



2007 Danone International Prize For Nutrition

Press Kit

July 11th, 2007

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MEDIA ALERT

**PROFESSOR JEFFREY FRIEDMAN (NEW YORK, USA),
PIONEERING RESEARCHER IN THE FIELDS OF NUTRITION
AND WEIGHT,
LAUREATE OF THE 2007 DANONE INTERNATIONAL PRIZE
FOR NUTRITION**

Paris, July 11, 2007 – The 6th Danone International Prize for Nutrition is awarded to Professor Jeffrey Friedman of the Rockefeller University and the Howard Hughes Medical Institute, New York, USA for his outstanding research on the endocrine function of leptin, the hormone he discovered, in the regulation of adipose tissue (fat stored in the body) and the role of genes in the regulation of body weight. He opened the door for research around the biology of obesity. The official announcement of Professor Jeffrey Friedman as the recipient of the 2007 Danone International Prize for Nutrition will be made on July 11, 2007 at the 10th European Nutrition Conference in Paris, France.

Obesity issue in a new light

Obesity and overweight have recently been recognized by the World Health Organization as one of the top 10 global health problems. They have reached epidemic proportions globally and pose a major risk for serious diet-related chronic diseases, including type 2 diabetes, cardiovascular diseases, hypertension and stroke, and certain forms of cancer. It is a very complex issue, closely linked with lifestyle and biological factors as well as social and psychological dimensions, which affects virtually all age and socioeconomic groups and that is present in both developed and developing countries.

While the problem of obesity has proven difficult to solve, great strides toward a thorough understanding of the biology of obesity have been made. Twenty years ago, little was known about the biological mechanisms that control body weight. While it was known that the hypothalamus, a region of the brain, regulates food intake and metabolism, the molecular elements of this system were not known.

In 1994, Professor Friedman identified a gene in mice and humans called obese and its product, the hormone leptin, as two of the molecular components of that system regulating appetite and adiposity. A revolution in the understanding and approach of obesity was started: these findings provided a basis for a new understanding of the system that controls weight. New theories on genetic and biologic causes of obesity were established.

Dr. Friedman's subsequent research on leptin and the identification of its receptors led scientists to understand that appetite and adiposity are regulated by a physiological system balancing food intake and energy expenditure. This system is based on the ability of the adipose tissue to produce leptin, a hormone reporting nutritional information to the hypothalamus. Increased body fat (adipose tissue) is associated with increased levels of leptin, which then act to reduce food intake. A decrease in body fat leads to decreased levels of leptin, stimulating food intake and reducing energy expenditure.

A completely new approach of the obesity issue: the implication of genetics in weight control

It is often considered that weight control is just a question of healthy eating and lifestyle, an assumption which, in the end, stigmatizes obese people, who are often perceived as lacking the willpower and discipline to lose weight. According to Professor Friedman, the current environment is partly responsible for the development of obesity. Most people in Western societies today have access to an abundance of food, and they lead a more sedentary life-style than did their hunter-gatherer ancestors. The environment has indeed contributed to the increase of the average weight of the population over time, but it can't be the cause of the huge differences in weight among the population at the present time. The perception that the lack of willpower to lose weight among obese people is the only determining factor is invalidated by a growing body of scientific evidence demonstrating that a precise and powerful biological system maintains body weight at a constant level. Voluntary efforts to reduce weight are thus resisted by potent compensatory biological responses.

Looking at the involvement of leptin in obesity, it was found that mutations in the obese gene result in an insatiable appetite, morbid obesity and numerous clinical abnormalities. Since then leptin

treatments have proven to be effective on rodents (up to 30% weight loss due to leptin injections), initial clinical trials have been done to test the efficacy of leptin against human obesity. The differences in weight loss among the subjects participating in the trials revealed the problem of leptin resistance. But major findings were that leptin successfully treats two rare diseases (a defect in the obese gene and lipodystrophy) and that leptin has a positive effect on insulin sensitivity among people with type 2 diabetes.

Today, scientists have identified other genes that play a role in obesity, demonstrating even more strongly the implication of genetics in obesity and the complexity of this system.

In the light of these elements, it becomes understandable why, if public health recommendations on healthy diet and lifestyle can have a positive effect on moderately overweight people, such measures have generally little results on obese people's health. For them, new scientific findings, to which Professor Friedman contributes, are providing new perspectives in the struggle against obesity.

"It is [a] propitious time to discuss the need for understanding the biological basis of obesity. A different kind of understanding is called for. Obesity is not a personal failing. In trying to lose weight, the obese are fighting a difficult battle. It is a battle against biology. It is our hope that a better understanding of the genes and genetic variants that cause obesity in humans will provide help to obese people. Still, patience is called for; scientific advances take time, and the translation of those in new treatments often takes even longer," says Professor Jeffrey Friedman.

By discovering leptin and by proposing a hormonal relationship of the adipose tissue with the centres in the brain responsible for satiety and hunger, Professor Jeffrey Friedman demonstrated that appetite and body weight depend on a complex physiological system . He opened research on the biology of obesity and brought new angles to research on nutrition and food intake. Today, Professor Friedman is still at the forefront of research, studying regulation of appetite and adipogenesis by leptin and other relevant new compounds.

In awarding the 6th Danone International Prize for Nutrition to Jeffrey Friedman, the Danone Institute International intends to reward his revolutionary approach in obesity research and underline his pioneering role in the field of research in nutrition.

The Danone International Prize for Nutrition

The Danone International Prize for Nutrition is awarded every two years, by the not-for-profit association 'Danone Institute International' with the scientific support of the French Medical Research Foundation (Fondation pour la Recherche Médicale [F.R.M.]). Created in 1997, the Prize celebrates its 10th anniversary this year.

The Prize stands for the commitment of Danone Institute International to promote and encourage innovative research in nutrition, and thus highlight the importance of nutrition in the overall field of human health.

The Danone International Prize for Nutrition awards 120,000 Euro (approximately \$150,000 U.S. dollars) to a researcher or team of researchers whose novel approaches and concepts have crossed the frontiers of nutrition by either basic or applied research.

The organisation of the award initially involves 650 nutrition research institutions worldwide in seeking out potential laureates. About 8 international key opinion leaders were involved in the final selection process of the laureate.

Today, the Danone International Prize for Nutrition is the world's most respected initiative within the field of innovative nutritional research.

More information: www.danoneinstitute.org

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FACTSHEET 1

OVERWEIGHT AND OBESITY: COMPLEX PUBLIC HEALTH ISSUES, SYNONYMS FOR TRUE CHALLENGES

What are overweight and obesity?

- Obesity can be described as an abnormal and excessive fat mass accumulation in the body.
- One of the most-used tools to classify overweight and obesity in adults is the body mass index (BMI). The BMI is defined as body weight (expressed in kg), divided by the square of the height (in metres).

The World Health Organization (WHO) defines "overweight" in adults as a BMI greater than or equal to 25, and "obesity" as a BMI greater than or equal to 30.

- For children, reference curves for BMI are needed because body composition is affected by age-dependent physiological variations. The upper percentile¹ curves delimit thresholds used to define excess fat in children. A BMI above the 97th percentile is generally considered to be a sign of obesity. However, weight status must be interpreted differently at different ages. After the age of 8 years, most children will remain in the same BMI category

What is the prevalence of overweight and obesity in Europe and worldwide?

- According to the latest estimates, 1 billion adults and more than 22 million children under five years around the world are overweight. Of these, 300 million adults are obese.
- The growth of obesity is global. It not only reaches developed countries; it is also increasingly extending to the developing countries, where it is estimated that over 115 million people suffer from health problems related to obesity.
- According to the European Charter on Counteracting Obesity², obesity poses one of the most serious public health challenges in the WHO European Region. The trend is particularly alarming in children and adolescents, thus extending the epidemic into later adulthood and creating a growing burden for the next generation. Experts have noted a rapid acceleration in the increasing prevalence of overweight and obesity: from 0.2% in the 70s, it is rising by 2% a year today, i.e. 400,000 additional overweight or obese young Europeans each year.

¹ A percentile is defined as the percentage of subjects with a BMI below the defined level. For example, 3% of the population has a BMI below the 3rd percentile and 97 % have a BMI below the 97th percentile.

² WHO European Ministerial Conference on Counteracting Obesity, Diet and physical activity for health, Istanbul, Turkey, 15-17 November 2006.

- According to WHO projections, by 2015, approximately 2.3 billion people will be overweight and 700 millions will be obese.

What are the causes of overweight and obesity?

Overweight and obesity are due to a lack of balance between caloric intake and physical activity. People with overweight consume too many calories in relation to the number of calories they spend. The caloric surplus is converted into fat, stored by the body in the form of adipose tissues.

Quite apart from this technical explanation, overweight and obesity are complex problems, depending on many different factors.

Genetic factors

- The first recessive gene involved in obesity in mice and humans was identified in 1994 by Professor Friedman³. Today, five mutations of this gene responsible for obesity have been identified⁴.
- It appears that predisposition to obesity is caused by a complex interaction between at least 250 obesity-associated genes. This would mean that people are not equal in their risk of developing obesity.

Early-programming and perinatal factors

- Nutritional factors during early life may modulate later obesity risk: a phenomenon called *metabolic programming* or *metabolic imprinting*.
- Animal studies have shown that dietary manipulation in the perinatal period, in particular an alteration of *protein intake*, have lasting effects on body weight in adult animals.
- Epidemiological studies have suggested a possible relation between the excess of proteins at the beginning of life and later obesity, as they observed that overweight or obese children had consumed more proteins than the others during their first year of life.⁵

Lifestyle factors

Diet

- Dietary habits and patterns play a key role in the maintenance of a healthy weight, or the development of overweight and obesity. They have dramatically changed over the last decades all over the world, with more people consuming energy-dense food, eating more calories than they need and, for some of them, eating often in the day even if they are not hungry.
- These feeding behaviours can lead to high dietary intakes and may contribute to overweight.

³ Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature*. 1994;372:425-432

⁴ Farooqi IS, O' Rahilly S. Recent advances in the genetics of severe obesity. *Arch Dis Child* 2000;83: 31-34.

⁵ Rolland-Cachera MF, Deheeger M., Akrouf M, Bellisle F. Influence of macronutrients on adiposity development: a follow-up study of nutrition and growth from 10 months to 8 years of age. *International Journal of Obesity*, 1995; 19: 573578

Physical activity

- Adults and children who lead a lifestyle characterised by lack of physical activity and excessive inactivity (static work, use of the car rather than walking, television viewing, computer games, etc.) may become overweight or obese.
- The influence of the changing environment may be profound in that highly energy-dense food is cheap and widely available, opportunities for energy expenditure may be reducing, and the attractiveness and availability of home screen entertainment is rapidly increasing. Whatever the age of onset, obesity will only develop if energy intake exceeds energy expenditure over a prolonged period of time. It is counterproductive to investigate the impact of eating or inactivity in isolation. The two combine to influence degree of fatness of the individual.

What are the common consequences of obesity and overweight on health?

Serious complications arising from obesity include

- Cardiovascular diseases: coronary heart diseases, hypertension and strokes
- Type 2 diabetes
- Dyslipidemia with, among other things, too a high bad cholesterol level
- Some cancers (breast, endometrial and colon)
- Asthma and sleep apnoea
- Gallbladder disease and gallstones
- Muscular and skeletal problems, especially osteoarthritis.

Besides its impact on physical health, obesity can also cause psychosocial troubles such as poor self-esteem, denial and lack of social experiences. It can result in depression or hyperactivity disorders amongst children, having consequences such as poor school results.

How to tackle obesity ?

Obesity is taken very seriously by international and national authorities.

It is generally recognised that overweight and obesity are very difficult to treat. They are multifactor health issues linked with lifestyle, education, socio-economic aspects, psychological factors and physiological elements. The complexity of the problem calls for complex solutions. This partly explains why obese people who lose weight thanks to a diet often regain their kilos.

Therefore, the current approach that is put forward is based on prevention.

In that framework, national governments are encouraged to set up local prevention programmes providing the following kinds of public health recommendations:

- To increase consumption of fruits and vegetables
- To increase physical activity
- To limit energy intakes: to limit consumption of energy dense-food (high in fats and sugar), fats and sugar
- To eat more fibre and vegetables
- To limit consumption of saturated fats and move towards unsaturated fats

The public-health challenge

Obesity is a global health issue affecting every part of world and all kinds of populations. Obesity rates have tripled since 1980 in the United Kingdom, Eastern Europe, Middle East, Pacific Islands, Australia, China and some regions of the United States. Contrary to what we usually think, obesity is present not only in industrialised countries but also in developing countries. In these countries, obesity is becoming another health issue, coexisting with under-nutrition. Today obesity has reached epidemic proportions worldwide and represents one of the main origins of chronic diseases and disabilities.

Even if this may sound less important, obesity is not only a question of health. It also raises economic questions. During the WHO European Ministerial Conference on Counteracting Obesity, the socio-economic burden of obesity was publicly recognised: as mentioned in European Charter on counteracting obesity⁶, 6% of health care expenditure in European regions are due to adult overweight and obesity. Moreover, these two health issues cause important direct costs linked to the loss of productivity and associated income. As obesity affects more people in the lower socioeconomic groups, this contributes also to the widening of inequalities.

Tackle obesity is today at the centre of socio-economic debates. Prevention has become a key word for international and national authorities. The WHO Global Strategy on Diet, Physical Activity and Health calls upon all stakeholders to take action at global, regional and local levels to reduce chronic diseases and other health risk factors related to obesity.

But the present situations and health predictions, which are not favourable, show how difficult it is to solve overweight and obesity. Nobody has found a solution yet. Researches on the causes of obesity and on new solutions to stop its progress are therefore crucial.

⁶ WHO European Ministerial Conference on Counteracting Obesity, Diet and physical activity for health, Istanbul, Turkey, 15-17 November 2006.

FACTSHEET 2

LEPTIN AND THE GENETIC IMPLICATIONS IN OBESITY

Three primary thoughts

Overweight and obesity are complex issues and have become major public-health concerns around the world. The current increase in the incidence of obesity despite awareness of the problem shows how difficult it is to find efficient solutions. Therefore, a deeper understanding of the causes of obesity should help in developing treatments. This requires a scientific approach.

- 1. The global increase in the weight of the population is not uniformly reflected among the population.** Differences in weight between people can be huge. Living in the same environment, some people become obese, while others maintain their normal weight. If it is recognised that the environment has an impact on weight gain, how can we explain that some people are more sensitive to this environment than others? The answer should be found in the physiological foundations of the people, that is in their genes and in the interaction of the genes with today's environment.
- 2. In some case, obesity is the result of hereditary factors.** Twin studies, adoption studies, and family aggregation studies confirm a major contribution by genes to the development of obesity^{7,8}. These studies compared BMI of twins growing up together or living in different families. In both cases, the correlation coefficient of BMI between identical twins was over 0.6 for women and 0.7 for men. That there are likely to be genetic forms of obesity is therefore strongly suggested.
- 3. The ability of the body to store adipose tissues can be a good thing, depending on the environment in which you (or your ancestors) find yourself.** For people who lived in times of privation, such as hunter-gatherers, food was not constantly available and the risk of famine was a daily reality. In such an environment, genes that predispose to obesity increase energy stores and provide a survival advantage in times of famine. For people descended from the inhabitants of the Fertile Crescent or, more recently, Western societies, the risk of starvation was markedly reduced. Today, the challenge is to stay lean in abundant environments: most people in Western societies have access to an abundance of food and have a more sedentary lifestyle than did hunter-gatherers. However, as a species, we carry the genetic legacy of both environments.
Might it be that it is the obese who carry the "hunter-gatherer" genes and the lean who carry the "Fertile Crescent" or "Western" genes? In support of this idea is the observation that populations

⁷ Stunkard, A.J., Harris, J.R., Pedersen, N.L. & Mc Cleary, G.E. The body-mass index of twins who have been reared apart. *N. Engl. J. Med.* **322**, 1483-1487 (1990).

that were historically most prone to starvation become the most obese when exposed to a Western diet and more sedentary lifestyle.

Based on these facts and the understanding that genes had something to do with weight regulation, Professor Friedman started his research on the role of genetics in obesity.

The theory of a physiologic system that regulates energy balance

Finding a solution to overweight and obesity issues implies first understanding the mechanisms regulating weight. Professor Friedman's belief that weight and appetite regulation was something complex and precisely regulated rests on the observation that human weight is, most of the time, remarkably stable. This can be illustrated by the fact that, during a decade, an average person consumes approximately 10 million calories, which, generally, provoke only a modest change of weight.

This is based on an easily understandable equation: for the weight of an organism to remain constant, the amount of energy eaten must equal the amount of energy consumed. Imbalances between food intake and energy expenditure result in a change in the amount of stored energy, mainly fat.

To maintain weight at such stability, the body must therefore be able to regulate energy balance with a precision of greater than 99.5%, which far exceeds what can be consciously monitored by people. This level of precision exceeds the ability of nutritionists to count calories.

Knowing this, the question is how can we explain the phenomenon of obesity in certain subjects? Before trying to find any other explanation, two main elements need to be taken into account:

- Unconscious control of food intake, willpower and diet

The hypothalamus has already been identified as the brain region managing basic and vital components: body temperature regulation, sexual behaviour, thirst, etc. The neural system that regulates appetite has also been localized to the hypothalamus.

However, one would say that, in humans, these basic mechanisms can be controlled by the desire to lose weight. But the basic neural system is powerful: even if we are aware of the conscious desire to eat less, the basic drive to eat is subconscious. Therefore, voluntary changes in behaviour generally induce short-term weight change, whereas the neural centres that control appetite soon overcome motivational factors and cause the lost kilos to be regained.

⁸ Stunkard, A.J., Foch, T.T. & Hrubec, Z.A. twin study of human obesity. *J. Am. Med. Assoc.* **256**, 51-54 (1986).

- **The importance of energy expenditure**

Energy expenditure can be defined as the number of calories expended per 24 hours. The level of energy expenditure depends on people's metabolism, metabolic rate, activity and the thermogenic effects of feeding. Not only is energy expenditure dependent on a person's physical activity therefore, but restricted physical activity also generally increases the propensity to gain weight.

Discussions of the causation of obesity have generally focused on the importance of food intake in the energy-balance equation. However, several pieces of scientific evidence indicate that energy expenditure is tightly regulated and that subconscious alterations of energy expenditure have a powerful influence on body weight. Energy expenditure is highly variable and, in prospective studies, people with lower rates of energy expenditure develop obesity more frequently than people with high rates⁹.

While scientists were aware of this complex system, it was poorly understood. And this became one of the main objectives of Professor Friedman and his laboratory: to identify the molecules involved in weight regulation. ***After eight years of research and working with genetically obese mice, he discovered the first of these: the obese (ob) gene and its product¹⁰, which he later dubbed "leptin" (from the Greek word for "thin").***

The discovery of the obesity gene and its hormone, leptin, by J. Friedman

- **Leptin and how it works**

Leptin is a 142-amino-acid peptide that functions as an afferent signal in a negative feedback loop that maintains body weight within a relatively narrow range¹¹. It is a hormone secreted by the adipose tissue that interacts with the hypothalamus. It plays a key role in weight and appetite regulation: increased body fat is associated with increased levels of leptin, which gives an order to the brain to reduce food intake.

A decrease in body fat leads to a decreased level of leptin, which produces a signal to stimulate food intake and reduces energy expenditure, so that energy can be stored by the body.

The discovery of leptin was a first step in the understanding of weight regulation. It opened the doors to further research towards understanding this complex system. As Professor Friedman says, feeding remains a complex motivational behaviour.

⁹ Ravussin, E. *et al.* reduced rate of energy expenditure as a risk factor for body-weight gain. *N. Engl. J. Med.* **318**, 467-472 (1998).

¹⁰ Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature.* 1994;372:425-432

¹¹ Friedman, J.M. & Hallas, J.L. Leptin and the regulation of body weight in mammals. *Nature* **395**, 763-770 (1998).

According to him, “many factors influence the likelihood that the behaviour will be initiated. These factors include the unconscious urge to eat that is regulated by leptin and other hormones, the conscious desire to eat less (or more), sensory factors such as smell or taste, emotional state, and others. Key neural centre(s) somehow process this diverse information. A genetic approach to the study of obesity will have as its objective to establish and to understand which roles obese (ob) and diabetes (db) genes have in genetic forms of obesity and to see which roles other genes could have. It is also important to have a fuller understanding of their function and a deeper knowledge of how their activity is modulated by environmental, developmental, emotional and psychological factors. This level of understanding will provide the foundation for the development of effective therapies”

- Leptin treatments

Once Professor Friedman had identified the ob gene in mice and discovered leptin, he soon located the corresponding gene (OB) in humans. These findings enabled scientists to find out that a part of the obese population (in rodents and humans) is leptin-deficient^{12,13} (due to mutations in genes). Leptin deficiency correlates with constant hunger, ravenous appetite, morbid obesity and other clinical abnormalities such as, among others, type 2 diabetes.

The next step of the research was therefore to see if the weight of these individuals could be brought to normal with leptin injections. In 1995, Professor Friedman and his colleagues published the results of this study: daily intraperitoneal injections of either mouse or human recombinant OB protein reduced the body weight of ob/ob mice by 30% after 2 weeks of treatment with no apparent toxicity¹⁴. Leptin treatments were also proven to have effects on leptin-deficient humans^{15,16}.

Lipodystrophy is another disorder that was found to be positively treated by leptin. Lipodystrophy is a metabolic disease characterized by abnormal and degenerative adipose tissue mass.

It is associated with extreme symptoms as, among others, severe type 2 diabetes and absence of fat cells in the body despite an insatiable hunger. People suffering from this disease are extremely thin. Treatments with leptin decrease the impact of the symptoms, including diabetes, which puts forwards the role that leptin could also play in treatment of this other important health issue.

¹² Montague, C. T. Montague, *et al.* Congenital leptin deficiency is associated with severe early-onset obesity in humans, *Nature* **387**, 903-908 (1997).

¹³ Y. Zhang, *et al.*, *Nature* **372**, 425 (1994).

¹⁴ Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM. Weight-reducing effects of the plasma-protein encoded by the obese gene. *SCIENCE* 1995 JUL 28;269(5223):543-546

¹⁵ Farooqi, I. *et al.* Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N. Engl. J. Med.* **341**, 879-884 (1999).

¹⁶ Farooqi, I.S. *et al.* Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J. Clin. Invest.* **110**, 1093-1103 (2002).

From there, one hoped that leptin could be the key element of an efficient treatment of human obesity. However, further clinical trials showed that some of the obese people undergoing treatment with leptin failed to lose weight. It appears that the intrinsic sensitivity to leptin is variable and that, in general, obese individuals are leptin-resistant. In humans or animals with normal weight, treatment with leptin in physiological amounts leads to loss of adipose tissue, weight loss and a significant increase in insulin sensitivity^{17,18}. Weight gain is associated with increased leptin levels and, in general, obese subjects have significantly elevated plasma leptin¹⁹. Among obese hyperleptinaemic humans or animals, only a subset of the subjects loses weight in response to leptin^{20,21}.

Understanding leptin resistance is another challenge for scientists. The solutions should be found in the understanding of the complex series of pathways that are activated by leptin.

Leptin resistance and future research perspectives

The molecular basis for leptin resistance is not yet fully understood, but some hypotheses have been developed:

- The role of the ancestral gene with today's environment: in time of famine, the role of the genes that predispose to obesity would have been to ensure an efficient retention of nutrients as adipose tissue. This could have led to leptin resistance in order to avoid the effect of the signal sent by leptin to reduce body weight. Consistent with this idea is the finding that obesity and an increase of plasma leptin levels, indicative of leptin resistance, are characteristic of Pima Indians living a "Western" life-style, whereas Pima Indians living a more "native" life-style remain leaner and have low leptin levels²².
- Several genes have been shown to contribute to leptin resistance^{23,24}.
- Leptin resistance might not be caused by abnormalities in the cells responding to leptin. It could be resulting from alterations somewhere else in the neural system that regulates food intake and body weight.
- Hedonic reward pathways could also lead to leptin resistance: hedonic sensations of food could develop reward pathways that could neutralise leptin-activated pathways.

¹⁷ Heymsfield, S. *et al.* Recombinant leptin for weight loss in obese and lean adults. *J. Am. Med. Assoc.* **282**, 1568-1575 (1999).

¹⁸ Halaas, J.L. *et al.* Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. *Proc. Natl. Acad. Sci. USA* **94**, 8878-8883 (1997).

¹⁹ Maffei, M. *et al.* Leptin levels in human and rodent: measurement of plasma leptin and *ob* BNA in obese and weight-reduced subjects. *Nat. Med.* **1**, 1155-1161 (1995).

²⁰ Heymsfield, S. *et al.* Recombinant leptin for weight loss in obese and lean adults. *J. Am. Med. Assoc.* **282**, 1568-1575 (1999).

²¹ Halaas, J.L. *et al.* Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. *Proc. Natl. Acad. Sci. USA* **94**, 8878-8883 (1997).

²² E. Ravussin, *Metabolism* **44**, 12 (1995)

²³ Zabolothy, J.M. *et al.* PTP1B regulates leptin signal transduction in vivo. *Dev. Cell* **2**, 489-495 (2002).

²⁴ Bjorbaek, C., Elmquist, J.K., Frantz, J.D., Shoelson, S.E. & Flier, J.S. Identification of SOC-3 as potential mediator of central leptin resistance. *Mol. Cell* **1**, 619-625 (1998).

A key objective will be to understand why the cellular response to leptin is abrogated in the leptin-resistant state. This is a real challenge, knowing that leptin acts mainly in the brain.

A complete understanding of leptin resistance may require understanding how the numerous inputs that regulate complex motivational behaviours are integrated.

The role of the environment and its interaction with obesity genes

If we consider that genes, and even ancestral genes, play a role in the obesity issue, then, what is the role of the environment? It is obvious that the increase in weight in our population is not evenly distributed; there has been a disproportionate increase in the number of massively obese people in recent years, especially in certain ethnic groups^{25, 26, 27, 28}.

There is substantial evidence that alleles which predispose to obesity may have conferred a selective advantage in times of hardship and that, when food is more available, these alleles lead to obesity. According to this logic, in modern times, obesity and leptin resistance appear to be the residue of genetic variants that were more adaptive in a previous environment. If true, this means that the root of the problem is the interaction of our genes with our environment. Lean people carry genes that protect them from the consequences of obesity, whereas obese people carry genes appropriate to times of nutritional privation in which they no longer live.

According to Professor Friedman, it is a combination of the influences of the current environment, in which almost everyone has essentially unlimited access to calories and lead an overall more sedentary lifestyle than our hunter-gatherer ancestors, and genetics that explains the overweight and obesity problems the world is facing today. The environment would be responsible for the global weight gain of the populations, while genetics would account for obesity problems in individuals.

Professor Friedman estimates that public health recommendations on healthy diet and lifestyle promoted today in Western countries can confer a significant health benefit to populations.

However, such measures have generally little effect on long-term maintenance of significant weight loss, especially among morbidly obese people. We can take as example an obese person who has lost 50 kilos. The mechanisms of the genes and the system that maintains energy balance will significantly reduce energy expenditure and increase hunger of this person.

²⁵ S. Kumanyika, *Ethn. Dis.* **12**, 316 (2002)

²⁶ G. Dowse, *et al.*, *Diabetes* **39**, 390 (1990)

²⁷ P. Zimmet, *et al.*, *Diabetes Res.* **1**, 13 (1984)

²⁸ B. Howard, *et al.*, *Am. J. Clin. Nutr.* **53**, 1577S (1991)

The combination of these two factors, more powerful than the conscious desire to be thin, contributes to the regain of weight and to the “yo-yo” effect after dieting. Extreme examples are people who have undergone bariatric surgery. This gastrointestinal surgery reduce caloric intake more than could be achieved voluntarily. But even if these people lose a significant amount of weight, most of them remain clinically obese. This would mean that metabolism of morbidly obese people is different: it acts independently of their caloric intake.

For these people, help will come with the identification of the genes that predispose to obesity, a fuller understanding of their function and a deeper knowledge of how their activity is modulated by environmental, developmental and psychological factors.

“We can only hope that advance in our understanding of the cause of obesity will lead to changes in the perception of what it means to be obese in a world of harsh judgments and easy conclusions that are not supported by a growing set of scientific facts”, says Professor Friedman.

Dr. Friedman also leads a team of Rockefeller researchers that is studying the genetic causes of a cluster of health problems called Syndrome X — obesity, diabetes, high blood pressure and high blood cholesterol — in a remote population of over 3,000 people on the Micronesian island Kosrae.

Current research projects

Today, research of Professor Friedman and his colleagues focuses on a range of questions about regulation of body weight for which a complete explanation is still being sought. Professor Friedman is currently investigating the following questions:

- How does the fat cell regulate how much leptin is made?
- How does a single molecule (leptin) change feeding, a complex behaviour?
- How do brain pathways that are modulated by leptin in turn regulate peripheral metabolism and insulin action?
- Does body weight depend on variation of the genes composing the physiological circuit (of which leptin is a component)?
- Does leptin treatment change the body's reaction to weight loss?

Professor Friedman's contribution to research on obesity

One of the main and most outstanding contributions of Professor Friedman in the field of research on obesity is, of course, the discovery of leptin. This discovery revealed the endocrine function of adipose tissue.

Thanks to the identification of this hormone, other scientists have come to understand the role of genes in the regulation of body weight. Since then, Professor Friedman and others have started to piece together the mechanism in order to understand which hormones affect several systems in the body and how they proceed, trying to identify and to understand pathways, their implications in the system and the influence of one on the others.

Therefore, besides leptin, we can say that Professor Friedman opened the door to thousands of scientific research projects aiming to better understand the regulation of body weight.

In addition, to carry out his work, he pioneered new research methods, such as using a fluorescent protein marker to trace neural pathways. This method could, in principle, be used to isolate additional components of leptin or other signal transduction pathways.

In conclusion, we can say that Professor Friedman has reinvented the study of the biology of obesity.

FACTSHEET 3

BIOGRAPHICAL SKETCH

Professor Jeffrey M. Friedman, M.D., Ph.D.

Professor Jeffrey M. Friedman was born in Orlando, Florida, on July 20, 1954 and grew up in North Woodmere, Long Island.

Education

He is graduated from Rensselaer Polytechnic Institute *magna cum laude* and received his medical degree from Albany Medical College of University in Albany, New York, at the age 22. While at Albany Medical College, he was elected to Alpha Omega Alpha, the medical honour society.

Career

After completing a residency in Internal Medicine at Albany Medical Centre Hospital, Dr Friedman came to Rockefeller as a postgraduate fellow and associate physician in 1980. From 1980 to 1981, he also served as a fellow in Gastroenterology at Cornell University Medical College. In 1981, he entered the Rockefeller University's PhD programme and, in 1986, received a Ph.D. under the tutelage of Professor James E. Darnell. In 1986, Dr Friedman joined the Rockefeller University faculty as an Assistant Professor. In 1991, he was promoted to Associate Professor and named Head of the Laboratory of Molecular Genetics at Rockefeller. He was promoted to Professor in 1995 and, in 1999, was appointed the first Marilyn M. Simpson Professor. He has been an investigator at the Howard Hughes Medical Institute since 1986.

Domain of research

Professor Friedman is a physician-scientist studying the genetic mechanisms that regulate body weight. His research on various aspects of obesity received national and international attention in late 1994, when it was announced that he and his colleagues had isolated a gene, called *ob*, in obese mice and its human homologue, and *ob*'s protein product leptin, a hormone secreted by adipose tissue. They subsequently found that injections of leptin decrease body weight of mice by reducing food intake and increasing energy expenditure. Current research is aimed at understanding the genetics of obesity in humans and the mechanisms by which leptin transmits its weight-reducing signal.

Recognition

Professor Jeffrey Friedman was elected to the U.S. National Academy of Science in 2001, the Institute of Medicine in 2005, and the Royal Swedish Academy of Sciences as a Foreign Member in 2005.

His work was referred to in Time Magazine's Best of Science Section in 1995 and 1996.

Professor Jeffrey Friedman also received several distinctions in recognition of his work:

- *Popular Sciences*, Best of Sciences Award, 1995
- Alumnus of the Year Award from the Albany Medical College, 1996
- Heinrich Wieland Prize, 1996
- Jacobaeus Prize, University of Goteborg, 1997
- Steven C. Beering Award, Indiana University School of Medicine, 1999
- Janssen Award for Special Achievement in Gastroenterology, 1999
- Endocrinology Transatlantic Medal, Society for Endocrinology, United Kingdom, 2000
- Osborne Mendel Award, American Society for Nutritional Sciences, 2000
- Rolf Luft Award, Karolinska Hospital, Stockholm, Sweden, 2000
- Bristol-Myers Squibb Award for distinguished Achievement in Metabolic Research 2001
- Passano Foundation Award, 2005
- Gairdner Foundation International Award 2005
- Kovalenko Medal of the National Academy of Sciences, 2007

Prof. Friedman was awarded an honorary doctorate in molecular genetics, Maastricht University, The Netherlands in 2006.

He has delivered:

- the Shelton Lecture, Harvard University, 1996
- the Peters' Lecture, Yale University, 1996
- the Carl Vernon Moore Lecture, Washington University, 1997,
- the Allan D. Bass Lecture, Vanderbilt University, 1997
- the Priscilla White Lecture, Joslin Diabetes Center, 1998
- the Chilton Foundation Lecture, University of Texas, 1998
- the Jack Gross Memorial Lecture, Israel, 1998
- the Van Wyck Lecture, University of North Carolina, 1999
- the Verna and Marrs McLean Lecture, Baylor College of Medicine, 1999
- the Banting Lecture of the British Diabetes Association, 2002

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FACTSHEET 4

DANONE INTERNATIONAL PRIZE FOR NUTRITION



A key initiative of the non-profit Association Danone Institute International at the service of human health

The non-profit Association 'Danone Institute International' with the scientific support of the French Medical Research Foundation (Fondation pour la Recherche Médicale [F.R.M.]) awards the Danone International Prize for Nutrition every two years. The Prize represents the commitment of the Danone Institute International to promote and encourage innovative nutrition-related research, and thus highlight the importance of nutrition in the overall field of human health. Created in 1997, the Prize celebrates its 10th anniversary this year.

Rewarding novel nutritional concepts and approaches

The Danone International Prize for Nutrition is the world's most respected initiative within the field of innovative nutritional research, rewarding those researchers and research teams whose novel approaches and concepts have expanded the frontiers of nutrition by either basic or applied research.

The Danone International Prize for Nutrition, amounting to 120,000 EUR (approximately \$150,000 U.S. dollars), is awarded to a researcher or team of researchers whose work on human nutrition has made a major contribution to public health in one of the following areas:

- the impact of nutrition on the identification, diagnosis, epidemiology and prevention and/or treatment of chronic diseases, including malnutrition;
- mechanisms involved in the abovementioned impact, including research in genetics and molecular biology that sheds a light on the role of nutrition in human health,
- the cultural, behavioural, anthropological, social, psychological, economic and toxicological aspects of human nutrition.

Individual researchers or research teams represented by an individual must conduct on-going and active research and be leader within their field of activity.

The amount of money is to be shared on a 50/50 basis between the winner and the Rockefeller University to support further research.

A selection procedure that guarantees complete independence and transparency

Three bodies are involved in the procedure.

The Prize Committee

The Prize Committee, which consists of 7 members, including members from the Danone Institute International and other experts appointed by the Board of the Association, is responsible for all scientific matters. More specifically, the Prize Committee:

- establishes the Nomination College
- requests proposals from the Nomination College
- collects information on nominees
- establishes the list of Jury members

The Nomination College

The Nomination College, made up of more than 650 institutions worldwide that are responsible for the promotion of nutrition research, is consulted to identify outstanding individual researchers or research teams who may be potential awardees of the Prize.

The Jury

Nominations are submitted to the Jury, presided by a Chairman appointed by the Board of the Association. The Jury is made up of 7 to 9 individuals, including members from the Association Danone Institute International and other individuals appointed by the Prize Committee as well as one member of the French Medical Research Foundation (Fondation pour la Recherche Médicale).

No more than 50% of the Jury members can belong to the Association Danone Institute International or Danone Institutes network. The Jury is charged with electing the recipient of the Danone International Prize for Nutrition by secret ballot.

Rewarding top-level laureates who challenged the frontiers of nutrition

- The first Danone International Prize for Nutrition went in 1997 to Professor Vernon Young (MIT, Boston, USA, deceased in 2003) for his contribution to the advances in protein and amino-acid metabolism studies leading to new WHO recommendations on protein intakes.
- The second edition of the Danone International Prize for Nutrition (1999) honoured Professor Leif Hallberg (University of Göteborg, Sweden) for his work on iron metabolism and nutritional needs, leading WHO to revise its recommendation of iron intake for women.
- In 2001, the Prize was awarded to Dr Alfred Sommer and his research team (Johns Hopkins University in Baltimore, Maryland, USA) in recognition of their outstanding contribution to the study of vitamin A in relation to the prevention of blindness and the decrease of childhood mortality.
- The fourth edition (2003) honoured Professor Ricardo Bressani (INCAP, Guatemala) for his lifetime contribution to advances in the application of local food resources to help solve the global issue of undernutrition.
- The last edition of the Danone International Prize for Nutrition in 2005 rewarded Professor David JP Barker (University of Southampton, UK) for his pioneering role within the field of early nutrition and chronic adult disease with the development of the novel concepts of IUGR (Intrauterine growth restriction) and fetal “programming” (Barker hypothesis)

The 2007 Prize award

- The 6th Danone International Prize for Nutrition is awarded to Professor Jeffrey Friedman (The Rockefeller University and Howard Hughes Medical Institute, New York, USA) for his revolutionary approach in obesity research, discovering the endocrine function of the adipose tissue, and underlines his pioneer role in the field of research in nutrition.
- The selection procedure of the 2007 Danone International Prize for Nutrition began in September 2006 with the consultation worldwide of more than 650 institutions promoting research in nutrition.
- The 36 nominations representing 12 countries were submitted to the Prize Committee, who selected a short list of 10 nominees fully complying with the rules of the Prize
- The Jury, consisting of 8 worldwide recognized scientists representing 7 different countries, met on March 6th, 2007 in Paris, France, to select the winner from among the pre-selected nominees.

The 2007 Prize Committee

- Zuzana BRAZDOVA, Ph.D., Masaryk University, Brno, Czech Republic (Chairwoman)
- Dennis BIER, M.D. (Baylor College of Medicine, Houston, USA)

- Diane FINEGOOD, Ph.D. (Institute of Nutrition, Metabolism and Diabetes, Vancouver, Canada)
- Joëlle FINIDORI, Ph.D. (Fondation pour la Recherche Médicale, France)
- Michio IMAWARI, M.D. (Showa University, Tokyo, Japan)
- Manuel SERRANO RIOS, M.D. (University Complutense, Madrid, Spain)
- Gunther WOLFRAM, M.D. (Technical University of Munich, Germany)

The 2007 Jury

- Stephanie ATKINSON, Ph.D. (Canada)
- Bernard DASTUGUE, Ph.D. (Clermond-Ferrand University, France – Representative of FRM)
- Helmut ERBERSDOBLER, V.D. (Albrechts University, Germany)
- Osman GALAL, M.D., Ph.D. (UCLA School of Public Health, USA)
- Johann JERLING, Ph. D. (Potchestroom University, South Africa)
- Emanuel LEBENTHAL, M.D. (Hadassah Hebrew University, Israel) – Chairman
- Daniel RICQUIER, M.D., Ph. D. (INSERM-CNRS, France)
- Emorn WASANWISUT, Ph.D. (Mahidol University, Thailand)

More information

www.danoneinstitute.org/danone_institute_prize_for_nutrition

FACTSHEET 5

DANONE INSTITUTES FAST FACTS



Danone Institutes are a forum where internationally renowned scientists in the field of nutrition, diet, lifestyle and health and Danone collaborators can:

- encourage research,
- promote the dissemination of relevant information,
- and therefore improve the quality of the diet, lifestyle and health of the general population.

The Danone Institutes are committed to taking a multidisciplinary approach combining medicine, biology, and human sciences.

A dynamic and fast-growing network at the service of consumer health

In 1991, Danone decided to create the *Danone Institutes* to promote research, information and education on diet and nutrition. Today, more than 250 international experts in diet and nutrition are involved in the 17 Danone Institutes around the world, including Belgium, Canada, China, Czech Republic, France, Germany, Israel, Italy, Japan, Mexico, Poland, Russia, Spain, Turkey, USA as well as an international entity. Most recently, the network has been expanded with a new Danone Institute in Indonesia.

Danone Institutes develop programmes on diet and nutrition for researchers, health professionals, educators and the general public.

More specifically, Danone Institutes' programmes are designed on two levels:

- On a local level, each Danone Institute develops programmes tailored to the specific needs of the country in which they operate
- On an international level, Danone Institute International, together with the local Danone Institutes, continuously strives to provide adequate answers to international challenges.

Danone Institutes: a strong ethical organisation

Danone Institutes are non-profit organisations and independent from the Danone Group. They define their own programmes in order to be relevant in their local environment.

- They have no commercial objective;
- They act freely and independently;
- They function on the basis of guidelines which guarantee a clear and democratic organisation;
- Danone Institute publications contain no commercial information.

Danone Institutes: overall activities

Danone Institutes focus their activities on topics related to major local nutrition and health issues, such as children nutrition and health, dietary habits and nutritional recommendations, health benefits of foods, etc.

Sponsorship of research related to health & nutrition

To date, Danone Institutes have sponsored more than 740 research projects amounting to more than 11.6 million EUR. Some examples are:

- Research grants (5000 to 25,000 EUR each) offered every year by Danone Institute Canada, China, Czech Republic, France, Germany, Poland, Spain to young scientists working within the fields of nutrition and nutrition-related diseases
- The Early Career Nutrition Sabbatical Programme (up to 46,000 EUR) created by Danone Institute of the USA to encourage nutrition researchers to enhance their career with the perspective of additional disciplines so as to support the development of future leaders in nutrition.
- Since 2002, involvement of Danone Institute International in the EU Childhood Obesity research programme investigating the hypothesis on the link between high early protein intake and later risk of obesity to disseminate new scientific knowledge to scientists and health professionals.

Prizes and awards

More than 150 prizes and awards have been awarded for outstanding research works and other professional initiatives for 1.6 million EUR.

This year, Danone Institute International celebrates the 10th anniversary of the Danone International Prize for Nutrition with the awarding of the 6th edition to Dr Jeffery Friedman for his revolutionary approach in obesity research.

Symposia, workshops and educational meetings

Danone Institutes frequently organise scientific conferences and educational programmes, involving top-level scientists within the field of health & nutrition. Since 1991, more than 175 events and meetings have reached more than 37.000 health professionals.

The most recent symposia have focused on: “Risks and benefits of rapid early growth” (Danone Institute International), “Toward healthy eating, multi-level strategies for changing nutrition behaviour” (Danone Institute Canada), “Probiotics and children health” (Danone Institute Italy), “Allergy: illness of the future?” (Danone Institute Belgium), “Prospects for registered dieticians” (Danone Institute Japan).

Publications related to health & nutrition

75 publications and 6 newsletters present professionals with overviews of recent developments, promote consensus and/or explore debate of relevant issues.

The most recent publications focused on ““Nutrition solutions to major public health issues of pre-school children: how to optimize health and development?” (Danone Institute International), “Diet, health, wellness: nutritional guidelines for the different phases of life” (Danone Institute Italy), “Calcium throughout life” (Danone Institute Belgium), “Dietary recommendations for the Mexican population” (Danone Institute Mexico), “Early Nutrition and later consequences: new opportunities” (Danone Institute International).

Education programmes for the general public

Danone Institutes believe that is crucial to help people become aware of the importance of adequate diet and lifestyle. In this light, 87 programmes towards the general public such as nutrition lectures, distribution of folders, brochures and pedagogic kits, broadcasting of radio and TV programmes, etc. have been organised.

The most recent programmes include “Full of food galaxy”, a computer game for children aged between 6 and 9 years produced by Danone Institute Poland, aiming at educating children to healthy dietary habits by presenting nutritional information in a fun and interacting way. For teachers in primary schools, Danone Institute Germany developed “Nutrition for children”, a new pedagogic kit aiming at promoting healthy lifestyle, through adequate food intake and physical exercise.

Danone Institute France also focused in 2006 on the promotion of physical activity in children through “Let’s move!”, a teaching kit providing primary school teachers with practical tips to organize games promoting physical activity among their pupils.

More information

www.danoneinstitute.org