Chapter 1

History of Obesity
Obesity has been evident in the human record for over 20000 years and affected numerous aspects of human life and society (Bray, 2007a; Bray, 2007b). This introductory chapter describes the early history of human obesity, and then reviews how understanding has developed in the basic biology of obesity, its definitions and measurement, the complications of the disease, and finally its management. Some of the major scientific and medical milestones in the history of obesity are shown in Table 1.1.

**Early human history**

**Prehistory**

Human obesity is clearly depicted in Stone Age artefacts, notably numerous figurines that have been found within a 2000-kilometre band crossing Europe from South-Western France to Southern Russia. Palaeolithic (Old Stone Age) statuettes, produced some 23 000–25 000 years ago, were made of ivory, limestone or terracotta. Most famous is the ‘Venus of Willendorf’, an 11-centimetre figurine found in Austria (Figure 1.1). Typical of many such figurines, the Venus shows marked abdominal obesity and pendulous breasts. Anne Scott Beller (1977) has suggested that ‘obesity was already a fact of life’ for Palaeolithic humans, although one can only speculate about the purpose or significance of these artefacts.

The New Stone Age (Neolithic) period, spanning the interval between 8000 and 5500 B.C., saw the introduction of agriculture and the establishment of human settlements. This era also yielded numerous statuettes depicting obesity, notably the ‘Mother Goddess’ artefacts found especially in Anatolia (modern Turkey). Similar figures from this period have been found in many other sites in Europe and other continents. Anthropological studies indicate that hunter-gatherers are typically lean and that overt overweight is unusual (Prentice, Rayco-Solon and Moore, 2005) – although the enhanced ability to store energy as fat would have clear survival advantages. This fact makes these representations of severe obesity all the more striking.

**The ancient period**

Obesity and its sequelae have long figured in the medical traditions of many diverse cultures. Ancient Egyptian stone reliefs show occasional obese people, such as a cook in Ankh-ma-Hor’s tomb (Sixth Dynasty; 2340–2180 B.C.), and a fat man enjoying food presented to him by his lean servant, in Mereruka’s tomb (Figure 1.2). Studies of the reconstructed skin folds of royal mummies suggest that some were fat, including Queen Inhapy, Hatshepsut and King Rameses III (Reeves, 1992). Overall, it appears that stout people were not uncommon in ancient Egypt, at least among the higher classes; interestingly, Darby et al. (1977) were led to conclude that obesity ‘was regarded as objectionable’.

Elsewhere in the world, corpulent human figures are depicted in artefacts from the ancient Mesopotamian civilization in the basin of the Rivers Tigris and Euphrates, and from the Meso-American cultures of the Incas, Mayans and Aztecs.

**Ancient Greece and Rome**

The health hazards associated with obesity were well known to the Ancient Greek physician Hippocrates, who stated that ‘sudden death is more common in those who are naturally fat than in the lean’ (Littré, 1839). Greek physicians also noted that obesity was a cause of infrequent menses and infertility in women.
Table 1.1 Some landmarks in the history of obesity since the seventeenth century

<table>
<thead>
<tr>
<th>Year</th>
<th>Event/Inventor/Scientist</th>
<th>Description</th>
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<tbody>
<tr>
<td>1614</td>
<td>Santorio</td>
<td>Uses beam balance to measure metabolism</td>
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<td>1628</td>
<td>Harvey</td>
<td>Discovers circulation of the blood</td>
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<td>1679</td>
<td>Bonet</td>
<td>First dissections of obese cadavers</td>
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<td>1727</td>
<td>Short</td>
<td>First English language monograph on obesity</td>
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<td>1760</td>
<td>Flemyng</td>
<td>Monograph on the treatment of obesity</td>
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<tr>
<td>1780</td>
<td>Cullen</td>
<td>Disease classification that includes obesity</td>
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<tr>
<td>1780s</td>
<td>Lavoisier</td>
<td>First measurements of heat production by living animals; formulated the ‘oxygen theory’ (which replaced ‘phlogiston’ of the Ancients)</td>
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<tr>
<td>1810</td>
<td>Wadd</td>
<td>Treatise on Corpulence</td>
</tr>
<tr>
<td>1826</td>
<td>Brillat-Savarin</td>
<td>Diet-based method for weight loss</td>
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<tr>
<td>1835</td>
<td>Quetelet</td>
<td>Obesity quantified as weight/(height squared)</td>
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<tr>
<td>1848</td>
<td>Helmholtz</td>
<td>Published Law of the Conservation of Energy (First Law of Thermodynamics)</td>
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<td>1849</td>
<td>Hassall</td>
<td>Described structure and growth of fat cells</td>
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<tr>
<td>1863</td>
<td>W. Banting</td>
<td>Letter on Corpulence Addressed to the Public (first widely popular diet book)</td>
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<tr>
<td>1879</td>
<td>Hoggard</td>
<td>Described growth of fat cells</td>
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<tr>
<td>1896</td>
<td>Atwater</td>
<td>First human calorimeter constructed</td>
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<tr>
<td>1900</td>
<td>Babinski, Fröhlich</td>
<td>Described syndrome of hypothalamic obesity</td>
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<tr>
<td>1912</td>
<td>Cushing</td>
<td>Described obesity caused by basophil pituitary tumour</td>
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<tr>
<td>1921</td>
<td>F. Banting, Best, Macleod &amp; Collip</td>
<td>Insulin isolated from pancreas and used to treat human diabetes</td>
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<tr>
<td>1927</td>
<td>Various</td>
<td>Dinitrophenol used to treat obesity (poor outcome)</td>
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<tr>
<td>1936</td>
<td>Himsworth</td>
<td>Insulin-insensitive diabetic patients identified</td>
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<tr>
<td>1937</td>
<td>Abramson</td>
<td>Amphetamine used to treat obesity</td>
</tr>
<tr>
<td>1944</td>
<td>Behnke</td>
<td>Underwater weighing used to estimate body density and composition</td>
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<tr>
<td>1947</td>
<td>Vague</td>
<td>‘Android’ (central) obesity predisposes to diabetes and cardiovascular risk</td>
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<tr>
<td>1949</td>
<td>Fawcett</td>
<td>Described brown adipose tissue (BAT)</td>
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<tr>
<td>1954</td>
<td>Stellar</td>
<td>Formulated ‘dual centre’ hypothesis to explain control of feeding</td>
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<td>1955</td>
<td>Lifson</td>
<td>Doubly-labelled water used to measure energy expenditure</td>
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<tr>
<td>1959</td>
<td>Berson &amp; Yalow</td>
<td>Discovered radioimmunoassay technique to measure insulin concentrations</td>
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<td>1962</td>
<td>Neel</td>
<td>‘Thrifty gene’ hypothesis</td>
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<tr>
<td>1963</td>
<td>Randle</td>
<td>Glucose-fatty acid (Randle) cycle described</td>
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<tr>
<td>1967</td>
<td>Stewart</td>
<td>First use of behavioural therapy to treat obesity</td>
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<td>1968</td>
<td>Various</td>
<td>Association for the Study of Obesity founded in UK</td>
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<tr>
<td>1968</td>
<td>Mason</td>
<td>Performed first gastric bypass operations to treat obesity</td>
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<tr>
<td>1973</td>
<td>Gibb</td>
<td>Cholecystokinin (CCK) found to induce satiety in rats</td>
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<tr>
<td>1979</td>
<td>DeFronzo</td>
<td>Insulin-glucose clamp developed to measure insulin sensitivity</td>
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<tr>
<td>1982</td>
<td>Nedergaard et al.</td>
<td>Thermogenin (later renamed UCP1) identified as source of heat production in BAT</td>
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<tr>
<td>1986</td>
<td>Various</td>
<td>International Association for the Study of Obesity founded</td>
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<tr>
<td>1988</td>
<td>Reaven</td>
<td>Described ‘Syndrome X’ (the insulin resistance or metabolic syndrome)</td>
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Some 500 years after Hippocrates, the leading Roman physician Galen distinguished ‘moderate’ and ‘immoderate’ forms of obesity, the latter perhaps anticipating the ‘morbid’ category of current classifications.

Obesity was also familiar to Abu Ali Ibn Sina (Avicenna in the westernized version of his name), one of the most prominent figures of the Arabic medical tradition. Avicenna was a prolific and influential author who published over 40 medical works and 145 treatises on philosophy, logic and theology. In his medical encyclopaedia, written in the early twelfth century, Avicenna described the sweet taste of diabetic urine, and also referred to obesity and its dangers to health.

**Eastern medical traditions**

The Hindu physicians, Sushrut (Susrata) and Charak (500–400 B.C.) are credited with very early recognition of the sugary taste of diabetic urine, and also observed that the disease often affected indolent, overweight people who ate excessively, especially sweet and fatty foods.

The seventeenth century Tibetan medical treatise entitled *The Blue Beryl* recognized obesity as a condition that required treatment through...
weight loss. The author, Sangye Gyamtso, noted scholar and Regent of Tibet, also wrote that 'overeating ... causes illness and shortens lifespan'. He made two suggestions for treating obesity, namely the vigorous massage of the body with pea flour, and eating the gullet, hair and flesh of a wolf (which was also recommended to treat goitre and oedematous states).

History of the biology of obesity

Adipose tissue: structure and function

Vesalius laid the foundations of modern anatomy with his famous treatise, *De humani corporis fabrica* (1543), which was based on his own dissections. The first dissections of specifically obese individuals are attributed to Bonetus (1679), followed in the eighteenth century by descriptions from Morgagni and from Haller, and in the early nineteenth century by the notable monograph, *Comments on Corpulency, Lineaments of Leanness*, of Wadd (1829). Wadd presented 12 cases, two of whom had been examined post mortem and were found to have extensive accumulations of fat (Figure 1.3).

Figure 1.3 Illustration from William Wadd's monograph, *Comments on Corpulency* (1829). Image reproduced courtesy of the Wellcome Trust's History of Medicine Archive.

Figure 1.4 Microscopic studies of adipose tissue and its development. Illustration from Hoggan and Hoggan (1879), reproduced courtesy of the Royal Microscopical Society, London.
The adipocyte was recognized as a specific cell-type when the first substantive text books of microscopic anatomy were published in the 1850s, and the growth and development of fat cells were described by Hassall (1849) and by Hoggan and Hoggan (1879) (Figure 1.4). In his early observations on the development of the ‘fat vesicle’ (adipocyte), Hassall suggested that certain types of obesity might result from an increased number of fat cells – the precursor of the concept of ‘hyperplastic’ obesity that twentieth-century workers such as Bjurulf, Hirsch and Björntorp would later elaborate.

Much work was conducted on digestion during the seventeenth and eighteenth centuries, leading in the early twentieth century to the seminal and long-lasting theory that hunger resulted from gastric contractions; this was based on direct measurement of gastric motility, and its association with hunger by Washburn and Cannon, and independently by Carlson.

**Descriptions and measurements of obesity**

The first monographs devoted to obesity appeared during the eighteenth century, notably two works published in English by Short (1727) and Flemyng (1760). Short’s work (Figure 1.5) opens with the statement: ‘I believe no age did ever afford more instances of corpulency than our own’. He believed that the treatment of obesity required restoration of the body’s natural balance and removal of secondary causes, ideally by living where the air was not too moist or soggy and avoiding flat, wet countries, cities and woodlands. Short considered that exercise was important and that the diet should be ‘moderate, spare and of the more detergent kind’.

Flemyng listed four causes of corpulency, beginning with ‘the taking in of too large a quantity of food, especially of the rich and oily kind’ – although he went on to note that not all obese people were big eaters. His second cause of obesity was ‘too lax a texture of the cellular or fatty membrane … whereby its cells or vesicles are liable to be too easily distended’, and the third an abnormal state of the blood that facilitated the storage of fat in the vesicles. The fourth cause was ‘defective evacuation’; Flemyng believed that sweat, urine and faeces all contained ‘oil’, and therefore that obesity could be treated by eliminating this oil through the administration of laxatives, diaphoretics or diuretics.

As already mentioned, observations made in antiquity by Roman and Indian physicians hinted at attempts to distinguish different types of obesity and diabetes. Many classifications of diseases have been proposed, with an early approach by the seventeenth century English physician, Thomas Sydenham (1624–1689). Perhaps the two best-known systematic classifications of diseases were those of William Cullen (1710–1790), a physician who became professor of chemistry in Edinburgh, and the French doctor Sauvages (1706–1767). Both referred to ‘polysarcia’, from the Greek for ‘much flesh’. In Cullen’s work, polysarcia falls in the ‘Order II’ (‘Intumescentiae’, or swellings) of ‘Class III’ (Cachexiae), with the generic name of *Corporis pinguedinosae intumescentiae molesta* (‘harmful swelling of the body’s fat’). During the nineteenth century, ‘obesity’ (from the Latin *obesitas* meaning fatness) gradually came to replace polysarcia and other terms such as ‘corpulence’ and ‘embonpoint’.

There have been numerous attempts to quantify excess weight in ways that are appropriate to clinical practice, research and epidemiology; of particular interest has been the relationship between the severity of obesity and the various diseases to which it predisposes (see Chapters 3 and 9). The Belgian statistician
Adolphe Quételet (1796–1874) was one of the early leaders in developing and validating mathematical measures of obesity (Figure 1.6). Quételet was responsible for the concept of the ‘average man’ and suggested that the ratio of the subject’s weight divided by the square of the height could be used as a measure of fatness that corrected for differences in height. This unit, the Body Mass Index (BMI), is still known as the ‘Quételet Index’ (QI) in some European countries; BMI has been shown to correlate with body fat content, and to predict risk for several of the comorbidities of obesity.

The twentieth century witnessed the application of a wide range of techniques to measure fatness with increasing sophistication, and to define the content and distribution of fat throughout the body, as well as its impact on metabolism. Body density (and thus body fat content) was first calculated by applying Archimedes’ Principle to the reduction in body weight when the subject was reweighed under water; the technique has been successfully adapted to the displacement of air rather than water, in the plethysmographic devices in use today (see Chapter 3).

The widespread clinical use of ultrasound, computerized tomographic (CT) scanning, dual-energy X-ray absorptiometry (DEXA) and magnetic resonance (MR) imaging has shown that all these techniques are useful in measuring aspects of body composition, and the distribution and volume of specific fat depots. In addition, the metabolic impact of obesity, notably the insulin resistance that it induces (see below), has been clarified using a variety of techniques, including the insulin clamp invented by Ralph DeFronzo during the 1970s, the minimal model intravenous glucose tolerance test devised by Richard Bergman, and the homeostatic modelling (HOMA) developed by David Matthews during the 1980s (see Chapter 3).

Metabolism and energy balance

The importance of oxygen in metabolism and indeed life itself was first revealed by the work of Robert Boyle (1627–1691), who established the concept of the chemical elements (Figure 1.7). Crucially, Boyle demonstrated that when a lighted candle went out in a closed chamber, a mouse confined to the same chamber rapidly died.

This theme was developed a century later by the French chemist, Antoine Lavoisier (1743–1794), whose research culminated in the Oxygen...
Theory that was to prove fundamental to the science of energy balance and obesity (Figure 1.8). Lavoisier, who died at the guillotine during the French Revolution, recognized that oxidation and combustion both entailed combination with oxygen. He conducted the first measurements of heat production (calorimetry) – calculated from the weight of ice melted by a guinea pig’s respiration – and inferred that metabolism was analogous to slow combustion. Helmholtz went on to develop the Laws of the Conservation of Mass and of the Elements. His work ultimately formed the basis for the Law of Surface Area, formulated by the German Max Rubner (1854–1932). Rubner adapted the bomb calorimeter method developed by Pettenkofer and Voit to determine expired carbon dioxide, and went on to measure energy expenditure in human subjects and experimental animals. He also observed a consistent linear relationship between energy expenditure and surface area among mammals of diverse species and sizes.

Interest in the Law of Conservation of Energy, and whether it also applied to humans, stimulated Wilbur Olin Atwater and Edward Bennett Rosa to construct the first human calorimeter at the Wesleyan College in Middletown, Connecticut in 1896. By measuring the oxygen consumed by a subject in a sealed chamber, they proved that humans, like all other animals, obey the first Law of Thermodynamics, namely that the energy expenditure of an individual in steady state equals their energy intake. Their basic concept is perpetuated in the human calorimeters in use today, albeit with much more sophisticated measurements of oxygen consumption and carbon dioxide production that can yield detailed information about minute-by-minute energy expenditure and the utilization of specific macro-nutrients (see Chapter 3).

Other modern refinements in the measurement of energy expenditure in humans have included portable hoods suitable for use at the bedside, and the ingenious ‘doubly-labelled water’ technique. The latter exploits differences in the ways that the hydrogen and oxygen atoms of the water molecule are metabolized in the body, and from the elimination rates of $^2$H (deuterium) and $^{18}$O after administration of a known dose of $^2$H$_2^{18}$O, energy expenditure can be calculated (see Chapter 3).

Application of these techniques has helped to unravel the complicated physiology of human energy balance, and has confirmed the fundamental principle that obese people in general expend more energy than the lean, and must therefore consume more energy in order to maintain their higher body weight. Interestingly, it has also been demonstrated that overweight people underestimate their food intake to a greater degree than do lean people. This finding has challenged the validity of a large body of research based on conventional dietary records, and has important implications for the practical management of obesity.

The organs and tissues that are most metabolically active and responsible for energy expenditure have attracted interest, including as potential sites of defects in energy expenditure that could contribute or lead to obesity. During the latter half of the twentieth century, much research focused on brown adipose tissue (BAT), or brown fat (Figure 1.9). This interesting tissue, first described in 1949 by Fawcett and Jones, is extremely rich in mitochondria and owes its brown colour to mitochondrial cytochromes. BAT is metabolically highly active and, in lower mammals, is an important physiological defence against cold (and in waking animals from hibernation). It has been shown that reductions in the thermogenic activity of BAT contribute to obesity in certain genetic obesity syndromes, such as the ob/ob mouse and fa/fa rat (see below). In humans, BAT is present in the neonate but soon atrophies and is now known to play no important role in common human obesity.
BAT oxidizes fatty acids to generate heat rather than adenosine triphosphate (ATP), a property finally explained in the early 1980s when Jens Nedergaard and colleagues discovered a protein that they named ‘thermogenin’ (Cannon, Hedin and Nedergaard, 1982). Thermogenin was shown the following year by Daniel Ricquier and colleagues in Paris to be a specific uncoupling protein, now termed UCP-1 (Ricquier et al., 1983). UCP-1 was shown to ‘uncouple’ fatty oxidation from ATP production by short-circuiting the proton electrochemical gradient across the inner mitochondrial membrane, thus producing heat. The mechanism of heat production in other tissues, which do not express UCP-1, was further clarified by the finding of other related uncoupling proteins, UCP-2 and UCP-3, by Ricquier’s group in France (Fleury et al., 1997), Lowell’s group in Boston (Vidal-Puig et al., 1997) and Boss and colleagues in Geneva (Boss et al., 1997).

During the nineteenth century, the prevailing concept was that only macronutrients – carbohydrates, proteins and fat – were needed to sustain human life. The discovery of vitamins in the early twentieth century overthrew this theory, and gave birth to the broader discipline of nutrition. Subsequently, the impact of macronutrients on human health and the development of obesity has returned to centre stage through the recognition of the role of dietary fats and simple sugars (for example in carbonated drinks) as causes of obesity and contributors to cardiovascular and other obesity-related diseases.

**Health hazards of obesity**

Ancient clinical observations, mentioned above, suggest that obesity was already recognized in association with both diabetes and sudden death, although the significance of the morbidity and excess mortality conferred by overweight and obesity has only been fully appreciated much more recently.

Interestingly, the life insurance industry can claim credit for having drawn attention to the relationship between obesity and premature death. As early as 1901, actuarial data showed that excess weight, especially around the abdomen, was associated with a shortened life expectancy. This risk has been confirmed by large numbers of systematic studies in numerous populations, and these led to the World Health Organization (WHO) classification of obesity which stratifies increasing degrees of risk according to rising BMI. This classification was first formulated in 1995 and has subsequently been modified to make allowance for the increased susceptibility of Asian populations to the adverse effects of obesity (see Chapter 9).

A particular relationship between abdominal obesity and early death could be discerned from the early life-insurance data, but it was the thorough studies of Jean Vague (1947) (Figure 1.10), working in Marseille, which clearly established the overriding importance of abdominal (central) obesity in conferring excess mortality. Vague’s conclusions were clear, but the ‘adipo-muscular ratio’ that he used to distinguish ‘android’ obesity (in the abdominal distribution typical of males) from ‘gynoid’ (gluteofemoral) adiposity characteristic of women was cumbersome. Simpler measures of abdominal obesity – the ratio of waist circumference to hip circumference, and even waist circumference alone – are now widely used in clinical practice and in research settings. Indeed, cut-off values of waist circumference that indicate increased cardiovascular risk and premature death have been proposed and these appear to be more powerfully predictive than BMI (see Chapter 9).
Obesity predisposes to type 2 (non-insulin dependent) diabetes, and is largely responsible for the current pandemic of the disease, which is predicted to double the number of diabetic people worldwide in just 30 years, from 150 million in 1995 to over 300 million in 2025 (see Chapters 2 and 10). The association between obesity and type 2 diabetes was highlighted in classical studies of isolated ethnic groups which, after centuries of active and frugal existence, had suddenly become sedentary and overfed. Notable examples were the Pima Indians living near the Gila river in Arizona and the inhabitants of the Pacific island of Nauru (Figure 1.11).

Such studies led to the ‘thrifty gene’ hypothesis proposed by Neel in the early 1960s. This postulated that ‘thrifty’ genes whose products promoted the storage of fat and ultimately diabetes might favour survival and therefore be selected in populations subject to periodic famine; however, in a westernized setting of inactivity and over-abundant food, obesity and type 2 diabetes might then emerge (Neel, 1962).

No ‘thrifty’ genes have yet been convincingly identified, but much progress has been made in elucidating the functional links between obesity and type 2 diabetes. Many of the metabolic consequences of obesity have been attributed to decreased sensitivity of various tissues and organs to insulin action (‘insulin resistance’). The concept of insulin resistance can be traced back to the English diabetologist, Harold Himsworth, who in 1936, classified diabetic patients as either insulin-sensitive or insulin-insensitive, according to whether or not their blood glucose level fell after the co-administration of oral glucose and intravenous insulin (Figure 1.12). The American diabetologist, Gerald Reaven coined the phrase ‘insulin resistance syndrome’ or ‘syndrome X’ (now generally known as the ‘metabolic syndrome’) in the late 1980s. However, this concept had been anticipated by Vague some 40 years earlier, who recognized that central obesity was associated with, and predisposed to, diabetes, atherosclerosis and gout – all core features of the metabolic syndrome. Indeed, the Swedish physician Eskil Kylin (1889–1975)

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**Figure 1.10** Jean Vague (born 1912), French endocrinologist. The image is from a medal, designed by his wife, and struck in 1981.

**Figure 1.11** A group of Nauruan Islanders, photographed in 1896. At this time, this population was generally lean and diabetes was a rare disease. Following the advent of a Westernised lifestyle, the prevalences of obesity and type 2 diabetes have risen progressively and are now among the highest in the world. From Krämer, A (1906). Hawaii, Osttimoresien und Samoa. Stuttgart: Schweizerbartsche Verlagsbuchhandlung, page 449.
had described the association of hypertension, diabetes and gout during the 1920s (Kylin, 1923). Other notable contributions include the demonstration in 1963 by Philip Randle, Nick Hales and colleagues in Oxford that high free fatty acid levels could interfere with glucose utilization (thus effectively counteracting the action of insulin) through the Randle or glucose-fatty acid cycle (Randle et al., 1963).

Other comorbidities of obesity have been recognized since antiquity. Associated respiratory problems – possibly reminiscent of the obesity hypoventilation syndrome – were described as long ago as the Greco-Roman era (Kryger, 1983). The first clear medical report of sleep apnoea was apparently that of Russell in 1866. The latter was published some 30 years after Charles Dickens’ novel Pickwick Papers, which features a fat boy, Joe, who frequently falls asleep – hence the alternative name of ‘Pickwickian’ syndrome that William Osler applied to the obesity hypoventilation syndrome. Fatty liver, long recognized as a consequence of overfeeding in geese (foie gras) and a feature of human obesity, was only identified in 1980 by Ludwig as a significant comorbidity that can lead to progressive liver damage.

Causes of obesity

The importance of overeating and inactivity was recognized by the Ancients and has continued to be assumed to the present day. In addition, many diseases that cause obesity have been identified, and during the last two decades attention has shifted to the nature of the inherited predisposition to obesity and the specific genetic defects that underlie this susceptibility. Striking genetic obesity syndromes in other species (especially rodents) have yielded valuable information about the normal regulation of energy homeostasis, and some of these ‘lessons of nature’ have helped to clarify the aetiology of certain subsets of human obesity.

The role of the brain in controlling body weight, initially highlighted by clinical cases, has been extensively explored. Obesity has long been recognized in association with hypothalamic damage (mostly caused by tumours), notably in the ’adiposogenital syndrome’ (obesity with sexual infantilism) described by Joseph Babinski (1857–1932) in Paris, and by A. Fröhlich (1871–1953) in Vienna (Figure 1.13) (Fröhlich, 1901). The co-occurrence of truncal obesity with hypertension and other characteristic features in subjects with a basophil (ACTH-secreting) tumour of the pituitary was described in 1912 by the American neurosurgeon Harvey Cushing (1869–1939), and the syndrome of glucocorticoid excess now bears his name.

These and other clinical observations stimulated interest in the central nervous system (CNS) and especially the hypothalamus, which in turn heralded the development of experimental techniques to produce localized brain damage in animals in order to identify the regions that controlled eating and body weight. These methods were made possible by the precise targeting of specific brain regions using the ‘stereotactic’ frame apparatus originally designed by the English neurosurgeon V.A.H. Horsley (1857–1916). Damage was induced by microinjection of toxins such as chromic oxide, or by localized heating or electrolysis produced by special probes. Classical findings included the dramatic hyperphagia and obesity induced by bilateral lesions of the ventromedial hypothalamus, in striking contrast to

Figure 1.12 The ‘insulin-glucose challenge’ test devised by Harold Himsworth (1936). This contrasts the typical responses in an ‘insulin-insensitive’ subject (Patient I) and an ‘insulin-sensitive’ subject (Patient II). Reproduced by kind permission of the editor of the Lancet.
the loss of appetite and wasting that followed destruction of the lateral hypothalamus. These observations led to Eliot Stellar, in the early 1950s, to advance the ‘dual centre’ hypothesis (Stellar, 1954). This proposed that feeding and weight were controlled by the balance between a ventromedial ‘satiety centre’ and a lateral hypothalamic ‘appetite centre’; the hypothesis shaped thinking about hunger and satiety for over two decades, although it is now recognized to be oversimplified.

Knowledge about the CNS has advanced in waves, driven by technological innovations. During the 1970s–1980s, refinements in methods such as radioimmunoassay and immunocytochemistry and the tracing of neuroanatomical tracts helped to identify the neurotransmitters that control energy balance; subsequent research, including advanced molecular and transgenic techniques, has clarified their sites of production and action, the factors regulating their activity, and the receptors that mediate their effects. These transmitters include classical monoamines such as norepinephrine-serotonin (whose potent appetite-suppressing action has been exploited in several anti-obesity drugs), peptides including the potent orexigen (appetite-stimulator) neuropeptide Y (NPY) and the anorectic melanocortin, α-MSH, and the endocannabinoids that stimulate feeding. Landmark studies include the demonstration by James Gibbs and colleagues in 1973 that injection of cholecystokinin (CCK), the gut peptide named for its ability to stimulate gall-bladder contraction, powerfully inhibited feeding in rats (Gibbs, Young and Smith, 1973); this indicated that the gut could communicate through secreted peptides with the CNS to control feeding (see Chapter 6). Subsequent research has shown that the hypothalamus and other regulatory regions of the brain are surprisingly accessible to circulatory hormones that are now known to signal fat mass and energy needs, such as insulin, leptin and ghrelin.

The first of the animal obesity syndromes to be understood at a molecular genetic level was the yellow obese (A’) mouse, whose striking coat colour had been prized in Ancient China. The cause, discovered in 1994 by Bultman et al., (1992) was ‘ectopic’ over-expression of a peptide termed ‘agouti’ in tissues where it does not normally occur. Agouti is an endogenous antagonist of α-MSH at its melanocortin receptors, leading to hyperphagia and obesity from inhibition of the appetite-suppressing effect of α-MSH in the hypothalamus, and lightening of the fur because agouti also blocks the melanocortin-mediated production of melanin in the hair follicle. Interestingly, mutations of the human proopiomelanocortin have now been identified as rare causes of obesity; some subjects have red hair, the counterpart of the yellow fur in the A’ mouse.

Other genetic obesity syndromes in rodents were soon to cast new light on the regulation of energy balance. Notable were the ob/ob (obese) and db/db (diabetes) mice, and the fa/fa (fatty) Zucker rat (Chapter 6). These mutants had been identified during the 1950s and 1960s as autosomal recessive traits that conferred hyperphagia and obesity. The causes were unknown, but meticulous cross-circulation ‘parabiosis’ studies by Coleman during the 1970s suggested that the ob/ob syndrome was due to deficiency of an appetite-suppressing hormone, whereas the db mutation apparently disabled the receptor that normally recognized this hormone (Coleman, 1973) (Figure 1.14). The hypothetical appetite-suppressing hormone would function as an ‘adi-postat’, whose existence had previously been postulated by Kennedy (1953) to explain how eating and energy expenditure were modulated...
appropriately under conditions of under- or over-nutrition so as to keep fat mass constant.

An important breakthrough in obesity research was the discovery by Jeffrey Friedman's team in 1994 of the \( \text{ob} \) gene by positional cloning, and the characterization of its protein product (Zhang et al., 1994) (Figure 1.15). This cytokine-like protein, which Friedman named 'leptin' (from the Greek leptos, meaning 'thin'), was secreted by adipocytes and circulated at concentrations proportional to total fat mass. Leptin was found to act in the hypothalamus to inhibit feeding and cause weight loss and therefore fulfilled the criteria for an adipostat, by signalling adiposity to the brain and effecting appropriate responses to maintain a constant fat mass. Hyperphagia and obesity were explained in the \( \text{ob/ob} \) mouse by the \( \text{ob} \) mutation deleting bioactive leptin, whereas the \( \text{db/db} \) and \( \text{fa/fa} \) syndromes were subsequently shown to be due to various mutations affecting the leptin receptor.

Very rare cases of human obesity are due to mutations of leptin or its receptors, causing a striking phenotype of severe hyperphagia and morbid obesity that develops in early childhood. The first case, who subsequently showed a dramatic response to treatment with recombinant human leptin, was reported by Stephen O'Rahilly's group in Cambridge (Montague et al., 1997). However, the vast majority of obese people have raised leptin concentrations, roughly in proportion to their increased fat mass, suggesting that leptin is
irrelevant to human energy balance as long as basal levels are present.

Research into the genetic susceptibility to ‘common’ human obesity has also benefited from advances in molecular genetics. Earlier observational and epidemiological studies included those of Charles Davenport in 1923 on the inheritance of BMI in families, and the work of Verscheuer in the 1920s, Newman *et al.* in the 1930s and Stunkard *et al.* in the 1980s on identical twins raised together or separately, with the aim of determining the contribution of genetic versus environmental factors. Studies by Claude Bouchard and others have suggested that genetic susceptibility is determined by multiple genes that individually have only minor effects. A large and growing number of candidate genes have been explored and several have been shown to make a significant but limited contribution.

**Treatment of obesity**

Restricting food intake and increasing physical activity have been the mainstays of managing obesity since antiquity. Many dietary regimes have been tried, ranging from total starvation to unlimited quantities of various foods. Success has generally been limited, and only achieved if a significant fall in energy intake can be sustained in the long term.

Numerous drugs have been used in an attempt to treat obesity, mostly acting by reducing appetite. During the eighteenth century, and perhaps following the lead of Flemyng (see above), various laxatives were employed, sometimes together with hydrotherapy. In the 1890s, the newly-discovered thyroid extract was given to treat obesity in euthyroid subjects, although inappropriate and potentially dangerous thyroid hormones were still being used in this context until recently. The notion of stimulating an underactive endocrine system has been repeatedly invoked, ranging from various proprietary drugs (see Figure 1.16) to the more recent use of human growth hormone and human chorionic gonadotrophin.

In the late nineteenth century, the synthetic organic chemistry industry yielded various compounds with weight-reducing properties such as derivatives of aniline, which was used to make dyes for fabrics. One such product was dinitrophenol, which was found to induce marked weight loss in workers who handled the compound; much later, the mechanism was shown to be an uncoupling of oxidative phosphorylation to produce heat instead of ATP, mimicking the action of UCP-1 in brown fat. Dinitrophenol was used to treat obesity during the 1930s, but was abandoned when it was shown to cause cataracts and peripheral neuropathy. This early therapeutic tragedy emphasizes the need for careful evaluation of the efficacy and safety of new drugs before their introduction into clinical practice.

Another early product of the organic chemical industry was D-amphetamine, synthesized in 1887. It was used during the 1930s as a stimulant to treat narcolepsy, when it was found to induce weight loss. Amphetamine was approved in the USA for the treatment of obesity in 1947, but was soon shown to be addictive, and its use declined markedly during the 1970s. Phentermine and diethylpropion, structurally related to amphetamine, were introduced into clinical practice during the 1950s and were widely promoted (see Chapter 17). All these drugs are sympathomimetic agents that enhance the action of noradrenaline in the CNS and thus reduce appetite. Another structurally-related compound, fenfluramine – which increases the release of the anorectic neurotransmitter, serotonin – was also shown to reduce appetite and weight. Fenfluramine and its dextroisomer, D-fenfluramine, were prescribed widely during the 1980s and 1990s, sometimes given together with phentermine. Fenfluramine was withdrawn in 1997 when it was shown that, it caused cardiac valvular disease and primary pulmonary hypertension – which had previously been recognized as a rare complication of anti-obesity drugs.
Other drugs that have been used to treat obesity, often without a specific licence, have included phenylpropanolamine and ephedrine (both sympathomimetic agents), the latter in combination with caffeine. Phenylpropanolamine was withdrawn because it was shown to cause stroke, and the safety and efficacy of ephedrine/caffeine remains uncertain. Various compounds designed to stimulate thermogenesis have been developed, and many have shown promising properties in animals. During the 1980s and 1990s, there was much interest in agonists at the $\beta_3$-adrenoceptor, responsible for activating heat production in brown fat and other thermogenic tissues including skeletal muscle. These compounds proved highly effective and relatively selective in animals, but because of differences between the rodent and human $\beta_3$-adrenoceptor proved to be ineffective or plagued by sympathetic side effects when tried in humans.

The three anti-obesity drugs in current use are described in Chapter 17. These are sibutramine, an inhibitor of the neuronal reuptake of serotonin and noradrenaline, which was found to induce weight loss in rodents when tested as an antidepressant; orlistat, an inhibitor of the gastrointestinal lipases that hydrolyse dietary triglyceride, thus decreasing lipid absorption; and rimonabant, an antagonist at the cannabinoid CB-1 receptor that mediates the orexigenic effects of the endocannabinoids.

A brief trawl of Internet sites will reveal the huge range of substances being sold as treatments for obesity. These include amphetamines and other compounds that have been withdrawn because of safety concerns; herbal, homeopathic and traditional remedies with no hard evidence of efficacy; diuretics and laxatives; and powerful endocrine agents such as anabolic steroids. The main motivation would appear to be cosmetic rather than health-related.

Bariatric (weight-reducing) surgery began in the mid-1950s with the Norwegian surgeon Hendrikson, who removed much of the small bowel to reduce nutrient absorption. This irreversible operation caused intractable losses of nutrients and electrolytes and was replaced in the 1950s by the jejuno-ileal bypass operation developed by Payne and DeWind and others. The jejuno-ileal bypass causes major side effects, notably the ‘blind-loop’ syndrome, and is now little performed. As described in Chapter 18, gastric bypass operation (developed during the 1980s by Edward Mason in Iowa) and various forms of gastroplasty (initiated by Mason in the 1970s) have now become popular (Figure 1.17). Recent innovations include the sleeve gastrectomy, gastric banding using an inflatable implanted band whose tension can be varied by injecting saline into a subcutaneously-buried port, and the adaptation of many bariatric techniques to be performed laparoscopically. In striking contrast to the poor outcomes of the early bariatric procedures, those in current use have proved effective, and the substantial weight loss that results can often improve or even reverse established type 2 diabetes. Modern bariatric procedures also have low rates of morbidity and mortality.

Numerous other forms of treatment for obesity have been attempted. One notable example was the use, for a brief period during the 1960s, of stereotactic lesioning of the lateral hypothalamus in an attempt to mimic the hypophagia and weight loss induced in rodents by this procedure. This approach was soon abandoned because of poor outcomes and anxieties about its safety.

**Growth of the scientific community**

It was not until the 1960s that concerted attempts were made to bring together those interested in the science and clinical management
of obesity. An early initiative, following the example of the long-established specialist societies in diabetes, endocrinology and other disciplines, was the formation of various national associations to promote research into obesity. The first, the Association for the Study of Obesity (ASO) in the UK, held its inaugural meeting in London in 1968. This was followed in 1973 by an American conference organized by the National Institutes of Health, in recognition of the important health problems posed by obesity, and in 1974 by the first International Congress on Obesity (ICO) in London. The North American Association for the Study of Obesity (NAASO) first met at Poughkeepsie, New York, in 1982, and the International Association for the Study of Obesity (IASO) was formed in 1986 under the leadership of Barbara Hansen.

Following the first ICO, it was clear that a specialist journal devoted to obesity was required, and the International Journal of Obesity began publication in 1976 under the joint editorship of Alan Howard and George Bray. Other journals have followed: Obesity Surgery in 1991, and Obesity Research (now renamed Obesity), published by NAASO, in 1993.

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