While the definition of clinical research is not easy to find today, how we define this term is critical in putting this crisis in clinical research into perspective. Therefore, we need to establish a standard definition of clinical research. Also, we need to identify why clinical research is so important, particularly with major public health problems such as obesity in America today. Obesity costs Americans billions of dollars each year: in medical care costs to the public and in health insurance and medical coverage costs for companies who employ people who are obese. After identifying why clinical research is important, we need to identify the challenges that face the clinical investigator. If we can identify these challenges, we can address them to improve clinical research.

DEFINING CLINICAL RESEARCH

The National Institutes of Health (NIH) has established a definition for clinical research: any research through which an investigator obtains data from a living individual through 1 of 2 ways—either by directly interacting with that person so the investigator has touched or and spoken with the person or by obtaining identifiable private information about an individual (http://www.nhlbi.nih.gov/crg/overview_index.php). If the investigator obtains information about an individual that does not include specific identifiers, the data does not qualify as clinical research.

These 2 broad definitions describe clinical research, and we then divide research into the general categories within these 2 broad definitions. These general categories include a large number of epidemiological studies and studies to evaluate therapeutic interventions, which are short-term and long-term studies. Within therapeutic interventions, we include specific types of clinical trials, which have led to major advances in certain treatment algorithms for patients with different diseases. We also include research that helps us understand the mechanisms of being healthy and of preventing diseases: the pathogenesis and pathophysiology of diseases, which are complex and require studies in humans, rather than because we cannot understand all of these interactions in animal or cell cultures. We need to research these mechanisms in humans to accurately identify and understand these processes.

Crisis in Clinical Research: Putting the Crisis Into Perspective

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Clinical research also includes health services research and patient-oriented research, which involves a direct interaction between an investigator and a subject and often involves a research unit for this interaction to occur. Finally, the NIH has encouraged a new category of research, which is now used worldwide; this category is termed clinical and translational research. In clinical and transitional research, we gather information from cells and the bench and animal models, translate them into unique designer studies in human beings, and then translate those studies into community and clinical practice and to new potential biomarkers and compounds for treating diseases. The process in this type of research is complicated, requires a strong infrastructure to succeed, and is very difficult to complete.

CONDUCTING CLINICAL RESEARCH IN OBESITY STUDIES

Obesity is a problem that affects almost every organ system in the body (Fig. 1). As a result, obesity is very expensive. Unfortunately, the prevalence of obesity is increasing. Most people are overweight or obese, and because of the economic impact of obesity and these related diseases, we need to understand what causes obesity, how we can prevent and treat it, and how obesity is related with these multiple diseases.

We know very little about why obesity causes these diseases. The disease most closely linked to obesity is type 2 diabetes, a disease caused by the resistance of different tissues in the body to the action of insulin, a hormone that the pancreas makes and that is important for the metabolic functions of many substrates, including glucose uptake by cells and glucose release from the liver. Glucose release interests researchers because insulin resistance may underlie the pathophysiological conditions associated with abnormal lipid metabolism, increased blood pressure, and nonalcoholic fatty liver disease, all of which are risk factors for heart disease and stroke, which are major killers in this country.

SHARING EXAMPLES OF CLINICAL RESEARCH IN OBESITY

Considerable breakthroughs in research technology have been made in the last 15 years, and these breakthroughs have led to dramatic and exciting discoveries in animal and cell systems, including the manipulation of genes in animal models so we can understand how various genes and proteins work. Among the most important breakthroughs is positional cloning, which led to the 1995 discovery of a protein, now called leptin. Leptin is made by adipose tissue, and if an animal is deficient in leptin, it will eat more, be less active, and have metabolic abnormalities. An animal homozygous for such a deficiency of leptin will be immensely more obese than a littermate that retains a functional copy of the leptin gene. Such animals have the same mother, but the animal deficient in leptin is immensely obese. If we give leptin to such an obese mouse that is unable to make leptin (defective of the ob/ob gene), this animal will become lean and

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metabolically normal. However, it is obviously important to translate what we have discovered in rodents to human beings. The translation can be difficult and even disappointing, but it is the translation of basic science discoveries to application in people that is critical for developing new and better therapies for human disease.

Unfortunately, leptin therapy resulted in only minimal weight loss in obese people, and many participants dropped out of the study because of adverse effects from the leptin injection. Recently, investigators found that treatment with amylin, a protein made by the pancreas, makes obese mice more sensitive to the weight loss effect of leptin, and this combination therapy is now actively being evaluated in obese people. In fact, data from a recent study found that obese people who are treated with leptin and amylin together experience greater weight loss than if they received amylin or leptin alone. This experience demonstrates the benefit of going back and forth, from humans to animals, in developing new treatments for human disease.

![Figure 1: Medical complications of obesity.](image1)

![Figure 2: Photograph (left panel) and abdominal magnetic resonance image of study subject before (above) and after (below) large-volume abdominal liposuction. These illustrations demonstrate the marked reduction in the panicultus of abdominal fat and in the volume of the rim of subcutaneous adipose tissue after the procedure. Adapted from Klein et al.](image2)
A strong clinical and basic science infrastructure is needed to conduct this kind of research.

In addition to clinical intervention research, we need to understand the metabolic pathophysiology of disease in humans, which requires specialized research centers. This research requires sophisticated technical approaches to ensure that trials with human subjects are conducted in a safe and efficacious manner.

Data from many studies have shown that even minor weight loss of 5% in an obese person can improve insulin sensitivity and reduce the risk of developing diabetes.

Therefore, we hypothesized that removal of fat by liposuction could have health benefits. Liposuction is the most common cosmetic surgical procedure in the United States, and more than 400,000 liposuction procedures are performed per year.

We performed the study in which we evaluated the effect of removing a large amount of body fat by using liposuction on metabolic health in obese women. With modern liposuction techniques, large volumes of subcutaneous fat can be safely removed in obese people. Our plastic surgeon removed 10 kg of body fat per participant, which equals approximately 12% weight loss if participants had lost the weight by dieting.

Figure 2 shows photographs and MRIs of one subject before (above) and after (below) liposuction that shows the decrease in the thick rim of fat around the outside of the abdomen (right panel).1

We were surprised to discover that despite removing 10 kg of fat, no metabolic benefits were observed. We studied these subjects carefully in a clinical research center and evaluated their sensitivity to insulin. We measured their insulin sensitivity by infusing insulin at a certain rate at a low dose in stage 1 and then at a higher dose in stage 2; through this procedure, we could measure glucose production by the liver, which was suppressed during stage 1, and glucose uptake by muscle tissue, which was stimulated during stage 2. Therefore, we could measure in vivo the whole-body system in these subjects to determine how sensitive they were to insulin action. Our data demonstrated that liposuction did not make an improvement in heart disease risk factors or insulin sensitivity.

To do this study, we needed a sophisticated clinical research unit with well-trained nursing and medical staff and the resources to recruit appropriate study volunteers. Because we had such a facility, we were able to demonstrate that to achieve the metabolic benefits of weight loss, obese people must undergo a negative energy balance; removing fat alone does not cause benefits. These findings help us to understand the potential mechanisms of why obesity causes metabolic disease and why weight loss improves metabolic disease. When we remove fat by liposuction, we remove billions of fat cells from the body. When individuals remove fat by eating less, they reduce the size of fat cells and eliminate fat from other organs such as the liver, the muscle tissue, and those inside the abdomen, which may be important for achieving metabolic benefits.

WORKING THROUGH THE LIFE CYCLE OF CLINICAL RESEARCH

What does one need to be a clinical investigator? What does a clinical investigator do today to conduct clinical research? What does the life cycle of a clinical research study include?

The life cycle of a clinical research study includes 5 phases. The most critical phase is the first phase: the development of the research study, the idea of what the researcher will study, the fine tuning to produce a protocol that will have some clinical importance—to help improve health or to prevent or treat disease. This phase requires that basic clinical researchers and a community of scientists interact; that interaction is critical so clinical researchers can learn from basic scientists who are working with cell cultures, with tissue, and with animal models—so we develop protocols that can translate laboratory findings into clinical trials. Successful protocols require a lot of interaction, knowledge, and discussion.

In the second phase, the clinical researcher plans the research protocol, develops the protocol, and submits the protocol for funding. This phase requires input from biostatisticians and statistical genetics specialists. Investigators must know regulatory requirements, which increase every year to protect study participants. Clinical researchers also need to obtain funding to pay for their research, which requires writing a grant application and submitting the document. This phase requires a lot of work, and, if the researcher fails to obtain funding, then the researcher’s work to date—the months of planning, the writing, and reviewing the literature—goes to waste.

Phase 3 requires that the researcher collaborate with many core services, such as facilities that process blood and tissue samples to analyze what the researcher wants to analyze. Some services are sophisticated, some are routine (like measuring cholesterol levels). Sometimes, the research protocol requires a specialized research unit with trained nurses and staff and appropriate supplies. The facility also needs to be able to collect and freeze tissue and blood samples and then process them with sophisticated technology that is now available for both clinical and basic science investigators.

In phase 4, once samples are collected and analyzed, the clinical researcher needs to collect and interpret the project’s data, which can sometimes be quite complex and require sophisticated bioinformatics programs. Once the data are interpreted, the researcher needs to present results to other researchers and to publish those results to disseminate the information.

When possible, the researcher wants to progress into phase 5 and translate the research results into real practice, which requires that the researcher interacts with potential commercial, community, medical society, and other partners, to really take clinical research results from the bedside to the community for use. To move results from the bedside to the community, the researcher must overcome hurdles. These hurdles include financial issues and regulatory and intellectual property issues. All of these must be accomplished with the highest ethics: with absence of conflict of interest that is being monitored regularly to ensure that application of results is a pure process.

PUTTING THE CRISIS INTO PERSPECTIVE

The number of clinical researchers with the MD degree is decreasing, and physician clinical researchers are more likely to leave research than are nonclinical researchers. Several reasons might be contributing.

First, the pace of clinical research is often slower than animal and cellular research, so a physician’s potential to be promoted and to advance and be recognized by the institutions is lower than a researcher in basic science research. Second, physicians must understand regulatory hurdles, which can require additional education and extensive paperwork and approval before a clinical researcher can begin to gather data. Third, clinical research applications to the NIH are not as well funded as are applications for basic science or nonclinical research.

Fourth, physicians are busy with clinical training, they must pay off educational debt, and they lack mentors. Clinical medicine has become more complex and burdensome. As a result,
a professional must overcome difficult odds to be an effective physician and an effective investigator at the same time.

Finally, basic research is attractive. Basic researchers make regular major breakthroughs, and they can use modern techniques that cannot be used in human research. Also, it can be easier to conduct excellent basic or nonclinical research than clinical research because modern research techniques, such as gene manipulation in rodent models, make it easier to directly address the cellular mechanisms responsible for the pathogenesis and pathophysiology of disease.

The world is complex for clinical investigators. As they are seeking funding from the NIH and other sources, they face distractions that can prevent funding. A physician researcher needs a large infrastructure of technicians, research coordinators, collaborators who recruit subjects, basic scientists, clinical scientists, trainees and fellows, and laboratory personnel, an entire system that makes a clinical research operation work. Establishing such a large complete infrastructure is complex and difficult. There is a growing fear that if we do not establish a better support system for clinical research, we will lose a generation of clinical investigators needed for sophisticated, scientifically valid clinical research.

**REFERENCE**