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DOI: 10.1056/NEJMp1311941

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HISTORY OF MEDICINE

The Biology and Genetics of Obesity — A Century of Inquiries

Chin Jou, Ph.D.

Related article, p. 1909

The obese lack willpower; they overeat and underexercise — or so believe a majority of Americans. A 2012 online poll of 1143 adults conducted by Reuters and the market research firm Ipsos found that 61% of U.S. adults believed that “personal choices about eating and exercise” were responsible for the obesity epidemic.¹ A majority of Americans, it seems, remain unaware of or unconvinced by scientific research suggesting that “personal choices” may not account for all cases of obesity.

Yet for more than a century, physicians have been proposing that some cases of obesity are a function of innate biologic mechanisms or heredity. In 1907, the German pathologist Carl von

Noorden delineated two types of obesity: exogenous and endogenous (1953; see box for historical *Journal* articles cited). Exogenous obesity, which accounted for most cases, was the consequence of external culprits — namely, food consumption in excess of energy expenditure. But some people had endogenous obesity, caused by hypometabolism or other thyroid disorders.

Some early-20th-century doctors bluntly dismissed the idea of endogenous obesity. George Van Ness Dearborn, a neuropsychiatrist who had been on the faculty at Harvard and Tufts, declared in 1917 that “the great and culpable majority of the obese achieve their uncomplimentary fatness.”² Nonetheless, a survey of medical journal articles on obesity in the 1910s and 1920s reveals that even physicians who might have shared Dearborn’s sentiments conceded that dietary excess and lack of exercise could not account for all cases of overweight. And although the hypometabolic thesis had fallen out of favor by 1930, when more accurate calculations of body-surface area indicated that the metabolic rates of the obese were normal, researchers in the second half of the 20th century continued to make the

case that some people were predisposed to obesity.

In the 1950s, for instance, the work of Rockefeller University’s Jules Hirsch showed that for obese people, long-term weight loss is a lifelong struggle. Hirsch found that although obese subjects could shed a substantial amount of weight through drastic calorie restriction, their metabolic rates would dip in response to calorie reductions. This effect meant, for example, that if an obese woman dropped down from 200 lb to 130 lb, she would have to consume fewer calories to remain at 130 lb than would a 130-lb counterpart whose weight had always held steady. The previously obese woman, then, required more “willpower” to maintain her reduced weight than someone who had never been obese. Decades later, in 1995, Hirsch and his former Rockefeller colleagues Rudolph Leibel and Michael Rosenbaum observed that just as the metabolism of subjects who had lost 10% of their body weight decelerated, the metabolism of those who had gained 10% of their body weight revved up (1995). These findings suggested that the body has built-in mechanisms that resist attempts to resize it for the long term.

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Courtesy of the Advertising Archives.

Historical Ads for Weight-Loss Products.
The ad for obesity soap is from 1903; the ad for Graybar is from the 1920s; and the ad for Appetrol, which appeared in the *Journal*, is from 1960. A slide show containing additional ads is available with the full text of this article at NEJM.org.

In the 1960s, prisoner feeding experiments by University of Vermont physician–researcher Ethan Sims also pointed toward metabolic homeostasis. In 1967, Sims fed inmates at the Vermont State Prison upwards of 10,000 kcal per day. Over 200 days on this overfeeding regimen, 20 inmates gained an average of 20 to 25 lb.³ The metabolic rates of these previously normal-weight subjects sped up in response to their increased caloric consumption, as if to defend their initial, lower weights. The men had difficulty maintaining weight gain, and most shed all the weight they had gained relatively easily once their calorie intake returned to normal. The exceptions were two inmates who gained weight swiftly and effortlessly but then struggled to lose that weight even after caloric consumption was reduced. That both these men had family histories of obesity added empirical support to the notion that overweight could be heritable.

In 1986, the University of Pennsylvania's Albert Stunkard offered the most compelling evidence yet that one's weight could be largely determined by one's parentage (1986). Stunkard and colleagues used a Danish adoption registry of 540 adults, the majority of whom had been adopted by the age of 1 between 1927 and 1947. The adoption records included the heights and weights of the adoptees' biologic and adoptive parents. Stunkard et al. used those data to compare the body-mass indexes of both sets of parents with those of the adoptees, most of whom had reached middle age by the time

of their study. They found that, despite having shared an environment with their adoptive parents, the adoptees' body-mass indexes approximated those of their biologic parents rather than their adoptive parents. Accordingly, most adoptees inherited their biologic parents' obesity: four fifths of those with two obese biologic parents were obese, as compared with one seventh of those with normal-weight biologic parents.

Four years later, Stunkard and another team of researchers used another twin registry, this time from Sweden, to find more support for the genetics of weight regulation (1990b). The Swedish twin registry included 247 pairs of identical twins — 154 pairs that had been raised together and 93 pairs that had been adopted by different parents. The identical twins, it turned out, had virtually the same weight regardless of whether they had grown up together or separately. As reported in another article in the same issue of the *Journal*, Claude Bouchard and colleagues at Laval University in Quebec had followed the effects of overfeeding on 12 pairs of adult, male identical twins over a period of 100 days (1990a). All the twins consumed the same number of calories — a total of 84,000 excess kilocalories over the course of the experiment. The subjects' resulting weight gain ranged from 4.3 kg to 13.3 kg, with considerable variation in body-fat percentage, fat mass, fat distribution, and deposition of both subcutaneous and visceral fat among the pairs of twins. But although the responses to overfeeding varied widely among the twin pairs, within each pair of twins there

was little difference in weight gain and even less difference in body-fat distribution and visceral-fat accumulation.

While twin studies and feeding experiments continued, obesity research also took a decidedly molecular turn with the discovery of the peptide hormone and satiety factor leptin in 1994. Building on the work that Douglas Coleman had been conducting at the Jackson Laboratory since the 1960s, as well as the mapping of obesity-gene mutations in mice performed by Leibel et al. in the 1980s and early 1990s, Jeffrey Friedman and colleagues at Rockefeller University cloned the gene *ob* that encodes leptin.⁴ In the years since, tens of thousands of articles have been published on leptin and related subjects, such as the hunger-stimulating hormone ghrelin, interactions between these two hormones and the neurotransmitter neuropeptide Y, and the signaling pathways of molecules involved in appetite and the genetic mutations that might interfere with these pathways.

Today, molecular genetics is central to obesity research. In 2007, Mark McCarthy, Andrew Hattersley, and their colleagues in the United Kingdom identified a common variant in *FTO*, the fat-mass and obesity–associated gene, and gene hunters aided by the use of next-generation–sequencing technology continue to identify gene variants or mutations such as the *DYRK1B* discovery presented in this issue of the *Journal* (Keramati et al., pages 1909–1919). These studies, of course, reinforce what some physician–researchers have been insisting for more than a century: that obesity is innate,

 A slide show of selected historical ads for weight-loss products is available at NEJM.org



An audio interview
with Dr. Jou is
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that weight regulation is not governed by a uniform tally of “calories in–calories out,” and to quote Jules Hirsch, that “there is a biochemical or basic biological element in what it is that we call ‘willpower.’”⁵ The views of many Americans notwithstanding, weight is clearly far from being entirely within an individual’s control. Genetic pre-

dispositions, in tandem with the development of food environments that facilitate overeating and built environments requiring minimal energy expenditure, may help explain why so many Americans are obese today.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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DOI: [10.1056/NEJMp1400613](https://doi.org/10.1056/NEJMp1400613)

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