin-dependent diabetes mellitus is no longer an uncontrollable disease. A return to normal levels of plasma glucose, insulin, and glycosylated hemoglobin are now attainable with gastric bypass in the majority of morbidly obese diabetic patients, especially if the therapy can be initiated in the first 2 years after the diagnosis of the disease. Whether the other bariatric procedures, such as the gastroplasties, produce similar levels of control remains to be determined.

Why the operation controls diabetes so well is not clear, but the major reason appears to be the reduction of caloric intake. There is some evidence that changes in the incretin stimulation of the islets by the gut may also play a role.

These studies provide new insights and opportunities to understand NIDDM and predict, with control of obesity, that this devastating disease may be curable.

**References**


Discussion

DR. LLOYD D. MACLEAN (Montreal, Quebec): I agree that surgery for obesity is gaining acceptance within the medical profession. This is in no small measure, I think, due to the efforts of Dr. Pories and his colleagues. It is also due to the willingness of the American Surgical Association to hear of the interests of its members, no matter how controversial. The first paper on this was given by Arnold Kremen in 1954. Some of you will remember that.

Dr. Pories has reported a large series with impressive results, and an even more remarkable follow-up, which he did not emphasize during his presentation.

We perform a similar operation with a small pouch, 10 to 15 mL. It is isolated from the rest of the stomach and the fundic side is inverted so there can be no mucosa-to-mucosa approximation. The operation is not dependent on staples. It is placed in the dependent position along the lesser curve of the stomach so there is no enlargement of the pouch over time. In contrast to Dr. Pories, we have made the anastomosis initially with a running nonabsorbable Prolene suture (Ethicon, Somerville, NJ). But when we resutched those people 1 or 2 years later, we invariably found the Prolene in the lumen. The anastomosis was the size of the jejunum and not confined by the running suture.

We have gone on to perform this operation without any attempt at narrowing the anastomosis using an absorbable suture. On 160 patients who have been followed between 3 and 7 years, 95% have a satisfactory result; that is, they are within 50% of ideal weight.

This only held for morbid obesity, that is, a body mass index between 40 and 50 and when a primary operation was performed. If it was a redo or revision operation, or if the patient was super obese with a body mass index over 50, our results were only 63% satisfactory. I wonder if Dr. Pories could comment on that.

I have four very brief questions.

How many of your patients do return to within 50% of ideal? You give your results as means with a wide variation around the mean; it is a little difficult to tell how many patients got a satisfactory result.

You have made a very good point that visceral obesity is associated with insulin resistance, hyperinsulinemia, and impaired glucose intolerance. In addition, I think you have data that are not in the paper on the dyslipidemic state, which is the strongest, after smoking, predisposing factor for coronary artery disease. I would be very interested in the incidence of coronary artery disease in your 600 patients. Is this less than might be expected in this group? Do they have to lose more weight than you have found so effective in the treatment of type 2 diabetes? There is a genetic predisposition to severe obesity and its distribution. I wonder, does a strong family history influence the likelihood of a successful result?

Finally, fewer super obese patients in our experience return to normal. I wonder if this has been your experience? And I wonder why that is? Do they eat more despite the operation than morbidly obese people?

The suggestion has been made by the recent cloning of an obesity gene that the product of that is a satiety substance released from fat cells throughout the body. This works in an exceedingly efficient manner for most of us, who gain approximately 10 kg over 20 years of adulthood, which is equivalent to about one too many carrot sticks a day.

I suspect this is a central defect in these people and they could have all the satiety hormone floating around that they would need, but it will not help and you will still have to operate on those people.


In the accompanying editorial, there is no mention of gastric surgery for obesity, but the possibility of brain surgery is raised (Bennett W. Beyond overeating. N Engl J Med 1995; 332:673–674).

The 14-year follow-up of gastric bypass patients from the Greenville, North Carolina group under the leadership of Dr. Pories emphasizes the dramatic long-term success this operation can provide. In addition to diabetes, it effectively reverses in most patients hypertension, sleep apnea, obesity hyperventilation, pseudo-tumor cerebri, venous stasis ulcers, gastroesophageal reflux, etc.

There are several other published studies, including our own, documenting the long-term efficacy of gastric bypass for this “intractable” problem.

In a previous study of glucose tolerance tests before and 1 year after vertical-banded gastroplasty or gastric bypass in severely obese patients who did not require medication for diabetes, we noted that the gastric bypass was associated with the loss of 65% of excess weight, and vertical-banded gastroplasty,