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NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

WORKING GROUP ON BARIATRIC SURGERY
May 8-9, 2002

Executive Summary

OPEN MEETING

I. Call to Order, Charge to the Working Group

Dr. Griffin Rodgers, Deputy Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), called the meeting to order and welcomed participants. He stated that this Working Group was convened as a state-of-the-art review of "what we know, what we think we know and what we can ask about bariatric surgery as it relates to obesity." Obesity is a major and growing public health problem in the United States. More than 25% of adult Americans are obese. Among African American women aged 40-60, the rate of those with a body mass index (BMI) of over 40 may be as high as 10%. The obese have a 50 to 100% increased risk of death, risk for cancer, coronary heart disease (CHD), musculoskeletal disease and a high risk of Type 2 diabetes. Treatment options and the development of approaches to treatment are critical. The Working Group will focus on bariatric surgery as a treatment of obesity.

Dr. Susan Yanovski, Executive Director of the National Task Force for the Prevention and Treatment of Obesity and Director of the Obesity and Eating Disorders Program at NIDDK next gave an overview of obesity in the U.S. with figures on the prevalence of co-morbid conditions attributable to obesity. These range from sleep apnea, to Type 2 diabetes, asthma, hypertension, CHD, osteoarthritis, gallbladder disease and several types of cancers, among other conditions. Dr. Yanovski termed this workshop a "landmark meeting" providing an opportunity for a small group of specialists from several disciplines to interact with each other on the subject of extreme obesity. She gave the Working Group its charge: to assist NIDDK staff in identifying areas of scientific research pertaining to bariatric surgery and its impact on obesity and co-morbid conditions. Dr. Yanovski summarized the two-day agenda and outlined research areas that would be discussed by speakers in each of the six scientific sessions. Questions and general group discussions followed several presentations.

II. Working Group Sessions

Session I: Overview of Bariatric Surgery in 2002

Ted Adams, Ph.D., M.P.H., of LDS Hospital in Salt Lake City, Utah chaired this session. He first introduced Dr. Robert Brolin, Professor, Department of Surgery and Chief at St. Peter's University Medical Center in New Brunswick, New Jersey. Dr. Brolin provided

an overview of bariatric surgical procedures. *Roux en y* gastric bypass (RGB) procedures are currently the gold standard and produce significantly greater weight loss than the gastric banding procedures. However, the mechanisms by which RGB works are still not known. Dr. Brolin described bariatric surgery as being in a class by itself since no other drug or surgical product can reduce the risk of mortality and diminish/resolve co-morbid conditions such as sleep apnea, diabetes, hypertension and GERD after a single intervention in the same manner. He called for an update of the NIH 1991 Consensus Document since gastric banding is no longer in favor and there is a question about whether biliopancreatic bypass surgery should be used for all or may be more appropriate in a subset of patients.

Dr. Michel Gagner, a bariatric surgeon skilled in laparoscopic surgery from Mount Sinai Medical Center, next spoke on the epidemiology of bariatric surgical procedures. Dr. Gagner presented data from a review of the literature comparing types of surgical procedures and data on the incidence of obesity in America with its associated increase in mortality risk. He also presented data from an evidence-based review of laparoscopic surgery. Evidence-based medicine allows the medical field to decrease the gap between evidence and clinical implementation. Use of laparoscopic bariatric surgery is relatively new; it was first used in 1993 for morbid obesity, which is the reason there is so little data on it in the literature. Dr. Gagner presented evidence-based information and data on a cohort of patients who have undergone laparoscopic bariatric surgery. Laparoscopic surgery is considered to be as safe as open surgery with less impairment of pulmonary function, decreased wound infection and incisional hernias, and shorter hospital stays, as a function of the type of operation. There are major and minor complications with laparoscopic surgery. The risk of complications and mortality increases with the size of the patient: The bigger the patient, the more mortality and complications. Also, results in the super obese are worse with a higher failure rate. Dr. Gagner delineated some of the problems associated with specific procedures: The *roux en y* carries a risk of stenosis of the connection requiring endoscopic dilatation; the duodenal switch has the best weight loss outcome with a higher mortality rate (1.4%) and a risk of infections; gastric banding has a poorer weight loss outcome and carries complications of band slippage, erosions and tubing problems. He concluded that laparoscopic surgery will be the most common in the next decade, but it requires a long learning curve and there are currently no good training programs for surgeons who have been doing open surgery for years. There is also no data currently to show that long-term outcomes with laparoscopic bariatric surgery are as good as those resulting from open surgery. Laparoscopic surgery may prove to be a preventive method in the near future to increase life expectancy and decrease co-morbidities associated with obesity. Dr. Gagner, like Dr. Brolin, called for an update of the 1991 NIH Consensus Document, particularly with regard to the vertical banded gastroplasty (VBG) procedure. Data from Europe, Australia and Mexico on gastric banding differ from the U.S. experience. Dr. Gagner warned that there might be an "explosion" of laparoscopic banding procedures among new surgeons in the field resulting in a bad reputation for bariatric surgery since laparoscopic banding has poorer results and must be redone in many cases.

Dr. Peter Jacobson of the Human Genetics Laboratory at Louisiana State University, next presented two and ten year data from the Swedish Obese Subjects (SOS) Study. This is a non-randomized, multi-center trial investigating the long-term effects of surgically induced weight loss on obesity-related morbidity and mortality. The primary study aim is to see the effects of bariatric surgery on total mortality with secondary analyses of areas such as risk factors, morbidity and mortality of specific diseases, obesity genetics, quality of life and health economics. The study has enrolled 2010 subjects in the surgery group and 2038 in the control group. Inclusion criteria included, among other parameters, age between 37 and 57 with a BMI of 34 or greater for males and 38 or greater for females. Subjects were not randomized; rather, patients undergoing surgical treatment for obesity were matched on a number of variables with subjects who did not undergo surgery, and received standard medical treatment for their obesity. The study has shown that surgical patients tended to have worse risk-factor profiles at baseline than controls. The gastric bypass procedure has shown the greatest results in terms of weight loss, although a relatively small percentage of patients underwent this procedure. The most common surgical procedure in the study was vertical banded gastroplasty. Surgery-induced weight loss had favorable effects on diabetes mellitus in terms of incidence and recovery, but there was no effect on incidence of hypertension and hypercholesterolemia. It appears currently that long-term maintenance of weight loss is better in the surgical group. Conventional weight loss programs seem to be ineffective and at best can only prevent further weight gain. There are no data yet reported on mortality differences between groups. There was a mortality rate of 0.25% in the surgical group due to complications of the surgery itself. If the study were to be done today, Dr. Jacobson would change the study design as follows: random assignment to treatment groups; gastric bypass in a larger proportion of the patients; more frequent and duplicate biochemical analyses including oral glucose tolerance tests and a shorter inclusion period. The study had a 13-year enrollment period.

Sasha Stiles, M.D., Director of Weight Management for Kaiser Permanente Hawaii spoke about her experience with a new bariatric surgery program. The program is based on a team approach with a bariatric surgeon, a behaviorist, internist, pharmacist and support group as important elements. The program involves an extensive multi-disciplinary pre-operative evaluation process, which lasts 6 months. The post-operative follow-up is lifelong. Dr. Stiles highlighted selection criteria and presented a cost-analysis for diabetic patients who undergo bariatric surgery showing the reduction in pharmacy costs post surgery. At any point in time, approximately 50-75% of the patients in the program are diabetic or glucose intolerant. Kaiser routinely collects data on patients such as co-morbidity labs, some visit information, vital signs and weights. They are refining the data collection and will incorporate patient information into a full registry. There have been some encouraging results in bariatric surgery patients to date.

Session 2: Bariatric Surgical Registry

James Everhart, M.D., MPH, Chief of Epidemiology and Clinical Trials, NIDDK, chaired this session. Dr. Everhart introduced Katherine Detre, M.D., Ph.D., Principal Investigator, Liver Transplantation Database, University of Pittsburgh. Dr. Detre has

considerable experience in setting up and running registries and databases. She started the Data Center at the University of Pittsburgh 25 years ago. She is of the opinion that bariatric surgery is ideally suited for a multi-center registry. She described the National Heart, Lung and Blood Institute's Percutaneous Transluminal Coronary Angioplasty (PTCA) registry as an example of a model registry, which has been of great value to the interventional cardiologists' community. A registry can incorporate randomized trials, allow subgroup analyses, give data on outcomes and predictors of outcomes, provide data for ancillary studies, etc. A registry can yield scientifically valuable standardized data. Examples of data found in a registry include inclusion/exclusion criteria, outcome measures such as event rates, results of follow-up exams, physical measures, and test results. In Dr. Detre's view, Core Laboratories should oversee the collection of specimens of blood or other tissues and details such as where specimens should be shipped, analyzed and stored for uniform interpretation should be clearly specified in the protocol. By establishing a registry for bariatric surgery with data collected and analyzed per protocol by Core Laboratories, the metabolic consequences of bariatric surgery and the genetic markers of the types of obesities will be established in an expeditious, systematic manner.

Walter Pories, M.D., Professor of Surgery and Biochemistry at East Carolina University and a member of the National Task Force for Prevention and Treatment of Obesity, next began his presentation stating, "We have to do better." Dr. Pories was a major force in setting up this Working Group meeting. He gave statistical information on the incidence of obesity in the U.S. Obesity causes early deaths, disabilities and impairments. The 1991 NIH Consensus Document concluded that diets, exercise programs, appetite suppressants, etc. are not enough and the recommendations on bariatric surgery in that document now are not enough and so this Working Group was convened. He reviewed the complications and improvements due to surgery in a large cohort of patients he followed at East Carolina University. Those who did not have surgery for insurance or personal reasons were found to have a 4.5% per year mortality rate, while the mortality rates were much lower in those who underwent surgery. Diabetes rates were also lower. This indicates that something can be done about mortality and conditions such as diabetes. Dr. Pories outlined his proposal for a multi-center study to compare standardized surgical procedures in a cooperative project. He further stated that an audited registry of bariatric surgery is needed to assess outcomes and operations. It would be a resource for health care planning and a model for other surgical procedures. It would also provide a framework for studies in basic science in diabetes, hypertension and other chronic diseases. The registry could help provide answers to the issues of who should have surgery, why and how. The predicted number of bariatric surgical procedures in 2003 is 100,000 and the cost of surgery at Dr. Pories' institution is 30,000 dollars. Answers are needed. A registry would be a good investment of research funds, he believes.

Dr. James Everhart then discussed registries and databases. He is an epidemiologist with an interest in diabetes and obesity. His job at NIDDK is to consider funding research projects. He defined a registry as being similar to a database in that both collect data on patients and outcomes. However, a registry collects limited data but on a large sample of

patients of interest. A database can be used to collect more information, especially for a purpose, but a database can be done only in a limited number of selected collaborating centers. NIDDK is more interested in databases and stresses collaborative research. A database is considered key in any collaborative research consortia. He then informed the group of types of data that are appropriate for a database and stated that it is funded via a U01, usually for several clinical centers and one data-coordinating center and results from a RFA. The Institute staff provide administrative and scientific input.

Session 3: Physiology, Energy Balance, and Behavior: What Can Bariatric Surgery Teach Us?

Mark Friedman, Ph.D., of the Monell Chemical Senses Center in Philadelphia, chaired this session. Dr. Friedman concurred that behavior and energy balance should be included in this discussion and introduced Tim Moran, Ph.D., from the Department of Psychiatry and Behavioral Sciences at Johns Hopkins University School of Medicine. Dr. Moran spoke on gastrointestinal control of feeding in animal models and discussed feedback controls of food intake that arise within a meal. He identified controls arising from the presence of food within the GI tract tied to the character of ingested nutrients, i.e. the volumes and chemical composition. He also identified some gastrointestinal peptides important to food intake such as gastrin releasing peptide (GRP), amylin, glucagon and cholecystokinin (CCK). CCK is a peptide hormone released from the small intestine. Exogenously administered CCK results in dose-related suppression of food intake. Studies in rhesus monkeys showed that the GI tract does contain feedback signaling for meal termination and highlighted the role of CCK. When endogenously released CCK is blocked, the baseline food intake increases significantly. The increased food intake with increasing doses of a CCK antagonist resulted primarily from a significant increase in the size of the first meal. Dr. Moran next discussed vagal afferent signals that provide one of the primary pathways for GI signals to get to the brain. Vagal afferent fibers respond directly to both gastric and duodenal volumes and to the chemical characteristics of duodenal contents. Vagal afferents also contain CCK receptors. Peptides and vagal afferent signaling play significant roles in food intake. When these controls are blocked, patterns of food intake are significantly changed. Both individual gastric and individual intestinal stimulation provide feedback cues for meal termination. If the duodenum is bypassed in surgery, CCK release is also blocked, as is the normal signal of satiety. These results have implications for human signaling and for different types of surgery that bypass certain sites and disconnect various neural feedback pathways.

Paul Berk, M.D. of the Division of Liver Disease at Mount Sinai Medical Center spoke on fatty acid kinetics and the pathogenesis of human obesity and fatty liver. He began with a review of some biochemical principles relating to fatty acids. Fatty acids enter cells by two processes: facilitated, protein-mediated uptake and passive diffusion. Three proteins have been proposed to function as long-chain fatty acid (LCFA) transporters: plasma membrane fatty acid binding protein (FABPpm), which is identical to mitochondrial aspartate aminotransferase (mAspAT); fatty acid translocase (FAT) and fatty acid transporting polypeptide (FATP). In the Zucker *fatty* rat, saturable LCFA

uptake by adipocytes is increased as much as thirteen-fold, but is essentially unchanged in other tissues such as liver and cardiac muscle. This selective up-regulation of adipocyte LCFA uptake diverts LCFA away from tissues where they would be metabolized to produce energy and toward adipose tissue where they are incorporated into triglycerides and stored as fat. In effect, the changes in adipocyte LCFA uptake alter nutrient partitioning and energy efficiency, contributing to the pathogenesis of obesity. Similar observations have been reported in various mouse strains that serve as obesity models. Dr. Berk reviewed the effects of leptin administration on LCFA uptake kinetics in leptin-deficient *ob/ob* mice. Leptin results in rapid down-regulation of adipocyte LCFA uptake that precedes weight loss. By contrast, in Zucker rat pups, selective up-regulation of adipocyte LCFA uptake precedes weight gain. Thus, regulation of adipocyte LCFA uptake may be an important control point for body adiposity. If the body can regulate this process selectively in one cell type it may be possible to do the same thing pharmacologically. One approach would be to determine how signaling pathways controlling adipocyte LCFA uptake are regulated downstream of leptin, and then develop selective small-molecule agonists that do not produce the global effect of leptin. On the other hand, leptin resistance is common in many forms of obesity. There have been rare human families with mutations in leptin production, but most obese humans are leptin resistant. Determining the mechanisms of leptin resistance will be essential in exploiting the hormone's weight-reducing capabilities. In working with human adipose tissue samples provided by Dr. Gagner's bariatric surgical procedures, Dr. Berk's lab has found that in samples from 10 obese human subjects- as in rats and mice- the rate of fatty acid uptake by adipocytes is significantly up-regulated compared with non-obese controls. They will also study the sex differences in LCFA uptake and look at differences between samples from different fat depots in the same patient as the number of patients studied increases. Dr. Berk then discussed hepatic steatosis (fatty liver). In both the rat and the mouse, histologically similar fatty livers due to obesity appear to have a different biochemical pathogenesis from those due to ethanol intake. Laparoscopic surgery in the obese patient makes possible safe performance of a wedge biopsy of the liver, portions of which can be used for research studies. Microarray analyses of gene expression in fatty livers from humans who are obese, alcohol consumers and others are just beginning and may identify differences in the pathogenesis of the observed fatty livers. As Dr. Gagner conducts a two-step bariatric surgical protocol in very obese patients, Dr. Berk's lab will receive tissue samples to study sequential changes in gene expression and fatty acid transport in adipose tissue and liver during the resulting weight loss. These studies are examples of a collaborative research effort between a bariatric surgery program and a basic science laboratory. Collaboration with bariatric surgeons is key to this research.

Harry Kissileff, Ph.D., of the Department of Psychiatry and Medicine at St. Luke's/Roosevelt Hospital Center next presented the results of his studies on gastrointestinal control of feeding in humans. His work provides a basis for understanding signals from the GI tract whose modulation could help to prevent or reverse human obesity. The basic paradigm is that eating occurs when the combined excitatory signals exceed inhibitory, and stops when inhibitory signals exceed excitatory. He reviewed the sites of signals to eat or not eat: stomach, oropharynx, intestine and liver

and the types of signals: neural, humoral such as CCK, hormonal such as insulin, glucagon, CCK, GLP-1, bombesin and ghrelin. Adipose tissue also plays a role and sends signals to the brain, via leptin levels, about the size of body fat stores. Neurotransmitters in the brain such as NPY, CART and MSH/AGRP, and cognitive and environmental factors also figure in eating and food intake. In studies of CCK, it was found that nutrients differ in their ability to release CCK and this difference could affect their satiating efficiency. D-phenylalanine increased plasma CCK and reduced food intake. Ghrelin is a recently discovered hormone that is synthesized in the stomach and increases food intake and is reduced by food consumption. Levels of ghrelin are reduced in the obese when compared to lean subjects. Ghrelin levels fall as the body mass rises. Obese subjects can tolerate a greater gastric distention than non-obese. Wall tension alone does not explain perception of satiety, because CCK reduces wall tension but increases feelings of fullness. It is hypothesized as a result of this research that obese subjects may be less sensitive to signals that arise in the GI tract or these signals themselves may be reduced in intensity in the obese. Research is needed on the heritability of responsiveness to CCK and changes in CCK receptor binding activity or synthesis, and dose response to CCK. It may be possible to therapeutically increase gastric sensitivity- surgically, nutritionally, pharmacologically, or possibly behaviorally.

Discussion: Opportunities for Clinical Research on Energy Balance and Appetitive Behaviors in Bariatric Surgery

Obesity is a symptom, or disease process or phenotype and it is associated with more morbidity on a daily basis than any other disease/condition, participants concurred and several critical areas for further research evolved during the discussion. Most of the following suggestions require a registry or database:

- Look at different types of surgical techniques to see if it is possible to arrive at some type of uniformity for a type of procedure among centers
- Establish a registry/database to look at outcomes, techniques, predictors of outcomes, what those outcomes are, then look for new outcomes reflected back on the predictors
- Study the metabolic consequences of surgery and whether or not those account for some of the changes post surgery
- Research the physiology of energy status (might lead to taking the next step which may not require surgery as the treatment, but another option)
- Must look at enough patients to reach statistical significance for conclusions regarding who should get what type of surgery
- Compare group that does not have surgery to see outcomes; perhaps use a lean group as a control?
- Look at endocrine levels of obesity and body composition
- Look at a broad overview of the cognitive and physical consequences of bariatric surgery

The group agreed that further study is critical in many areas related to bariatric surgery. A registry or database would be an essential tool in answering some of these questions.

Session 4: What Can Bariatric Surgery Teach Us About Obesity-Related Co-morbid Conditions?

Harry Sax, M.D. from the Department of Surgery at the University of Rochester chaired this session. He introduced Jerry Palmer, M.D., from the Department of Medicine at the DVA Puget Sound Health Care System who spoke about insulin resistance and beta cell recovery. Bariatric surgery has a dramatic effect on Type 2 diabetes. It often resolves. This is an area for collaborative research. Dr. Palmer outlined the current research findings on insulin sensitivity/insensitivity and beta cell loss. In Type 2 diabetes which is common in the obese, there is a combination of insulin resistance and beta cell dysfunction as the patient becomes hyperglycemic. In subjects who go from normal to impaired glucose tolerance to Type 2 diabetes, there is a progressive beta cell lesion. Their insulin sensitivity gets a bit worse, but the progressive worsening of beta cell function is what really harms these patients. BMI is not an accurate representation of insulin sensitivity. The cause of beta cell dysfunction is not really known, although genetics, glycotoxicity, lipotoxicity and amyloid all play roles in the decrease. Obese patients produce more insulin post bariatric surgery once the glyco-and lipo toxicities are removed. It is thought that there is a functional, reversible lesion in these patients. Dr. Palmer outlined results of studies on ghrelin and Rosiglitazone and concluded with thoughts on the opportunity posed by bariatric surgery to investigate the pathophysiology of Type 2 diabetes.

Brent Neuschwander-Tetri, M.D., Associate Professor of Medicine, Saint Louis University, next spoke about his research on NASH, or non-alcoholic steatohepatitis. Nonalcoholic fatty liver or NAFL represents a spectrum from benign steatosis to severe NASH. NASH can progress to cirrhosis and is defined histologically. It encompasses fat, hepatocellular injury and inflammation. Obesity and diabetes are major risk factors for NASH. Insulin resistance may be a key predisposing abnormality. Insulin resistance is defined as impaired insulin-dependent glucose disposal by adipocytes and muscle. There are genetic factors that impact on the development of insulin resistance, NAFL and NASH. Dr. Tetri summarized early results of a Phase II trial of Rosiglitazone for NASH. The drug is in the class of thiazolidinediones (TZDs). These drugs are ligands for the PPAR-gamma nuclear receptors and increase insulin sensitivity, reduce insulin levels and could have idiosyncratic hepatotoxicity. This class of drugs alters insulin signaling by changes in gene expression. In the study, Rosiglitazone improved insulin sensitivity although not to the point of normal. It also decreased liver fat and reduced aminotransferase elevations. The biopsy results are still pending. Dr. Tetri concluded with a review of studies of restrictive surgery and liver disease. Restrictive surgery, it was shown by limited data, could worsen inflammation but improve steatosis and long-term follow-up is needed to learn more. Malabsorptive surgeries may be beneficial in liver disease, but the blind loop should be avoided.

Lee Kaplan, M.D., Ph.D., of the MGH Weight Center in Boston, next discussed the medical implications of obesity. He outlined the many types of co-morbidities associated with obesity. These range from metabolic, to anatomic to degenerative and neoplastic. He concurred with Dr. Palmer regarding some of the questions regarding the relationship

between diabetes and obesity and with Dr. Tetri regarding unknown factors in NASH in the obese. He outlined several areas for future research as well as some of his research on the "Bounce Effect," especially as seen in arthritis in non-weight bearing joints and sleep apnea. He then detailed some of his findings regarding phenotyping. What is called an outcome today may be a phenotype tomorrow. He looks at seventy factors in doing phenotype clustering. He does non-invasive phenotyping which complements data found through invasive phenotyping. It is possible to use the same kinds of statistical analyses on these phenotype parameters as that used on individual genes and their expression in an affymetrix or microarray system. Patients then begin to fall into different clusters. These parameters can be combined with those in a snip analysis or from a gene expression analysis. This process underscores the idea that phenotype, genotype and outcome are really one and the same and are interrelated. Dr. Kaplan concluded that bariatric surgery may be the most physiologic and natural mechanism available to date and may open the way to other less invasive mechanisms in the future.

A group discussion about scientific opportunities followed Dr. Kaplan's presentation. Several areas were highlighted in the discussion:

- Site of fat disposition in the muscle/intramuscular lipids and their role in insulin resistance
- Role of insulin in hepatogenesis
- Bariatric surgeons can supply the following tissues for research:
  * Tissues for fat location in cell such as skeletal muscle, quad muscle
  * Blood vessel, mesenteric cells
  * Liver- (to study mitochondrial changes and relation of fatty liver to BMI) *Note: avoid subcapsule of the liver; it gives misleading "answers."*
  * Bile
  * Splanchnic/portal blood
  * Fat (mesenteric, body wall, look at normal weight vs obese)
  * Small bowel
  * Stomach

It may also be possible to get IRB approval to do a biopsy of the pancreas. There was some debate concerning the ethics and safety of getting portal blood due to concerns about thrombosis. The group generally agreed that the issue of bariatric surgery in children/adolescents should be considered separately from issues in adult surgery, and may benefit from a separate meeting at some future time. There are issues in the pediatric population such as obesity causing serious life-threatening co-morbidities; when to operate-before or after growth period; family and support and psychological issues. They also agreed that bariatric surgery has a checkered past and the serious researchers in the group do not want to see that past repeated. There is a compelling need to "reign in" bariatric surgery and get good data by studying the different types of procedures in an organized/rigorous manner.

Session 5: Is There a Role for Genetic Studies of Bariatric Surgery?

Rudolph Leibel, M.D., Professor Pediatrics and Medicine at Columbia University College of Physicians and Surgeons, chaired this session. He gave an overview of some areas which could provide opportunities for genetic analysis such as the following:

- studies of patients with high degrees of obesity in which it may be possible to see extreme phenotypes and who represent a productive pool for genetic contributions;
- studies of phenotypes such as blood pressure, NASH, diabetes (these could segregate patients in interesting ways);
- genetic predispositions to responses to surgery--predictions concerning who will do better with a particular procedure. In some patients with severe obesity there may be single gene disorders with mechanisms concerning energy that will provide insight.

Dr. Leibel introduced Claude Bouchard, Ph.D., Executive Director, Pennington Biomedical Research Center who spoke about what bariatric surgery studies can teach about genes of obesity and co-morbid conditions. Dr. Bouchard began with a discussion of familial risk which has been proven. There is a paradigm for a genetic predisposition to obesity. He went over the formula to compute the lambda coefficient or the magnitude of the increase in risk among biological relatives compared to the population prevalence of the condition. With a BMI of 30, the lambda is 3; BMI of 40, the lambda rises to 5 or 6; BMI of 45 the lambda rises to about 7. A genetic predisposition can affect any of the determinants of energy balance: energy intake, energy expenditure, energy partitioning and adipogenesis. All of these factors are probably affected in some way in morbid obesity. Dr. Bouchard proposed studying key questions on genetics and weight loss induced by bariatric surgery via a registry of 10,000 obese patients with a minimum BMI of 35-5000 who have surgery with one of the modern techniques and 5,000 from the same cohort matched or randomized based on selected criteria to a control group. These patients would then be followed for a period of time after surgery via the registry or database. In addition to providing data to answer many questions, the registry or database would have enough power to consider genes with small effects and even minor gene-to-gene interaction effects. It could also look at the heterogeneity of obesity phenotypes. Moderate and even mild obesity is a complex disease in which many genes with large and small effects are likely to be involved. Morbid obesity seems to differ from mild obesity in that in morbid obesity single gene deficiencies can cause the condition. The level of penetrance of genes in this later case appears to be higher. It is possible that a number of genes exhibit allelic variations that are predictors of risk. Dr. Bouchard concluded that if it were possible to identify those who will become obese, it could revolutionize preventive medicine. It may not be possible, however, to identify those who will become only moderately obese since environment plays such an important role. A registry could help discover whether or not there are alleles conferring even higher risk levels. The human obesity gene website can be found at: *http://obesitygene.pbrc.edu*

Ted Adams, Ph.D., MPH, from LDS Hospital at the University of Utah, then briefly described a NIDDK funded study being done at his institution. The study is designed to look at morbidity and mortality related to gastric bypass surgery. The study is in its

second year and will enroll approximately 8200 *roux en y* patients in the mortality study arm who have undergone surgery since 1989 with a follow-up of 13.9 years. In the morbidity arm, they are recruiting 3 groups of 400. They are including patients who were denied surgery due to insurance reasons. The specific aim of the study is to look at the effects of surgery on co-morbidities and how those change in the surgery vs non-surgery groups. The other aim is to assess mortality in a 15-year period.

The final speaker was Patrick O'Neil, Ph.D., a psychologist and Professor at the Medical University of South Carolina. He summarized some of the psychological aspects of bariatric surgery. There is no evidence for an obese personality, although among those who seek treatment, there is a higher prevalence rate for psychological disorders. Cluster analytic studies found that personality profiles of the obese do not differ from those of the general population. There are frequently some eating disturbances in surgery applicants such as binge eating disorder, bulimia nervosa and night eating syndrome. Binge eating does connote a greater risk of other psychological disorders and higher rates of depression. Bariatric surgery itself has generally good behavioral and psychological impacts. Patients also report less discrimination, improved to normalized body image, reduced or resolved binge eating, improvement in eating patterns, increased cognitive restraint and less negativism and improved self-esteem and less depression. However, a preoperative eating disturbance may presage some weight regain post surgery or eating disturbance that appears about two years post surgery. In general, however, it is difficult to find psychosocial predictors.

III. Conclusion

The Working Group unanimously agreed that this meeting brought together an incredible assemblage of experts linked in various scientific areas to obesity who would otherwise never have come together. It was a very good opportunity to interact and share research ideas. Bariatric surgery is currently the most effective treatment for morbid obesity. Although traditional randomized, controlled clinical trials may be difficult in an area in which different surgeons practice different surgical techniques and laparoscopic surgery may replace today's current methodologies, it seems important to conduct such trials in this area. One important surgical area is the comparison of restrictive v malaborptive procedures. There are some issues to address in doing a surgery trial. In order to overcome some of the obstacles in a surgery trial, it might be worthwhile to conduct a non-randomized study, pooling results from surgeons expert in a particular procedure and compare those to the pooled data from other surgeons expert in another alternative operation. The pooling of data may minimize the impact of individual differences in technique among surgeons and therefore some generalization of results may be possible. However, the lack of randomization may be an issue. Other problems associated with a clinical trial of bariatric surgery are selection bias-some patients are refused surgery for insurance reasons; difficulty in standardizing surgical procedures and insufficient data at present to know the optimum timing of surgery relative to the course of the illness. However, despite trial design problems there is general agreement that some sort of clinical studies need to be done. The surgeons can also supply human tissue for important research work. Surgical trial site personnel should be equipped to provide such

information as the following on patients who undergo bariatric surgery: metabolic rates, surgery-related changes in nutrient partitioning, metabolic rates, fecal calorie loss, insulin and leptin levels and energy efficiency among other study variables. These measures could give needed insight into obesity and the effects of bariatric surgery upon obesity. Surgery can also yield human tissue to learn about the pathophysiology of obesity. In using human tissue samples, researchers could look at effects of specific surgical procedures on plasma levels of hormones and peptides such as glucagon, leptin, ghrelin and others yet to be discovered, as well as on the process of leptin and insulin resistance. They could also define basal levels of hormones and other peptides. In addition to providing human adipose tissue for research, bariatric surgery could provide smaller quantities of other tissues thereby permitting characterization of the effects of obesity and surgically induced weight loss on processes such as nutrient transport and RNA for microarray analysis. The genetic basis of human obesity might therefore be better understood.

There was also consensus that a registry or database would be extremely valuable to the study of obesity. A registry could capture important demographic, epidemiologic and descriptive information about patients undergoing bariatric procedures, while a database could be a valuable research tool. It could capture data on all patients pre and post surgery and could include those who ultimately do not undergo surgery. It would also allow hypotheses to be tested from the data set. In both cases, investigators must be committed to entering quality data in the appropriate timeframe. A database may require professional staffing and a good data management center to manage the information.

There was a suggestion, synthesizing some of the presented ideas, to undertake a multi-center study with the following elements: perhaps 5-6 participating centers; a CRC for physiologic studies and sample collection; committed medical and surgical staff at each center to carry out appropriate studies and furnish quality data in a protocol defined manner to a core database or biostatistical facility and tissue and blood/plasma samples to investigators and core facilities; and, finally, funded investigators to conduct obesity-related research on human samples. The database/biostatistical center, serum/tissue bank and core laboratories would ideally be centralized or they could be parts of the participating surgical centers.

In order to reach some agreement on the design of a multi-center study some funding would be required to explore the feasibility of such an approach.

Additional suggestions for further research from participants are categorized in the tables following the text and fall generally into three broad research areas:

- Use bariatric surgery as a vehicle to understand the physiology of obesity and co-morbid conditions such as NASH, diabetes, etc. as well as some psychological issues
- Study different types of procedures being done
- Opportunity to study basic scientific issues in areas related to obesity/bariatric surgery such as genetics, psychology, phenotyping, etc.

Dr. Susan Yanovski thanked the group for their input and encouraged participants to email or telephone her with additional research ideas. The NIDDK staff will review the results of this meeting and suggest an appropriate initiative for the Institute to undertake in the area of bariatric surgery.

IV. Research Suggestions

SURGERY SPECIFIC SUGGESTIONS
1) Research optimum length of *roux* limb and pouch sizes. Relationship of length to outcome.
2) What is optimum amount of gastric restriction? Too much restriction results in serious metabolic problems.
3) Should biliopancreatic bypass be the primary surgery for all patients? Compare BPD to other types of surgery. Standard thought now is that *roux en y* results in better weight loss than VGB.
4) Controlled studies of duodenal switch research; two thirds of stomach is restricted
5) Need risk/benefit analyses of the different types of surgeries. Are gastric banding surgeries appropriate or not, or worth "retaining" for a particular subgroup of patients?
6) How does gastric bypass work? Assume it functions via malabsorption, but need to know how much malabsorption occurs/whether it occurs.
7) What is role of energy expenditure in differentiating bypass from gastroplasty?
8) Need data on relationship between surgery-induced weight loss and reduced mortality; clinically known, but need data to prove relationship.
9) Need long-term data on the safety and efficacy of laparoscopic surgery.
10) Need clinical trials on the different types of surgery/techniques to arrive at some standardization in procedures.
11) Need to evaluate surgery in terms of a multi-modality approach. How does bariatric surgery differ from other therapies?
12) Research the ideal time to do surgery in the etiology of the disease; is harm incurred in waiting to do surgery?
13) Study the effectiveness of surgery in drug-induced obesity.
CO-MORBIDITIES
1) Research bariatric surgery's effects on co-morbidities, analyzed individually.
2) Study effect of late weight regain (i.e. about 3 years post surgery) on co-morbidities. Do they return/ worsen, resolve, etc.?
3) Study impact of the "Bounce Effect" on co-morbidities such as arthritis and diabetes.
GENETICS
1) *Note: see summary of Dr. Bouchard's presentation for additional suggestions.* Are there differences in changes in risk factors or morbidities for the same amount of weight loss?
2) Are there individual differences in the amount of weight loss for a given surgical technique?
3) Are there familial predictors of weight loss?
4) To what extent can weight loss be predicted from molecular markers?
5) Are there underlying genes that play a role in obesity and also affect phenotype of insulin resistance; this is suspected but not well established.
6) Study inter-individual genetic differences which play a role in the variability in susceptibility of the very obese to the co-morbidities of obesity such as diabetes, hypertension, dyslipidemias, NASH, etc.
7) *Note: one researcher was of the opinion that studies of gene expression in tissues obtained at the time of bariatric surgery are more likely to reflect secondary consequences of the obesity and accompanying metabolic disturbances (and/or clinical manipulations prior to surgery) than primary molecular processes.*
PHYSIOLOGY/METABOLISM
1) Study the effect on hormones, peptides, cytokines, and mediators of malabsorption techniques.
2) How does rearrangement of the gut post surgery affect weight loss?
3) What happens when patients plateau in weight loss post surgery? Need studies on an organized approach to achieve additional weight loss when the plateau is reached or when the patient regains weight. A

registry could aid in finding what impacts the plateau or energy expenditure.
4) What are the metabolic consequences of bariatric surgery on adipose tis sue, on the liver? Are they related?
5) How does bariatric surgery impact brain metabolism?
6) Do the metabolic consequences of bariatric surgery account for some of the changes seen post surgery? Research impact of surgery on ghrelin and other hormo nes in the gut.
7) Research what happens with peptides and meal-related cck, insulin and insulin sensitivity in patients who undergo gastric bypass. .
8) Study metabolic and endocrine levels of obesity and body composition. Need body composition to show tissue type, i.e. not cardiac or other type of tissue.
9) Study the physiology of energy status. Study a subset of patients who have rigorous, pre-ordained pre-procedures to see the metabolic consequences.
10) What is causing differences in insulin sensitivity? Is it based on where fat is located?
11) What is ghrelin's effect on beta cells and other endocrine cells?
12) Study treatments for NASH and how insulin resistance leads to an accumulation of fat in the liver. Related question: Study methods of dealing with insulin sensitivity. If insulin sensitivity is improved, it may have a positive effect on NASH.
13) Study cravings post surgery. Surgery may cause different cravings in different subgroups.
14) Do a Starling curve to look at beta cells and insulin resistance.
15) Study what insulin does to hepatogenesis.
16) Study the effect of bariatric surgery on NASH.
17) What are the physiological and behavioral determinants of weight loss?
18) Are there *in utero* factors that increase the risk of obesity via imprinting on pathways, etc.
29) Target the super obese first in doing genetic research since the results may be better. Look for divergent phenotypes in the super obese and extremes that may lead to the discovery of new genes.
20) Study families of the obese with few or none of the co-morbidities. They are good candidates for mapping. One in four or five families has some significant discordance that would be useful to study.
21) Does amount of weight loss differ as a function of BMI number, e.g. BMI over 60?
22) What is the effect of binge eating?
23) What are the effects of other, select eating behaviors?
24) Study these subjects who are in a chronic hypo-caloric state to see the physiology of the reduced-obese who achieve and maintain lower body weight by dietary/physical activity interventions.
SUBPOPULATIONS
1) Need studies on subpopulations that do better or worse post surgery. There is some data suggesting that African American women do less well.
2) Need research, perhaps in a multi-center study or via a database or registry, on who should have surgery and what type?
3) Need research on subtypes of binge eaters with clear definitions and measures for subtypes and for the psychological variables involved.
4) Study different subcategories of patients --patients with BMI of 30 or 35, patients with NASH, with diabetes, severe hypertension, etc. to see the effects of different types of surgeries in these patients as well as the outcome of the co-morbid conditions. Use patients undergoing standard medical therapy as the control group and assess whether surgery treats those co-morbid conditions.
5) Study Pima Indian group with high incidence of diabetes to find interrelationships to obesity.
6) Query subpopulations to facilitate mechanistic and genetic studies.
OUTCOME
1) Need predictors of outcome.
2) What amount of weight reduction post surgery results in a "healthy weight," i.e. if a person starts with a BMI of 55 and gets down to a BMI of 35 post surgery, is that enough?
3) What effect does bariatric surgery have on neural enervation?
4) Need research on outcomes of bariatric surgery. Are there surgery specific outcomes? Does outcome on co-morbidities differ by type of surgical procedure?
5) Does outcome differ by patient subgroup?

STANDARDS
1) Research a unisex BMI standard versus a gender-based BMI standard. May also need BMI standards based on ethnic origin.
2) Need a common standard to compare medical therapies with surgical therapies.
3) Need database/registry related standards such as agreements on how measurements are made, how data is defined, etc.
4) Need validated rating scales with explicit wording.
5) Develop standardized procedures for psychological screening of bariatric patients. Need better psychological contraindications with standardized measures to be used across centers. *Note: need a research agenda here to ascertain what screening has predictive value while not endorsing concept of an "obese personality" or somehow perpetuating weight-related bias.*.
DATABASE/REGISTRY
1) Proposal from Dr. Pories (mentioned in text) for cooperative project to find some standardization in procedures, etc.
2) Set up a database to study the different types of procedures.
3) Use database to assess healthcare utilization costs and how they change post surgery. Could also provide an economic analysis of bariatric surgery.
4) Query the database to answer basic and clinical questions.
5) Ask what are the predictors of outcome, what those outcomes are, then new outcomes reflected back on the predictors.
6) Use a database to sort phenotypes.
PHENOTYPES
1) Do physiologic studies of the obese phenotype.
2) Do microarray analysis of human tissue samples to enhance understanding of the genetic basis for the obese phenotype.
3) Use phenotyping to find direct causes and types of obesity.
4) Use phenotyping in evaluating potential therapies for obesity.
5) Stratify patients based on phenotype clusters for bariatric surgery to look at the effect on outcomes and specific phenotypic parameters.
6) Quantify the relevant phenotypes (gut calorie loss, energy expenditure, ingestive behaviors).
GENERAL
1) Study interventions other than bariatric surgery such as drug intervention therapy.
2) Study the pathogenesis of obesity.
3) Study the effects of body fat distribution, duration of obesity, age of onset.
4) Surgery is currently the most effective long-term treatment for severe obesity. However, there is a need to study the immediate and long-term risks of surgery (such as rates of cardiovascular-related, etc. morbidities and mortality v other approaches to long-term weight loss).
5) Study the functional and molecular consequences of the surgery-induced lower weight/hypo-caloric state on aging.
6) Study the best strategy for providing pre and post surgery education and behavioral training for patients. Life-long follow-up by clinicians of these patients may be a necessary component to a successful course.
7) Some patients shift from an eating addiction to another type of addiction post bariatric surgery. Can this behavior be prevented or better understood?

V. Attachments

1. Agenda
2. List of Participants