Chapter 1
The Evolution of Mammalian Adipose Tissues

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Abstract Anatomical organization, genes and metabolic pathways in white, beige and brown adipose tissues are traced from their invertebrate origins through lower vertebrates to mammals and birds. Invertebrate storage organs and adipose tissues of lower vertebrates are also metabolic regulators. In large turtles, some depots are thermogenic or insulators. Reptilian, avian and mammalian adipocytes sort fatty acids, especially essential polyunsaturates. All mammals have numerous adipose depots, many with site-specific properties including thermoregulation, structural roles or paracrine interactions with contiguous tissues. Paracrine provisioning of lymph nodes with fatty acid sorting optimizes cellular nutrition during fasting or on deficient or imbalanced diets, averts competition with other tissues and utilizes scarce resources efficiently. The mechanisms may be defective in HIV/AIDS and Crohn's disease and some obesity-related diseases. Thermogenesis by shivering and non-shivering mechanisms in muscle occurs in some lower vertebrates and, in birds, is as effective as mammalian brown adipocytes. Facultative thermogenesis emerged gradually in birds and mammals, utilizing genes of reptilian ancestors, including some resembling uncoupling proteins. Mammalian thermogenic tissue evolved from muscle that lost contractile functions and expanded its mitochondria and lipid-storage capacity, thus generating confusing resemblances to white adipocytes. As well as storage and endocrine functions, adipose tissues' capacities for paracrine interactions, fatty acid sorting and thermogenesis supported the evolution of mammalian heterothermy (i.e. diet-induced thermogenesis, torpor and hibernation), lactation and their ability to exploit nutritionally imbalanced diets. These features probably appeared early in mammalian evolution enabling rapid colonization of new habitats, including efficient utilization of poorer quality diets, and metabolic support of lactation that enables fast-growing young to delay maturation of specialised dentitions. The contribution of 'grandmothers' to their descendants' evolutionary fitness drove selection for post-menopausal longevity, aided by larger lower-body superficial depots that protect cardiovascular and metabolic health. Sex differences in human adipose tissue distribution evolved under such sexual selection plus

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adaptations to heat dissipation. Natural obesity without metabolic impairment found in some arctic mammals evolved by numerous genetic modifications over at least a million years, much longer than human adjustments to modern diet, cooking, heating and clothing.

Keywords Comparative • Reptiles • Mammals • Birds • Primates • Apes • Bears • Paracrine interactions • Immune system • Fatty acids • Perinodal • Crohn's disease • Colitis • Lipid-soluble toxins • Hibernation • Diet-induced thermogenesis • Herbivory • Lactation • Thrifty genes • Sex differences • Cold adaptation

1.1 Introduction

For many centuries, comparative biology and medicine advanced in parallel, with many practitioners making important and mutually beneficial contributions to both fields. Increasing specialization in the twentieth century forced them apart until the rise of molecular phylogeny, medical genomics and developmental biology in the 1990s reunited the estranged partners. Adipose tissues have been one of the most spectacular beneficiaries of this rapprochement: comparative and medical biologists now recognise that their findings are as mutually supportive to each others' progress as they have even been. This chapter is a three-way synthesis of comparative concepts from wild animals in natural systems, experimental data from laboratory animals & *ex vivo* cultures and human studies to elucidate the normal functions and pathologies of adipose tissues.

Although research involving adipose tissues has expanded enormously during the past 50 years (Rosen and Spiegelman 2014), evolutionary and comparative studies lagged behind metabolism, endocrinology and human epidemiology. Both white (WAT) and brown (BAT) adipose tissues have been largely omitted from genetic and developmental investigations into the origins and evolution of tissues and cell types that complement the long-established discipline of comparative anatomy, functionality and adaptation because they appear too variable, too closely linked to diet and body condition to reveal any general principles determining their site-specific properties and anatomical distribution or phylogenetic relationships to 'lean' tissues.

Interest in its origins and evolution was stimulated by recognition of WAT's endocrine and paracrine relationships, its role in metabolic regulation and its value as a source of stem cells and in reconstructive surgery as well as lipid storage and recently accelerated by the study of the uniquely mammalian tissues BAT and beige or brite adipocytes (Cohen and Spiegelman 2015). Understanding of adipose tissues has progressed from its dismissal by comparative anatomists to its recognition as central to the evolution of the skin, immune system, thermoregulation, mammalian lactation and the metabolic control that underpins these systems. This chapter outlines the origins and evolution of the anatomy, physiology and many functions and

specializations of adipose tissues and their relevance to medical sciences; the evolution of the genes involved is left to experts (Caesar et al. 2010).

1.1.1 Comparative Perspectives on Obesity and Diabetes

Obesity and adipose tissues, almost synonymous in the mid-twentieth century, drifted apart as the focus of the former shifted to appetite control and inheritance and of the latter to adipokines (Dodson et al. 2014; Sanchez-Gurmaches and Guertin 2014), development (Chau et al. 2014; Sanchez-Gurmaches and Guertin 2014) and involvement in inflammation and immunity (Exley et al. 2014; Mraz and Haluzik 2014; Couturier et al. 2015).

Of several recent attempts to account for the evolution of obesity in humans, some hardly mention current understanding of the organisation and basic properties of adipose tissues (Power and Schulkin 2009; Isler 2014), while others recognise their central, distinctive roles in human appearance, social and sexual behaviour and metabolism (Wells 2006, 2010).

Obesity is unusual among human diseases in that very similar conditions are integral and essential components of the habits and life history of certain wild animals. Natural obesity, like pathological obesity, arises from 'overeating', periods in which animals become hyperphagic, in some cases aided by sedentary habits. But in wild animals, obesity is always transient and controlled: hyperphagia and fat deposition are followed by periods of anorexia and/or intensive exercise, leading to weight loss (Pond 1998). Adaptive obesity is never a direct cause of diabetes, cardiovascular disease or reproductive dysfunction. The study of natural obesity can reveal much about the 'ideal' structure, composition and anatomical distribution of adipose tissue, the neural and endocrine control of blood composition, appetite and energy expenditure and about the causal relationships between high levels of stored lipid and the adverse metabolic changes that are so frequently associated with obesity in humans.

The origins and incidence of Type 2 diabetes have been explored in many dimensions from metabolism, molecular signalling and immunity to human evolution, ecology and social behaviour (Watve 2012). A general theory of macronutrient nutrition, food selection and foraging (Simpson and Raubenheimer 2012) integrates the scattered and fragmentary information about wild species with human nutritional problems, including obesity. Validated by observations and experiments on organisms ranging from fungi and flies (Solon-Biet et al. 2015) to bears (Erlenbach et al. 2014), its tenets unite nutrition with an impressive range of topics in ecology, cell biology, physiology, immunology, psychology and lifespan (Simpson et al. 2015), though not yet with gross anatomy and the contributions of different organs and tissues. The evolution of adipose tissues, their gross anatomy and relations with other tissues, and, at the microscopic level, adipocytes and the many other cell types they incorporate, have until recently received little attention.

Comparative physiology and genomics during the past 20 years have demonstrated remarkable similarities in the relationships between diet, metabolic control, energy storage and key life history parameters including longevity and fecundity (Fontana et al. 2010). Concepts developed from the study of insects (*Sophophora*, formerly *Drosophila*), nematode worms (*Caenorhabditis*) and other 'lower' organisms have entered medical thinking (Blüher 2008) and the search for new drugs (Hofbauer and Huppertz 2002). Therefore, it is appropriate to begin with an evolutionary and comparative perspective on the structure and functions of adipose tissues.

1.2 Storage Tissues

Tissues and physiological control systems that enable animals to survive long periods of fasting, during which body fabric is depleted and metabolism adjusted, arose early in evolution, so many similarities, but also some important contrasts, are found among living phyla.

1.2.1 Invertebrates

Many invertebrates, especially those that undergo diapause or metamorphosis, have specialised liver-like tissues involved in whole-body metabolic regulation and energy storage. The most thoroughly studied is the insect 'fat body'. This irregularly shaped, sometimes relatively large, structure develops in the abdomen, an anatomical position that maximises contact with the haemolymph and permits large changes in volume with minimal impact on other organs. Its most abundant cell type, called 'adipocytes' by some authors, store glycogen and acylglycerols, releasing the breakdown products in response to metabolic demand from other tissues (Arrese and Soulages 2010). The basic mechanisms of fatty acid uptake and transport, lipogenesis and lipolysis are essentially similar in insect 'adipocytes' and vertebrate white adipose tissue.

The insect fat body also secretes several peptide metabolic regulators (Slaidina et al. 2009) that, at least in drosophila (Arthropoda, Insecta, Diptera), function remarkably like insulin-like growth factors in vertebrates (Okamoto et al. 2009). Neuropeptide Y belongs to an ancient family of peptides that mediate signals between storage cells and the nervous system in various invertebrates (de Jong-Brink et al. 2001; McVeigh et al. 2005).

Insulin is another ancient signal molecule known in *Caenorhabditis elegans* (Nematoda) (Michaelson et al. 2010) and in drosophila (DiAngelo and Birnbaum 2009) as well as all vertebrates. In lower vertebrates such as teleost fish, cells other than pancreatic β cells may be competent to secrete insulin (Roy et al. 2003).

Genes coding for and regulating these messenger molecules and their receptors are among the many gene families that diversified in early vertebrate evolution

(Larsson et al. 2008). Most of the signals and receptors shown to be regulators of appetite and energy storage in mammals are known in the sea squirt *Ciona* (Ascidia, Chordata), an invertebrate chordate (Kawada et al. 2010). The appetite-suppressing hormone leptin seems to be specific to vertebrates, probably appearing early in the evolution of fish (Gorissen et al. 2009), thus long preceding the evolution of adipocytes that are its major producers in higher vertebrates. Insects have analogous peptides that signal peripheral energy stores to the nervous system (Al-Anzi et al. 2009).

1.2.2 Vertebrate Adipose Tissues

Most animal cells contain small quantities of triacylglycerols that serve as energy reserves. Triacylglycerols spontaneously form homogeneous compartments in an aqueous environment. In most tissues that store substantial quantities (brown adipocytes, angiosperm seeds, etc.), the lipids form droplets a few microns in diameter, or around 1–10 fL (10^{-14}–10^{-15} L) in volume (Cinti 2007). Extending the interface between triacylglycerols and lipolytic enzymes may facilitate rapid mobilisation of the lipid stores that supports abrupt transitions between dormancy and vigorous activity. The evolution from yeasts to mammals has been traced for intracellular lipid droplets (Ottaviani et al. 2011) and wider aspects of the biochemistry of lipid storage and its metabolic control (Birsoy et al. 2013).

Single large lipid droplets, usually 0.1–1 nL (10^{-8}–10^{-9} L) in volume, are a special feature of vertebrate white adipocytes. The unusual arrangement is mediated by adipose-specific protein 27 (FSP27) (known in humans as cell death-inducing DFF45-like effector C (CIDEC)) that promotes lipid uptake and coalescence of droplets while reducing the maximum rate of lipolysis (Puri et al. 2007). Experimental reduction of CIDEC in isolated adipocytes increases lipolysis (Ito et al. 2010). The protein probably functions in conjunction with perilipin forming the interface between lipids and proteins (Brasaemle et al. 2000; Shen et al. 2009). FSP27/CIDEC is unique to vertebrates though structurally similar proteins are found in several invertebrate groups (Wu et al. 2008).

From a comparative perspective, these findings suggest that white adipose tissue evolved as a readily deposited, slowly mobilised lipid store suitable both for taking up circulating fatty acids following large, rich meals and for supporting prolonged fasts with low rates of energy expenditure. The evolution of jaws equipped early gnathostome vertebrates as top predators that probably ate relatively large, nutrient-dense prey irregularly and sometimes infrequently (Janvier 2009). The special features of white adipose tissue compared to invertebrate storage tissues exemplify its role as protection for other tissues against lipotoxicity due to excessive lipid accumulation as well as long-term storage (Unger 2002; Unger and Scherer 2010). White adipocytes may be among the novel cell types to appear during early vertebrate evolution, alongside diversification of cell types in the immune system such as mast cells (Crivellato and Ribatti 2010). Advances of vertebrate over invertebrate storage tissues include protection for other tissues against lipotoxicity due to

excessive lipid accumulation as well as long-term storage (Unger 2002; Unger and Scherer 2010) and its metabolic support of cellular immunity (van Niekerk and Engelbrecht 2015).

1.2.3 Fish, Amphibians and Reptiles

Many extant fish, especially the primitive groups, store large quantities of triacylglycerols in the liver and/or skeletal muscle as well as adipose tissue. Quite closely related species show distinct patterns of deposition and mobilization of lipids from the various depots (Weil et al. 2013) but the functions and mechanisms involved are poorly understood.

Almost all adipokines known from mammals have been identified in bony fish (Nishio et al. 2008; Murashita et al. 2009; Ronnestad et al. 2010). Rainbow trout (*Oncorhynchus mykiss*) migrate long distances, fuelled almost entirely by fatty acids that are stored in adipose tissue and transported to muscles by extremely efficient lipoproteins (Weber 2009). Under the highly artificial conditions of fish farms, salmon adipocytes display some of the pathological changes known in obese mammals (Todorčević et al. 2010), but there are no reports of similar effects in wild fish. Transgenic manipulation of the zebra fish (*Danio rerio*) has developed a teleost model of obesity that is remarkably similar to the mouse (Song and Cone 2007; Holtta-Vuori et al. 2010). Messenger molecules with some resemblance to mammalian leptin can be detected in this fish, of which one may have some involvement in energy metabolism (Gorissen et al. 2009), but in a related teleost, its main source is the liver, not adipocytes (Huising et al. 2006).

Most adult amphibians hibernate (or aestivate) for long periods supported by fat accumulated during (often brief) periods of food abundance. Much of the triacylglycerols are stored in paired fat-bodies that are loosely suspended in the abdomen, much like those of insects, and in some species, in and under the thin, distensible skin (Wygoda 1987). In these sites, expansion and shrinkage of the storage tissue avoid distorting adjacent organs.

Blood pressure is higher in reptiles and their body shape is more constrained by tougher, less distensible skin so adipose tissue is more compact and its anatomical arrangement is more varied. Most snakes and lizards have a few large depots but in Testudines (tortoises and turtles), adipose tissue is partitioned into numerous small depots that superficially resemble those of mammals (Pond and Mattacks 1984), an arrangement that may maximise storage capacity while minimising distortion of contiguous tissues.

In the enormous leatherback turtle (*Dermochelys coriacea*), the anatomical distribution and chemical composition of adipose depots seem to be specialized to thermal insulation (Davenport et al. 1990), perhaps extending the range of these partially endothermic reptiles to cooler seas. As well as ‘blubber’ under the carapace and around the viscera and muscles, the abundant adipose tissue in the turtle’s head and neck suggest that it insulates key neural, glandular and vascular structures

from the surrounding water and from the oesophagus, cooled by ingestion of large volumes of low-nutrient food (Davenport et al. 2009).

Very low rates of energy expenditure interspersed with brief periods of much higher metabolic rate are fundamental strategies in nearly all extant reptiles (Secor and Diamond 1997, 1999). They fatten readily and can withstand and recover completely from very prolonged fasts (McCue 2010). However, reptiles are nutritionally fragile, with poor capacity to rebalance dietary minerals and other micronutrients (Frye 1981; Allen and Ullrey 2004). Nutritionally imbalanced diets are a major cause of morbidity in captive reptiles, including severe obesity (Frye 1981). Adipose tissue triacylglycerols are particularly important for provisioning yolk-rich eggs (Warner et al. 2008) so female reptiles are often fatter than conspecific males just before the breeding season and more dependent upon accessing suitable diets.

1.3 White Adipose Tissue in Mammals and Birds

White adipose tissue was presumably named from post-mortem observations on wild insectivores and piscivores or young domestic livestock. It appears yellow to brown in older herbivores and their predators, and in human consumers of dairy products, as accurately illustrated in Rembrandt's 1632 masterpiece *The Anatomy Lesson of Dr. Nicolaes Tulp*. The colour arises from passive (i.e. non-enzymatic and probably non-functional) accumulation of carotenes and any other lipid-soluble residues, including synthetic toxins ingested with food (Polischuk et al. 2002). Thus sequestered, they are mostly harmless until released into the circulation during prolonged fasting or exercise, lactation, egg production or cachexia (Yordy et al. 2010; Fang et al. 2015). Their presence in mobilized and secreted lipids constitutes a major hazard to wildlife, especially during reproduction (De Andres et al. 2016), and in humans is implicated in infant health (Lignell et al. 2011), cardiovascular disease (Bergkvist et al. 2015), cancer (Irigaray et al. 2007) and dementia (Kim et al. 2015).

Dissectible WAT comprises >0.5–50% of the live body mass of free-ranging wild mammals, with an average of about 7% (Pond and Mattacks 1985c). Tissue from wild species generally contains less lipid and more protein, especially collagen, than homologous samples from people and laboratory and domesticated livestock (Pond and Mattacks 1989). Regardless of fatness, the white adipose tissue of large species is composed of fewer, relatively larger adipocytes than that of smaller species of similar dietary habits in both mammals (Pond and Mattacks 1985c) and birds (Pond and Mattacks 1985b). In this respect, adipocytes resemble neurons and contrast with most other cell types in mammals (Savage et al. 2007). Lipid droplet volume, the principal determinant of adipocyte size, is itself related to lipolysis (Ito et al. 2010). By controlling the rates of mobilisation of stored fatty acids and clearance of excess energy absorbed from the diet, white adipocytes are central to metabolic rate during feasting as well as fasting. This scaling of adipocyte volume to body size may reflect the complex and very controversial relationship between

body mass and basal metabolic rate (Kolokotrones et al. 2010). The topic has not been thoroughly investigated in reptiles or any other lower vertebrates.

Comparative biology shows that some functions of the liver in lower vertebrates take place in adipose tissue in mammals. Leptin was first described as a secretion from mammalian adipose tissue, the archetypal adipokine (Caro et al. 1996). Adipose tissue is its main source in all extant mammals including the most primitive (Doyon et al. 2001). Very similar molecules that regulate appetite and energy metabolism are known in all the major classes of vertebrates (Dridi et al. 2004). Although adipose tissue is present, sometimes in substantial quantities, the liver is the main source of leptin in teleost fish (Huising et al. 2006) and in birds (Taouis et al. 2001). Comparative data are too sparse to establish how many other hepatic functions have been 'taken over' by adipose tissue in mammals.

As well as its central role in lipid storage and metabolism, mammalian adipose tissue also participates in amino acid metabolism, particularly that of the non-protein, energy-supplying amino acid, glutamine (Curthoys and Watford 1995; Kowalski et al. 1997). Site-specific differences in glutamine synthesis and turnover suggest depot specialization comparable to that of fatty acid metabolism (Digby and Pond 1995; Digby 1998). Many years after these studies, the role of glutamine as a precursor to fatty acid synthesis (Crown et al. 2015) and in adipocyte differentiation and maturation (Green et al. 2016) are now being investigated.

White adipose tissue of mammals (Pond and Mattacks 1985b), and to a lesser extent that of birds (Pond and Mattacks 1985a), is partitioned into a few large and numerous small depots that merge only when greatly expanded. White adipose tissue metabolism and its neural and endocrinological controls are similar in both groups (Price et al. 2008) as are its involvement in immune function (see Sect. 1.6.1). Avian adipocytes mature much earlier in embryonic development, where they manage yolk lipids, directing appropriate fatty acids into structural lipids and others to oxidation (Speake et al. 1998).

1.3.1 Anatomical Distribution and Site-Specific Properties

In all mammals, white adipose tissue is distributed to a common pattern, though with substantial differences in relative mass between (Pond 1998), and to a lesser extent within species (Pond et al. 1995).

Depots were characterized first by site-specific differences in relative adipocyte volume and various biochemical features (Pond 1992, 1998). Then within-depot differences were shown to enable functionally important paracrine relationship with embedded lymphoid structures (Pond and Mattacks 1995, 1998, 2003; Pond 2007). Site-specific differences in human adipose tissues, until recently regarded as irrelevant, are now identified by a widening range of genetic, developmental and functional properties, many of significance to medicine (Sbarbati et al. 2010; Macotela et al. 2012; Pinnick et al. 2014; Sanchez-Gurmaches and Guertin 2014; Gil-Ortega et al. 2015; Karpe and Pinnick 2015) and livestock production (Dodson et al. 2014).

The largest depots in mammals are found inside the abdomen and between the skin and superficial musculature. Intra-abdominal depots include the mesentery and the omentum, a uniquely mammalian structure, and small quantities associated with the gonads. The adipocytes in these depots plus those surrounding the heart share common developmental origins distinct from that of the superficial sites (Chau et al. 2014). The epididymal depots are exceptionally large and easily dissected out in murid rodents (rats, mice & hamsters) and for this reason alone have been intensively studied. In other mammals, the depots on the inner walls of the abdomen extending around the kidneys and into the pelvis are usually bigger. Detailed study of adipose depots in domestic livestock reveals their cellular compositions and metabolism to be complex and often variable (Dodson et al. 2014); the same may also be true of humans.

The cellular composition of superficial adipose tissues is complex and diverse with functions other than lipid storage (Alexander et al. 2015). Comparison of mammals of body mass 0.1–500 kg and similar proportions of adipose tissue shows that the superficial depots are both thicker and more extensive in larger specimens than in smaller ones because the ratio of surface area to volume is lower (Pond and Ramsay 1992). The resulting confluence of depots that appear discrete in smaller species can impede identifying homologous depots with larger ones, including humans. Abdominal volume and body surface area decrease relative to body mass with increasing size, so superficial adipose tissue can be impressively thick in large mammals, creating the impression they are ‘fatter’. Total dissection is essential to establish body composition.

One of the largest such depots, the inguinal depot on the anterior thigh and abdominal wall (often just called ‘subcutaneous’ in lab rodents and ‘femoral’ in humans), is also the most consistently present in mammals (and birds) (Pond and Mattacks 1986b; Pond 1998). Genetic, physiological and epidemiological studies in humans (Karpe and Pinnick 2015) suggest an explanation: inguinal adipose tissue can accommodate additional lipid stores without promoting inflammation and increased risk of cardiovascular and metabolic disease. In other words, these specialized depots support rapid fattening without diminishing fitness in endothermic animals of high metabolic rate, a fundamental capability for mammalian reproduction (see Sect. 1.7.3).

Many birds and mammals become transiently obese during migration, breeding, moulting or before seasonal food shortages but most remain ambulatory and some perform prolonged, strenuous exercise. Some species of knot (small seabirds, Charadriiformes) carry relatively enormous fuel loads for long-distance migration by selective atrophy of non-essential organs and appropriate redistribution of adipose tissue (Piersma et al. 1999; Battley et al. 2000). In such ‘adaptively obese’ in animals, the additional body mass imposes surprisingly low, sometimes undetectable, additional energetic costs in flight and, perhaps even more surprisingly, in walking. For example, locomotion is unusually efficient in camels, partly through replacement of some limb muscles by non-energy consuming tendons (Alexander et al. 1982). Locomotory efficiency is unimpaired by adipose tissue that can reach 32% body mass in Svalbard rock ptarmigans (*Lagopus muta hyperborea*) (Lees et al. 2010).

After decades of confusion, the tangled relationship between adipose tissues and thermoregulation, both thermogenesis (Sect. 1.4.1) and thermal insulation, is becoming clearer. Many large, naturally obese mammals occur in areas that are seasonally cold, giving rise to the long-standing and widely disseminated belief that adipose tissue accumulates between the skin and underlying body muscles an adaptation to thermal insulation. However, comparative data on the partitioning of white adipose tissue between superficial and internal depots in the mammalian order Carnivora of similar body conformation but widely different sizes do not support this theory (Pond and Ramsay 1992). The superficial depots are simply the most convenient repository for large quantities of lipid regardless of habits and habitats.

The contributions of fur and superficial adipose tissue to body insulation have been studied in marine mammals (Cetacea, Pinnipedia, Sirenia). In those such as fur seals that retain body hair, its main function is energy storage as in Carnivora, but in whales and others with reduced hair, the outer layer is specialized to adjustable thermal insulation mainly by efficient control of blood flow, and the inner layer to storage (Liwanag et al. 2012). UCP1 has been detected in the inner layer of blubber of porpoises and other small cetaceans, suggesting it may thermogenic as well as insulatory (Hashimoto et al. 2015).

The recent identification in laboratory mice of dermal adipose tissue, a small (only a few adipocytes thick) layer distinct from the often more massive subcutaneous layer (Alexander et al. 2015) is consistent with these findings in aquatic mammals and with the site-specific differences identified in layers of subcutaneous adipocytes in pigs (Hausman et al. 2007; Klein et al. 2007) and humans (Ardilouze et al. 2004). Murine dermal adipocytes serve as an insulating sleeve that thickens up to fourfold following prolonged exposure to cold. Those around hair follicles support hair growth, have antimicrobial roles and contribute to wound healing (Alexander et al. 2015; Zhang et al. 2015). The possibility that they also detect cooling (Ye et al. 2013) should be investigated. Thermal insulation in endothermic mammals must be adjustable because the metabolic rate of small mammals is high and during energetically demanding activities such as lactation, dissipation of heat generated as a by-product of digestion and metabolism, is limiting (Król et al. 2007). In experimentally overfed mice, too much superficial adipose tissue decreases skin thickness and elasticity (Ezure and Amano 2010). Additional superficial adipose tissue would exacerbate these problems so in wild mammals, its abundance and distribution must be well controlled.

1.3.2 Cellular Structure of Adipose Tissue

The total number of white adipocytes scales to (Body Mass)$^{0.75}$, and they range in volume from 0.01 nL in bats and shrews, to up to 4 nL in well-fed baleen whales (Pond and Mattacks 1985c). Carnivorous mammals and ruminants have about four times more adipocytes than non-ruminant herbivores (whose energy metabolism is based mainly on glucose) of the same body mass but are not on average fatter,

because the adipocytes are smaller. By coincidence, the adipocytes of rats and mice, small non-ruminant herbivores, are about the same size (0.1–1 nL) as those of humans, large omnivores who these days eat a high-fat diet.

Wild mammals that naturally become obese have up to 5 times, usually only 2–3 times, more adipocytes than would be expected in comparable non-obese species. Western adults have at least ten times more adipocytes in proportion to their body mass than would be expected from the comparison with wild mammals (Pond 1998). The limited information on other primates suggests that their adipocyte complements can also become disproportionately large (Pond and Mattacks 1987; Pereira and Pond 1995). Thorough studies of wild mammals always reveal much inter-individual variation in the total number of adipocytes that cannot be attributed to age, sex or any obvious feature of dietary history, particularly in carnivores (Pond et al. 1995). The number of adipocytes does not seem to be a major determinant of the capacity for fattening even in naturally obese species. In these respects, humans (van Harmelen et al. 2003; Spalding et al. 2008) are similar to other mammals.

1.3.3 Structural Adipose Tissue

Small depots, consisting of large quantities of extracellular material enclosing pockets of metabolically inert adipocytes are found in all tetrapod vertebrates. The firm, resilient tissue absorbs impact forces during locomotion and distributes weight in the feet, especially those of large terrestrial mammals such as elephants (Weissengruber et al. 2006). Fatty tendons around the knee of emus and other large running birds may have a similar role (Regnault et al. 2014). The fetal development (Shaw et al. 2008) and adult functions (Theobald et al. 2006) of Kager's fat pads in the human heel and around the Achilles tendon have been studied in detail. As well as acting as shock absorbers, the adipose tissue protects blood vessels and facilitates movement (Theobald et al. 2006). Injury or atrophy of structural adipose depots in the extremities lead to pain and debilitation that can be exacerbated by diabetes (Chatzistergos et al. 2014). So the study of these tissues using modern biomechanical concepts (Mihai et al. 2015) and techniques (Payne et al. 2015) is timely.

Several small structural depots help shape the face in humans (Kahn et al. 2000), other primates and certain large birds (Pond 1998). The buccal (Bichat's) fat pads are particularly large in human and other higher primates where they contribute substantially to facial appearance from infancy to old age (Yousuf et al. 2010), and, for reasons that remain unclear, sometimes regress in HIV infection (Agarwal 2014).

The white adipose tissue in the orbit behind and around the eye is also primarily structural (Wolfram-Gabel and Kahn 2002) but it may be less metabolically inert and more like 'typical' depots than had been supposed. Adipocyte volume differs consistently in different parts of the orbit and the cell sizes of both samples scale to body mass in mammals ranging in size from whales to voles (Pond and Mattacks 1986a) as in the more abundant metabolically active depots (Pond and Mattacks

1985c). In adult guinea-pigs, total adipocyte complement in the intra-orbital depots correlates with that of the rest of the adipose mass, with corresponding differences in mean volume that enable the depot to occupy a constant space (Mattacks and Pond 1985). Lymph vessels permeate the tissue in certain chronic inflammatory conditions of the eye (Fogt et al. 2004) in which inflammatory cytokines and prostaglandins can be detected (Schäffler et al. 2006). Infiltration of immune cells and the formation of additional adipocytes in the intra-orbital depots are characteristic of Graves' ophthalmopathy (Heufelder 2001; Schäffler and Büchler 2007). Most innate and acquired lipodystrophies involve facial and intra-orbital depots (Garg 2000).

The use of such material, both whole tissue and the stem cells derived from it, for reconstructive and cosmetic surgery (Clauser et al. 2008; Stillaert et al. 2010) has reinvigorated the study of previously neglected tissues structural depots in the human face (Yousuf et al. 2010) and limbs (Panettiere et al. 2011) are being re-examined.

1.4 Brown and Beige Adipose Tissue

Brown adipose tissue (though not non-shivering thermogenesis) are unique to mammals (Cannon and Nedergaard 2004). The comparative anatomy and histology of white adipose tissue were studied in detail (Hoggan and Hoggan 1879) 40 years before similar investigation in brown 'adipose tissue' began (Rasmussen 1922, 1923). The similarities between the names of these tissues and their contrasting but apparently complementary contributions to obesity prompted biologists to emphasise their resemblances, an attitude that recent molecular and developmental findings reveal to be misleading.

The pattern of gene transcription in stem cells differentiating into brown adipocytes resembles that of muscle more closely than that of white adipocytes (Timmons et al. 2007). Brown adipocyte precursors can be detected in skeletal muscle (Crisan et al. 2008) and muscle-specific microRNAs can be found in such cells in tissue culture (Walden et al. 2009). Both muscle and brown adipose tissue have numerous mitochondria, rich blood perfusion and high capacity for uptake and oxidation of fatty acids, some of which may be stored as triacylglycerols in small droplets. In a further similarity to adipose tissue, skeletal muscle is now believed to secrete 'myokines' especially when strenuously active (Pedersen 2011). The resemblances between brown and white adipose tissue arose convergently and long-established histological methods emphasise their similarities more than their contrasts.

The situation is further complicated by the identification of beige or brite adipocytes, that arise from, and in intimate association with, white adipocytes (Wu et al. 2012) and occur in traditional 'brown' adipose depots (Lidell et al. 2013). Under beta-adrenergic stimulation, beige adipocytes may acquire thermogenic, energy dissipating properties similar to those of brown adipose tissue (Wu et al. 2013; McMillan and White 2015), though at rates well below those of brown adipose

tissue (Shabalina et al. 2015). Their presence in many intra-abdominal and superficial depots may contribute to the relationship between body fat patterning and metabolism (Sanchez-Gurmaches and Guertin 2014). Beige adipocytes may be the basis for tissues in laboratory rodents that appear to be mixtures of interconvertible brown and white adipocytes (Giordano et al. 2014). The presence of beige adipocytes may also explain the observations that 'white' adipose tissue of free-living wild mammals, particularly arctic species, contains a greater proportion of protein, even in obese specimens, than the corresponding depots of laboratory rodents or humans (Pond and Mattacks 1989).

The anatomical distribution of beige adipocytes is yet to be studied as thoroughly as that of white or brown and preliminary reports suggest that their physiological roles may extend beyond thermogenesis. Gene activation in beige adipocytes that accumulate around chronic rotator cuff tears indicate that they also promote muscle repair (Meyer et al. 2015).

1.4.1 Origins of Thermogenic Mechanisms

Various tissues and metabolic pathways contribute to whole-body metabolic rate and facultative thermogenesis in lower vertebrates, many of them with common endocrine control (Silva 2006). A recent synthesis of the evolution of thermogenesis in vertebrates (Rowland et al. 2015) concluded that most ancient form of heat generation shivering in skeletal muscles was supplemented in teleost fish by non-shivering thermogenesis 'futile' cycles of calcium ion transport across the sarcoplasmic reticulum. At least two lineages of fish have evolved specialised 'heater organs', derived from skeletal muscle with greatly reduced contractile proteins and extensive, often folded, sarcoplasmic reticulum (Rowland et al. 2015). Some fish, especially large deep-water species, are functionally endothermic (Wegner et al. 2015) with white adipose tissue insulating the brain (Runcie et al. 2009).

Proteins resembling mammalian uncoupling proteins are also expressed in a reptile (the common green lizard, *Lacerta vivipara*) (Rey et al. 2008) and teleost fish (Jastroch et al. 2005) but reptiles, including dinosaurs (Grady et al. 2014) and their descendent groups (including prototherian and metatherian mammals) generate heat (that incubates eggs and other functions) in their extensive musculature by shivering and non-shivering biochemical cycles similar to those of fish (Rowland et al. 2015). Beige adipocytes have been proposed as an intermediate stage in the evolution of brown adipose tissue in eutherian mammals (Li et al. 2014).

The internal body temperature of almost all adult birds is slightly higher than that of euthermic mammals (Schleucher 2004) and in both groups, endothermy uses energy at 5–10 times the rates measured in ectotherms of similar body mass (Hulbert and Else 2000). Many birds, including some very small species, live in polar climates and/or swim in very cold water and, although feather insulation is as good or better than that provided by hair, endogenous thermogenesis is likely during sleep

and other periods of inactivity. Many nestling birds, and adults of a few species, become torpid at night or during periods of fasting and re-warm themselves with a mixture of shivering and non-shivering thermogenesis (Schleucher 2004; Geiser 2008). In spite of much wishful thinking and fruitless searching (Oliphant 1983; Saarela et al. 1989), brown adipose tissue cannot be demonstrated in birds (Mezentseva et al. 2008). Nonetheless, birds do have an uncoupling protein (UCP) that is structurally similar to UCP1, the key component of thermogenesis in mammalian brown adipose tissue (Raimbault et al. 2001; Emre et al. 2007).

Birds' relatively massive muscles are the principal source of thermogenesis, not adipose tissue. As well as shivering muscle mitochondria are uncoupled by membrane protein, adenine nucleotide translocase (ANT) not UCP, increased Na^+/K^+-ATPase activity on the plasma membrane (Walter and Seebacher 2009). Thermogenic substrate cycle involving the Ca^{2+}-ATPase pump on internal membranes regulated by sarcolipin also occur in mammalian skeletal muscle (Bal et al. 2012). The decline in activity from the maxima in neonates can be delayed by cold exposure (Pant et al. 2015). Such cycles of calcium ion transport across the sarcoplasmic reticulum are also found in their poikilothermic ancestors (Rowland et al. 2015).

Substrate cycles ('futile' cycles) in liver, muscle and white adipose tissue were described more than 30 years ago as mechanisms of metabolic regulation and thermogenesis (Newsholme et al. 1984). In small hamsters, rates of adipose tissue cycles of triacylglycerol lipolysis and fatty acid re-esterification differ between adipose depots, highest in small intermuscular sites, and respond to exercise (Mattacks and Pond 1988). Such cycles continue using significant amounts of energy even during starvation in rabbits suggesting that they are fundamentally important (Weber and Reidy 2012). With new findings in brown adipose tissue, interest in non-UCP dependent thermogenesis in mammalian adipose tissues waned, until recently revived (Flachs et al. 2013).

UCP1-based thermogenesis in adipose tissues evolved first in eutherian (placental) mammals probably closely linked to reproduction (Oelkrug et al. 2015). Thus the current hypothesis is that UCP is an ancient protein that in mammals evolved to the new role of thermogenesis by uncoupling the mitochondrial respiratory chain (Hughes and Criscuolo 2008). Facultative thermogenesis in skeletal muscle became so important that the contractile components disappeared, though the very small, rapidly mobilisable lipid droplets remained, ATP synthesis was much reduced though mitochondria became numerous, thus diverting myogenic pathways to form brown adipose tissue (Timmons et al. 2007; Mezentseva et al. 2008). Gene transcription studies reveal similarities between beige adipocytes and smooth muscle (Long et al. 2014) suggesting parallel evolution from contractility to thermogenesis (Rowland et al. 2015). Muscle-derived tissue is the primary source of non-shivering thermogenesis as well as shivering in mammals, as it is in birds. Both inherited this fundamental role for muscle from their reptilian ancestors. The mammalian tissue's confusing resemblances to white adipose tissue arise from its specialisation to thermogenesis fuelled by locally stored lipids at the expense of contractility.

This evolutionary perspective on recent molecular and developmental findings reveals the name 'brown adipose tissue', chosen after careful consideration of a

wide range of evidence from wild animals as well as humans (Rasmussen 1923), to be inappropriate leading to decades of the mistaken belief in its close resemblance to white adipose tissue, and later confusion with beige adipose tissue. A new name, perhaps 'thermogenic tissue', reflecting function regardless of developmental origin, would clarify the situation.

1.5 The Specificity of Fatty Acids

Since leptin was discovered in the early 1990s, the secretion and reception of adipokines has been centre stage in adipose tissue research, emphasising its similarities to other tissues of the immune and endocrine systems (Fantuzzi and Mazzone 2007; Galic et al. 2010). Nonetheless, improvements in equipment and techniques for separating, characterizing and quantifying lipids have greatly advanced understanding of adipose tissue's specialised roles in the sequestration, sorting and selective management of fatty acids and triacylglycerols.

1.5.1 Structural Lipids

All living cells are bounded by fatty membranes and most can oxidise fatty acids or their derivatives. After many years focussed on heritable information and protein synthesis, lipid membranes as barriers and in cell proliferation are now well recognized as central to the evolution of cellular life (Szostak et al. 2001; Stano and Luisi 2010).

Plants and algae synthesise fatty acids from primary photosynthetic products as and when they need them but animals obtain most of theirs from food. In vertebrates, most fatty acids are derived from the diet, with only minor metabolic modifications. For most animals most of the time, *de novo* synthesis contributes only a little, the main exceptions being those that fatten rapidly on a low-fat diet, often prior to reproduction, migration, diapause, hibernation or other prolonged fast.

Membrane fluidity is closely linked to the cells' capacity to support channels and receptors and to deform during movement. Failures in these processes are the principal mechanism of death during hypothermia in mammals such as humans that cannot hibernate (Boutilier 2001). Temperature modulation of membrane fluidity is determined mainly by fatty acid composition of the phospholipids, though the exact relationships are complex (Hayward et al. 2007). Several essentially similar mechanisms that adjust the fatty acid composition of membrane lipids to temperature are found in microbes, plants and animals (Guschina and Harwood 2006). Heterothermic animals most clearly demonstrate the relationships of dietary lipids and their metabolic modifications and anatomical organisation to physiological capacities. For example, the diurnal desert iguana, *Dipsosaurus dorsalis*, can tolerate a wide range of body temperatures (<5 to >40 °C); feeding experiments demonstrate that the fatty

acid composition of dietary lipids determines the temperature at which the lizards choose to rest (Simandle et al. 2001). The effects develop over several weeks and presumably involve alterations in the fatty acid composition of lipid membranes, though the neural links between diet, membrane composition and behaviour are unknown.

Structural lipids are also becoming more important in biomedical sciences. The fatty acid composition of membrane lipids has been implicated as a determinant of natural longevity in several lineages (Hulbert et al. 2014; Galván et al. 2015) and dietary fats correlate with certain psychiatric conditions including long-term cognitive impairment among elderly humans (Solfrizzi et al. 2010).

Although it is generally assumed that some, perhaps many, of the fatty acids in an animal's structural lipids have been components of its own or its mother's storage lipids, trafficking between neutral lipids and phospholipids has been little studied. An exception is the demonstration of the resemblance between the compositions of fatty acids in newly formed lymphoid cells and the triacylglycerols in contiguous adipocytes, suggesting that specialised adipocytes supply fatty acids to adjacent immune cells (Pond and Mattacks 2003; Mattacks et al. 2004a; Pond 2009).

1.5.2 Storage Lipids as Fuels

As well as providing fatty acids appropriate to structural lipids in various kinds of cells operating under various physiological conditions, the composition of triacylglycerols is important to their role as energy stores during strenuous exercise, immune responses and thermogenesis. Biomechanical and metabolic studies show that human running is not very efficient compared to that of animals adapted to fast long-distance travel (Alexander 2004). However, exercise physiologists recognize that comparative studies can offer tips on improving athletic performance.

Long-distance migration in birds, especially small species, is among the most metabolic demanding of all activities, fuelled almost entirely by fast, sustained mobilisation of storage lipids (Weber 2009). Sandpipers (*Calidris pusilla*) demonstrated selective incorporation of dietary fatty acids into structural or storage lipids and evidence for adaptive desaturation that maximises energy density and efficient mobilisation of the storage lipids during prolonged flight (Maillet and Weber 2006). However, studies of another species of sandpiper (*Philomachus pugnax*) produced no evidence for similar selectivity of fatty acids mobilised during shivering elicited by prolonged exposure to cold (Vaillancourt and Weber 2007). This comparison suggests that active lipid management entails some physiological cost: the process is essential preparation for migration (Weber 2009) which requires precise coordination between muscles during flight but is dispensable for shivering, a more chaotic activity. Similar investigations on mammals have not yet been performed.

1.5.3 Fatty Acid Sorting

In mammals including humans, selective deployment and transport of fatty acids begins as dietary lipids are absorbed from the gut (Hodson et al. 2009; Hodson and Fielding 2010). Both brown and white adipose tissue can harbour triacylglycerols of a wide range of compositions and various lipid-soluble substances, including potentially toxic contaminants and metabolic waste products. As well as storing and mobilizing metabolically useful lipids and glutamine, adipose tissue is a repository for such unexcretable end-products, especially in elderly.

The capacity of rat adipocytes for selective release or retention of fatty acids that differ in chain length and degree of saturation was identified more than 20 years ago (Raclot and Groscolas 1993). The process has been demonstrated in several mammals including humans and the cellular mechanisms are now well understood (Raclot 2003). Fatty acids released from adipocytes into the circulation contain more highly unsaturated fatty acids and fewer long-chain saturated and monounsaturated fatty acids than the triacylglycerols from which they are derived. Raclot (2003) concludes that 'the observation that the molecular structure of fatty acids seems to govern their release does not support the idea of a particular demand of the body for specific fatty acids.' Comparative studies in a broader context reveal this conclusion to be unduly pessimistic. When supplemented by fatty acid synthesis and modification, dietary choice and selective intake, these mechanisms contribute to lipid deployment and storage appropriate to temperature and other conditions.

This important biochemical mechanism has been little studied in other vertebrates. Experimental starvation of diamondback rattlesnakes (anatomically advanced, physiologically versatile snakes) kept at temperatures at which they would normally feed found some evidence for selective retention of essential polyunsaturated fatty acids in whole-body homogenates (McCue 2007). Studies of egg formation and embryonic development in the viviparous lizard *Pseudemoia entrecasteauxii* also reveal some capacity for fatty acid sorting in reptiles (Speake et al. 1999).

The process is much more specific and efficient in birds (Speake and Thompson 1999). Avian embryos oxidise mostly carbohydrate in the early stages of development, later switching to lipids. In domestic chickens, the cells lining the embryonic gut start 'eating' droplets of yolk around the twelfth day of incubation and pass its lipids into the blood as lipoproteins. At the same time, mature white adipocytes appear (early compared with mammalian fetuses) and take up the yolk-derived lipids. The adipocytes and the lipoproteins manage the embryo's irreplaceable lipid provisions, incorporating appropriate fatty acids into structural lipids while others are oxidized (Speake et al. 1998). For example, most polyunsaturated fatty acids in the yolk lipoproteins of king penguin eggs are preferentially incorporated into structural lipids in the brain and eyes, while the more abundant saturates are used in energy production (Groscolas et al. 2003). The composition of yolk lipids is similar in several species of penguin in contrasting habitats (Polito et al. 2012).

This capacity for fatty acid sorting is one of the major advances of avian embryos over their reptilian ancestors and is essential to the growth and maturation of the large complex brain and eyes (Speake and Thompson 1999). For example, only 0.24% of the key neural polyunsaturate, docosahexaenoic acid (22:6*n*-3), in the egg yolk of water pythons ends up in the structural lipids of the hatchlings' brains compared to nearly 20% in bird embryos (Speake et al. 2003).

By adjusting the relationship between diet and egg composition, fatty acid sorting facilitates utilization of new foods and extension of range, including breeding in captivity. The avian capacity for fatty acid sorting may be retained into adult life, contributing to selective incorporation of certain polyunsaturated fatty acids into adipocyte triacylglycerols and muscle membranes during the fattening period that precedes long-distance migration, thereby improving the efficiency of prolonged, strenuous exercise (Maillet and Weber 2006; Weber 2009). The fact that fatty acid sorting by adipose tissue has been investigated thoroughly only recently, more than 100 years after its role as a lipid repository was recognised, reflects the progress of scientific concepts and instrumentation.

1.6 Paracrine Interactions with Adipose Tissue

Functional interpretation of the anatomy of brown adipose depots was established long ago: its thermogenesis warms essential organs by direct conduction into contiguous tissues and by convection via the blood (Heaton 1972; Rothwell and Stock 1984; Cannon and Nedergaard 2004). But attempts to interpret the anatomy of the many minor depots of white adipose tissue that are intimately associated with the vasculature, skeletal and cardiac muscle, skin and the immune system have lagged far behind.

Until the 1990s, physiological studies of white adipocytes concentrated heavily on the large depots, especially epididymal and perirenal, which provide enough 'pure' adipose tissue for most biochemical analyses. Adipocytes in the small and large depots are histologically similar, so were assumed to be physiologically and functionally similar as well. Doubts raised by the observation that lymph nodes (in neonatal guinea-pigs) are firmly attached to the surrounding adipose tissue were ignored (Gyllensten 1950). The anatomical arrangement attracted little interest until site-specific properties indicating paracrine interactions between minor adipose depots and contiguous tissues were demonstrated, first in perinodal adipose tissue about lymph nodes (Pond and Mattacks 1995), then in 'adventitious' perivascular tissue around blood (Löhn et al. 2002) and lymph vessels (Dixon 2010).

The concept of 'paracrine' was originally, and largely still is, associated with control systems rather than cellular nutrition (Grossman 1979), reflecting the emphasis on informational mechanisms that has prevailed since the 1960s. Evidence for 'paracrine' interactions between mature adipocytes and other tissues was presented in the mid-1990s (Pond and Mattacks 1995, 1998) but the universality of the mechanism was not recognised until the late 1990s (Trayhurn and Beattie 2001).

These days, the paracrine relationships involving white adipose tissue are mainstream (Rosen and Spiegelman 2014) and are investigated as routes for drug delivery (Trevaskis et al. 2015).

The best understood are with muscle, lymphatics and blood vessels, but in mammals, 'yellow' bone marrow adipocytes secrete several adipokines and may interact locally with osteocytes (Hardouin et al. 2014; Devlin and Rosen 2015). The adipose tissue surrounding the prostate may also modulate its properties (Sacca et al. 2012). Even the epididymal depot of murid rodents, so widely studied as 'archetypal' white adipose tissue that it seemed to have evolved for scientists' convenience, has been recognised as essential to spermatogenesis in the contiguous testes (Chu et al. 2010). Recently, beige adipocytes have been implicated in paracrine mechanisms of tissue repair (Meyer et al. 2015).

1.6.1 The Immune System

The involvement of adipose tissue in immune function was inferred 70 years ago from developmental and anatomical observations (Gyllensten 1950) but became widely recognised in the 1990s, with reports of localized interactions around lymph nodes (Pond and Mattacks 1995) and systemic effects (Grünfeld et al. 1996). Other chapters address the exchange of signal molecules and the role of macrophages in inflammation of adipose tissue in obesity. This section concerns the evolution of functional, non-pathological relationships between adipose tissue and immune structures.

According to a recent theory (van Niekerk and Engelbrecht 2015), the capacity of white adipose tissue to support the metabolic costs of the cellular responses to pathogens was more important for the evolution of adaptive immunity in early vertebrates (i.e. jawless and jawed fish) than gene evolution or selective pressures. Many invertebrate lineages have the necessary genes and are similarly exposed to pathogens (Downs et al. 2014), but inadequate metabolic scope prevented the evolution of adaptive immunity as efficient as that of vertebrates.

The evolution of relationships between adipose and immune tissues can be traced through fish and poikilothermic tetrapods, but has been most thoroughly studied in mammals. At all levels from gross anatomy to molecular complexity, both the immune system and adipose tissues are more elaborate and diverse in mammals than in reptiles. Mammalian lymphoid organs are more numerous and elaborate, and involve more genes, proteins and cell types than those of other vertebrates, and many components are efficiently deployed only in association with membranes of appropriate composition (Zapata and Amemiya 2000). Although anatomically complex lymph nodes widely distributed throughout the body were described long ago as a characteristic feature of eutherian (placental) mammals, immunologist and lymphologists took longer to recognise their functional relationships to adipose tissue (Harvey et al. 2005; Harvey 2008).

Comparative studies show that associations between the immune system and adipose tissue evolved early in mammalian evolution (Pond 2003b). In the echidna

(*Tachyglossus*), a primitive prototherian mammal that lays large eggs (but feeds its nestlings on secreted milk), tiny lymph nodules embedded in fatty tissue are present throughout the chest, neck and pelvic regions (Diener and Ealey 1965). The larger, more complex lymph nodes of Metatheria (marsupials) are surrounded by adipose tissue in adult kangaroos (Old and Deane 2001). Although the authors do not mention adipose tissue, their images of developing lymph nodes in another small metatherian, the quokka (*Setonix brachyurus*), reveal adipocytes surrounding lymphoid tissue by the age of 2 weeks (Ashman and Papadimitriou 1975).

Parallel advances in the anatomical, and probably physiological, relations between adipose and immune tissues also evolved in birds, endothermic descendents of a different group of reptiles. Lymph nodes in birds are smaller, simpler and less abundant than those of mammals, but are nonetheless associated with adipose tissue: 'The simplest [lymph nodes in birds] represent non-encapsulated lymphoid infiltrates embedded in the fat tissue' (Zapata and Amemiya 2000). In the more complex lymph nodes of domestic chickens, lymphoid cells are intimately associated with adipocytes in various ways (Oláh and Glick 1983). Thus close association between lymphoid and adipose tissues seems to be a fundamental feature of endothermic vertebrates.

1.6.2 Perinodal Adipose Tissue Around Lymph Nodes

Investigations into the adipose tissue surrounding lymph nodes were prompted by the observation that these small clumps of adipocytes retained their lipid content in very lean but otherwise healthy wild mammals in which most other adipose tissue—cardiac depots being another important exception—had been depleted to invisibility.

Apart from slightly smaller volume and more extracellular and vascular material, perinodal adipocytes are anatomically indistinguishable from those elsewhere in the same individual and are identified only by biochemical properties (Pond and Mattacks 1995; Pond 2005). All such properties are most pronounced in the adipose tissue nearest to nodes and diminish with distance from them. Perinodal adipose tissue is arbitrarily defined as within a radius of 10 mm around a lymph node. Many, possibly most, of the fatty acids incorporated into lipids in lymph node lymphoid cells that are newly formed in response to immune stimulation are derived from triacylglycerols in perinodal adipocytes (Pond and Mattacks 2003). *In vitro* studies demonstrate that adipose stromal cells migrate from perinodal adipose tissue into adjoining lymph nodes where they interact with indigenous cells (Gil-Ortega et al. 2013).

The adipocytes in depots containing lymph nodes, especially perinodal adipocytes, seem to be partially emancipated from supplying lipolytic products to more remote tissue. Although such adipocytes respond *in vitro* more strongly to maximal noradrenalin, *in vivo*, they contribute less lipolytic products to the circulation during fasting than those in depots containing few or no lymphoid structures (Mattacks and Pond 1999). The basal rate of lipolysis in perinodal adipocytes is slightly lower than

that of other adipocytes but significant increases can be detected within an hour of an experimentally elicited immune response (Pond and Mattacks 1998). Increased release of fatty acids from perinodal adipocytes around the lymph node(s) draining the site of the immune stimulus reaches a maximum after about 6 h and then wanes, disappearing totally after about 24 h, unless prolonged by further stimulation. With repeated immune stimulation, increased lipolysis and responses to interleukin-4 and tumour necrosis factor-α spread to adipocytes situated further from the simulated lymph node within 12 h and to perinodal adipocytes around other, remote, lymph nodes within 24 h (Pond and Mattacks 2002).

The appearance of more receptors for tumour necrosis factor-α on perinodal adipocytes follows a similar time course in response to mild immune stimulation (MacQueen and Pond 1998). Perinodal adipocytes respond much more strongly than those not anatomically contiguous to lymphoid structures to tumour necrosis factor-α, interleukin-4 and interleukin-6 and probably other cytokines (Mattacks and Pond 1999). These signal molecules may mediate the paracrine interactions between adipocytes and the lymphoid cells that they supply.

The popliteal perinodal adipose tissue is most frequently studied only because these depots are easily accessible and being paired facilitates experimental design. The responses of perinodal adipocytes around other lymph nodes are qualitatively similar but differ quantitatively. The largest and most sustained responses are consistently found in the mesentery and omentum of rodents (Pond and Mattacks 2002; Mattacks et al. 2004a; Sadler et al. 2005), and probably also in humans, in which the patterns of site-specific differences in adipocyte triacylglycerol composition (the property most easily measured in preserved samples) are similar (Westcott et al. 2005).

Many of the site-specific differences in gene expression in murine mesenteric adipose tissue compared to epididymal or inguinal (Caesar et al. 2010) can be explained as adaptations to interactions with lymphoid cells within or emanating from lymph nodes. Human visceral depots include more blood vessels, especially in obesity, and are more susceptible to inflammation than superficial adipose tissue (Villaret et al. 2010). The gene products mediating the relationship between lymph vessels and adjacent adipocytes have been identified (Harvey et al. 2005). Chronic inflammation and induced genetic defects in lymph vessel growth can stimulate adipose tissue formation in quantities amounting to obesity (Harvey 2008). Perilymphatic adipose tissue (PLAT) exchanges signal molecules with cells in the lymph vessels it surrounds (Souza-Smith et al. 2015).

1.6.3 Permeating Dendritic Cells

Dendritic cells interact with adjacent adipocytes. Those extracted from the adipose tissue stimulate lipolysis, while those from adjacent lymph nodes inhibit the process, though the effects are strong only in perinodal and milky spot-rich samples and minimal in the adipocytes extracted from adipose sites more than 10 mm from

lymph nodes (Mattacks et al. 2005). Inducing mild inflammation by injection of lipopolysaccharide amplifies these effects, suggesting that they are integral to immune responses. Switching from anti-lipolytic to pro-lipolytic secretions seems to be among the transformations that dendritic cells undergo as they migrate from the lymph nodes through the adjacent adipose tissue, and thus should be considered as part of the maturation process (Mattacks et al. 2005). The lymph vessels that permeate the perinodal adipose tissue facilitate the uptake of dendritic cells from among the adipocytes and return them to the nodes, where they contribute to the inflammatory responses (Kuan et al. 2015).

The fatty acid compositions of lipids in intercalated dendritic cells closely resemble those of adjacent adipocytes (Mattacks et al. 2004a). Site-specific differences and experimental changes of the dietary lipids alter the fatty acid composition of both types of cells, but the similarities between cells that were contiguous *in vivo* remain. The simplest explanation for this resemblance is that maturing dendritic cells acquire fatty acids (and perhaps other precursors) from adjacent adipocytes, rather than from remote sources via the blood or lymph, as was previously assumed (Mattacks et al. 2004a). Structural lipids are the most easily traced, but those used for the production of signal molecules or ATP are probably of similar origin.

In all normal monogastric mammals that have been investigated, the triacylglycerols of adipocytes near to lymph nodes are disproportionately rich in polyunsaturated fatty acids, including the specific precursors of eicosanoid and docosanoid signal molecules that are integral to lymphoid cell function (Mattacks and Pond 1997; Pond 2003c). These differences in composition presumably arise by selective uptake and/or release of fatty acids that differ in chain length and degree of unsaturation (Raclot 2003). The site-specific differences in adipocyte-derived fatty acids thus conferred on intercalated dendritic cells add another source of structural, and perhaps also functional, diversity to these cells that hitherto have been classified by genes activated and proteins synthesised (Gehring et al. 2008).

In rats fed unaltered or sunflower oil-supplemented diets, prolonged experimental inflammation alters the composition of fatty acids in lipids of perinodal adipose tissue, and hence that of fatty acids incorporated into permeating dendritic cells (Mattacks et al. 2004a). But the fatty acid composition of phospholipids in such dendritic cells from unstimulated and immune-stimulated rats whose diet over the previous 6 weeks has been supplemented with fish oils are indistinguishable from those of immune-stimulated rats eating standard diets and hardly change under experimental inflammation. These data imply that diets enriched with fish oil create membrane compositions in dendritic cells that are ideal for supporting the immune response, thus eliminating the need for further adaptation in response to immune stimulation. Over a period of several weeks, the ratio of *n*-6/*n*-3 fatty acids in triacylglycerols in the perinodal adipose tissue surrounding the locally inflamed lymph node also changes, partially rectifying the composition imposed by dietary imbalances (Mattacks et al. 2004a). This mechanism may be among the ways that perinodal adipocytes minimise the impact of fluctuations in dietary lipids on whole-body immune function and may be physiologically important, especially during fasting and hibernation (Pond 2009).

The involvement of perinodal adipocytes in immune responses not only begins within minutes but can persist for months. In a rat experiment to explore recovery from simulated low-level chronic inflammation, the numbers of dendritic cells recovered from the locally stimulated lymph node and its perinodal adipose tissue were found to rise at least tenfold within 4 weeks of local subcutaneous injection of 20 μg of lipopolysaccharide three times a week and remained high for as long as this regime was applied (Sadler et al. 2005). Dendritic cell numbers were still significantly above baseline 12 weeks after termination of the regime of simulated low-level chronic inflammation. These effects were observed in node-associated adipose tissue remote from the site of stimulation as well as that adjacent to it with parts of the mesentery and omentum being among the most responsive. The mesenteric lymph nodes and their contents atrophy in mice made obese by a high-fat diet, apparently poisoned by high concentrations of fatty acids and lipoproteins (Kim et al. 2008). These findings have implications for slow, deleterious changes in both the immune system and adipose tissue induced by chronic stress and prolonged inflammation.

1.6.4 Adipose Tissue in Normal Immune Function

Immune cells of the innate and adaptive systems, including macrophages, neutrophils, B cells and T cells permeate adipose tissue at normal body composition and, in greater numbers, in obesity (Grant and Dixit 2015; Travers et al. 2015). But 'ordinary' subcutaneous white adipocytes respond to infections in adjoining skin by secreting antimicrobial peptides, supplemented by local proliferation and maturation of preadipocytes (Zhang et al. 2015). Inflammatory processes in metabolically active adipocytes are an integral component of adipose tissue's response to demand for increased fat storage (Asterholm et al. 2014). Although impaired interactions between the tissues are fundamental to obesity (Grant and Dixit 2015), the attitude that adipose tissue is controlled by the immune system (Brestoff and Artis 2015) is questionable.

Perinodal adipose tissue is specialized for more precise, localized paracrine interactions with the immune system, as summarized in Fig. 1.1. Many immunologically important fatty acids are dietary essentials, and hence can be limiting, especially during anorexia associated with major inflammatory diseases (Johnson 2002). By ensuring that the immune system has priority access to essential lipids, this mechanism complements sickness-induced anorexia, an ancient mechanism that has been demonstrated in arthropods (Adamo et al. 2010) and lower vertebrates as well as in mammals (Johnson 2002; Straub et al. 2010).

Without effective lipid management, key precursors may not be available when and where they are needed and could be squandered by increased oxidation of lipids during anorexia. By releasing appropriate fatty acids to lymphoid cells when and where they are required, the perinodal adipose tissue promotes efficient utilization of essential fatty acids and partially emancipates immune function from fluctuations

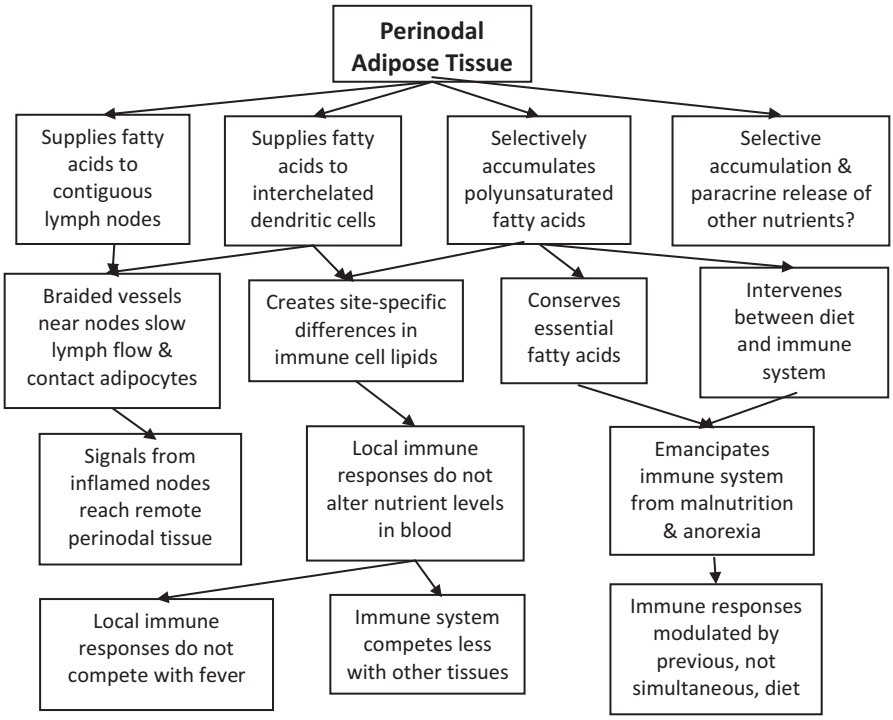

Fig. 1.1 Summary of the structure, properties and functions of mammalian perinodal adipose tissue and their roles in metabolism during immune responses

in the abundance and composition of dietary lipids (Pond 2003b). In rats, the selective accumulation of polyunsaturated fatty acids that generates the *n*-6/*n*-3 ratio appropriate for lymphoid cells is quite slow (Mattacks et al. 2004a) and can probably be overwhelmed by prolonged dietary deficiencies or excesses. Nothing is known about the extent to which the efficiency and robustness of these mechanisms differ between individuals or between species, thus making their immune systems more, or less, susceptible to impairment by dietary imbalance or insufficiency.

Paracrine control of lipolysis by lymphoid cells reduces competition with other tissues for specific, essential lipids, thus enabling fever and other energetically expensive defences against pathogens to take place simultaneously with proliferation, maturation and activation of lymphoid cells and with functions such as lactation and exercise, even during anorexia or starvation (Pond 2007). Under some circumstances, notably prolonged anorexia nervosa, immune function remains surprisingly efficient in spite of massive reduction in adipose tissue mass (Nova et al. 2002), less fever in response to infection (Birmingham et al. 2003) and altered plasma cytokines (Brichard et al. 2003). As long as local interactions between adipose and lymphoid tissues are unimpaired, the mammalian immune system can probably function over a wide range of body compositions. Obvious cachexia with extensive muscle

depletion occurs about the same time as perinodal adipose tissue disappears. Deficiencies in its capacity for preferential support of immune function, rather than reduction in whole-body energy supplies *per se*, may be the mechanism by which nutritional 'stress' impairs immune function.

Paracrine supply from specialised adipocytes to the immune system ensure supplies while minimizing lipid traffic in blood and its associated actions on metabolism and appetite and risk of damage to blood vessels. The concept is a special case of the hypothesis proposed by Unger (2003), Unger and Scherer (2010): adipocytes store fuel reserves safely, protect other tissues from fluctuations in the quantity and quality of dietary lipids and ensure that their 'client tissues' are appropriately supplied. Although more difficult to demonstrate experimentally, adipocytes may supply other nutrients to lymphoid cells. Glutamine is a likely candidate in view of its importance in nutrition of the immune system (Ardawi and Newsholme 1985) and its site-specific metabolism in adipose tissue (Digby and Pond 1995; Digby 1998).

Paracrine interactions with adipocytes may also account for some features of the anatomy of lymph vessels and nodes (Gyllensten 1950; Pond 1996; Harvey et al. 2005). The branching of fine lymphatics near nodes would slow the passage of lymph and bring a greater surface area of vessels into contact with adipocytes, thus facilitating the exchange of signals, nutrients and metabolites. Adipocytes specialised to interact with adjacent immune cells have been demonstrated in a variety of monogastric mammals but seem to be absent or at least to have very different properties in ruminants (Pond 2003c). Ruminant artiodactyls pass much more globulins and other components of passive immunity to neonates in the colostrum than most other mammals (Langer 2009). The functional and phylogenetic relationships between this habit and ruminants' unusual perinodal adipose tissue would be interesting.

A notable feature of naturally lean mammals (other than ruminants) is the retention of a small amount of perinodal adipose tissue around major lymph nodes, probably because prolonged fasting does not raise lipolysis in perinodal adipocytes as much as in adipocytes not anatomically associated with lymphoid tissue (Mattacks and Pond 1999). Lymphoid-associated adipose tissue also regenerates sooner. After experimental lipectomy of the epididymal fat pads of adult rats, compensatory regrowth of adipose tissue is significant 16 weeks later in the node-containing mesenteric and inguinal depots but not in perirenal (Hausman et al. 2004). All these site-specific properties are consistent with the indispensible paracrine support of immune function by specialized adipocytes.

The importance of membrane lipids to prompt, efficient immune responses (Heller et al. 2003; Serhan et al. 2008) and the local interactions hypothesis (Knight 2008) are becoming more widely accepted among immunologists but have been criticised by Schäffler et al. (2006) for lack of evidence that 'perinodal adipocytes and derived adipokines can directly influence the lymph node function in a paracrine manner during local inflammatory processes'. This comment misses the point common to most nutritional deficiencies and therapies. In providing appropriate membrane composition and precursors, perinodal adipocytes may equip lymph node lymphoid cells to respond appropriately and promptly to other signals, rather

than themselves generating short-term signals that can be easily measured in the laboratory. Although ill-defined, slow-changing and difficult to quantify, nutrition may be as important to well coordinated and regulated immune responses as the transiently-acting adipokines.

With the rise of lipidomics (Ivanova et al. 2004; Quehenberger et al. 2008) and better understanding of the roles of dietary lipids in immune function (Enke et al. 2008), the contribution of adipocytes to lymphoid cell diversity and function merits further investigation. Reports of translocation of lipid from adipocytes to human tumour cells in culture (Gazi et al. 2007) and its roles in human bowel disease (Zulian et al. 2013; Kruis et al. 2014) should prompt further study of paracrine mechanisms.

1.6.5 Human Perinodal Adipose Tissue

Perinodal adipose tissue is now recognized as an integral part of the lymphatic system, and as such, is under investigation as a potential drug target, especially for lipid-soluble agents (Trevaskis et al. 2015), and for conditions in which the tissue is directly involved.

Dietary lipids have long been implicated in both ulcerative colitis and Crohn's disease (Ananthakrishnan et al. 2014), as have adipocytes in their capacity to modulate interchelated macrophages by adipokine secretion (Kredel et al. 2013), but the relationships prove complex. Increased incorporation of *n*-3 polyunsaturated fatty acids into complex lipids usually suppresses inflammatory markers both *in vitro* and in chronic inflammatory diseases (Calder 2007). But blood-borne mononuclear cells from Crohn's disease patients contain more, not less, *n*-3 polyunsaturated fatty acids than those of the controls, and are deficient in arachidonic acid (Trebble et al. 2004). The site-specific differences in fatty acid composition of lipids in the mesenteric adipose tissue expected from animal studies (Pond 2003c) are absent from patients with Crohn's disease, though they were found in similar samples from the controls (Westcott et al. 2005). The composition of lymphoid cells in mesenteric lymph nodes resembles that of the adjacent perinodal adipose tissue in the controls, but not in the Crohn's diseased patients, which suggests that their adipocytes are not supplying fatty acids to cells in the adjacent lymph nodes. In the sample studied, the lymph node lymphoid cells from the Crohn's disease patients contained only 23% as much of the eicosanoid precursor arachidonic acid (C20:4*n*-6) as the controls. Its major fatty acid precursor, linoleic acid, and linolenic and docosahexaenoic acids, the precursors of docosanoids, were also significantly depleted. Such defects in lipid metabolism are not reflected in the fatty acid composition of superficial adipose tissue (Westcott et al. 2006) so would be difficult to identify without abdominal surgery.

Insufficiencies in the synthesis of eicosanoid and docosanoid signal molecules may contribute to the inappropriate inflammation characteristic of Crohn's disease and to its anomalous responses to anti-inflammatory drugs (Gassull et al. 2002;

Trebble et al. 2004). Induced colitis in rats increased the proportion of *n*-6 fatty acids in mesenteric perinodal adipocytes as well as modulating adipokine secretions (Acedo et al. 2011). General defects in perinodal adipose tissue leading to impaired immune function could explain the association between the bowel disorders and other chronic diseases such as arthritis, eczema and rhinitis (Book et al. 2003). Ingesting excess alcohol can disrupt its relationship in mesenteric lymphatics, causing inflammation in the adipose tissue and promoting onset of the metabolic syndrome linked to alcohol abuse (Souza-Smith et al. 2015).

'Fat wrapping' is local hypertrophy of mesenteric adipose tissue around the inflamed intestine, although nearly all patients undergoing laparotomies for Crohn's disease are lean following prolonged disruption to appetite, digestion and absorption (Westcott et al. 2005). As expected from the animal studies (Pond and Mattacks 2002), visceral adipose tissue remote from the diseased intestine as well as the contiguous 'wrapped fat' are inflamed in chronic Crohn's disease (Zulian et al. 2012). In rats, prolonged inflammation causes maturation of additional adipocytes and hence permanent enlargement in adipose tissue in the lymph tissue-rich intra-abdominal depots (Mattacks et al. 2003a; Sadler et al. 2005). The anomalous growth of adipose tissue in Crohn's disease may be induced by signals arising from adjacent immune cells unable to access sufficient, appropriate fatty acids to support inflammatory responses.

The roles of bacterial translocation into adipocytes (Kruis et al. 2014), inflammation in adipose tissue (Kredel et al. 2014; Gonçalves et al. 2015), impaired adipocyte apoptosis (Dias et al. 2014) and connective tissue changes (Shelley-Fraser et al. 2012) in inflammatory bowel disease are under active investigation. Site-specific differences in adipocyte susceptibility to bacterial colonization have been demonstrated between ulcerative colitis and Crohn's disease (Zulian et al. 2013). The roles of adipose tissue and the origins of its pathognomonic appearance are still hotly debated (Kredel et al. 2014).

HIV-associated adipose redistribution syndrome (HARS) is another chronic disease in which prolonged inflammation causes site-specific atrophy of some adipose depots alongside adipocyte hyperplasia and hence permanent enlargement of others, especially those that incorporate infected lymphoid cells (Pond 2003a). The condition is exacerbated by long-term treatment with antiretroviral drugs (Domingo et al. 2012) but such slow effects on adipose tissue are difficult to demonstrate *in vitro* (Mattacks et al. 2003b). HIV proliferates as an intracellular parasite in lymphoid cells, particularly dendritic cells (Lehmann et al. 2010). Mesenteric lymph nodes are important reservoirs of quiescent HIV (Estaquier and Hurtrel 2008). Recent findings reveal that adipose tissue harbours HIV and its simian counterpart in macaque monkeys (Damouche et al. 2015) and HIV-infected memory CD4+ T cells selectively accumulate in perinodal adipose tissue (Couturier et al. 2015).

Comparisons between node-containing depots show that paracrine interactions between perinodal adipocytes and dendritic cells are strongest in those around the numerous mesenteric lymph nodes and omental lymphoid tissue (Mattacks et al. 2004b, 2005; Sadler et al. 2005). Perinodal and omental adipocytes may proliferate (i.e. the depots enlarge) as part of their response to 'garbled messages' emanating

from HIV-infected dendritic cells (and other lymphoid cells including macrophages). HARS has been attributed to impairment of adipocyte mitochondria and regarded as a form of premature ageing (Caron-Debarle et al. 2010) but irreversible hypertrophy induced by prolonged paracrine interactions between parasitized lymphoid cells and adipocytes specialized to support immune function can explain the manifestation of the syndrome in drug-naïve as well as treated patients. Expert opinion on the mechanism of HARS now favours site-specific differences in inflammation of HIV-infected adipose tissue over the mitochondrial impairment hypothesis (Gallego-Escuredo et al. 2013).

1.6.6 Paracrine Interactions with Muscle

Lipolytic products as fuels for skeletal muscle have a long history and are well understood (Frayn 2010). Metabolic processes within adipocytes, such as intracellular re-esterification, as well as those in adipose tissue regulate levels in the circulation. In humans, mobilisation of local sources of lipid fuels within the muscle itself can make a substantial contribution. Intra- and inter-muscular adipose tissue and intramyocellular lipids are generally more conspicuous in large mammals and in muscles adapted to very frequent, sustained use, suggesting that these findings may apply generally to large species. Intramuscular adipocytes have distinctive site-specific properties (Gardan et al. 2006), though in early investigations, some were confused with features arising from proximity to lymph nodes embedded in small peripheral depots near skeletal muscle (Pond et al. 1984; Mattacks et al. 1987; Pond and Mattacks 1991).

Intramuscular lipids increase in athletes trained for sustained exercise and seem to be more quickly metabolised (van Loon and Goodpaster 2006). Paradoxically, intramuscular lipids increase in the leg muscles of healthy young people after a few weeks of experimental inactivity (Manini et al. 2007) and many reports link their presence to insulin resistance (Machann et al. 2004). Muscle satellite cells, stem cells essential to muscle repair and plasticity, can acquire features of adipocytes that could explain the enormous increase in such adipose tissue in humans (Vettor et al. 2009) and domestic mammals bred and raise for meat (Hocquette et al. 2010).

1.6.7 Cardiac Adipose Tissues

Until the 1990s, the adipose tissue in the human heart and pericardium was dismissed as pathological, irrelevant to normal function (James et al. 1982; Szczepaniak et al. 2007). Its gross anatomy and basic properties were introduced alongside appeals for further research (Iacobellis et al. 2005; Sacks and Fain 2007). Understanding of the normal function and pathology of cardiac adipose tissues has

advanced amazingly fast, aided by improvements to echocardiography, MRI and increased availability of biopsy samples (Iacobellis 2015). Cardiologists recognise a role for paracrine interactions involving musculature of the heart and major vessels and the small quantities of adipose tissue surrounding them (Hassan et al. 2012; Fitzgibbons and Czech 2014).

Both epicardial and pericardial adipose tissue are found in most lean, healthy wild mammals, especially large species (Marchington et al. 1989), and large birds such as swans (*Cygnus olor*), but are absent in the huge marine turtles (Braz et al. 2016) and probably other lower vertebrates. They are selectively spared in starvation, so both emaciated and very lean, healthy specimens may have lipid-filled adipocytes only in the cardiac and perinodal depots (see Sect. 1.6.2). As in humans (Sacks and Fain 2007), epicardial adipocytes are not bounded by fascia and always adhere tightly to the myocardium. In species that naturally become obese, no correlation between the masses of these depots and those elsewhere in the body is found (Pond et al. 1992, 1993, 1995) and the much more thorough studies of humans reveal surprisingly weak associations (Rabkin 2007).

Epicardial and pericardial adipose tissue are minimal in murid rodents so can only be studied experimentally in guinea-pigs or larger animals or *in vitro* (Marchington and Pond 1990; Swifka et al. 2008), until improved techniques enabled the depots to be studied in mice (Yamaguchi et al. 2015). Preliminary experiments 25 years ago suggested that these small depots are specialised to protect the heart from toxic levels of fatty acids by uptake and esterification, as well as to supply the cardiac muscle with fuel (Marchington and Pond 1990). The range of adipokines secreted from these specialised depots (Iacobellis and Barbaro 2008) and the finding that isolated rat heart muscle exports excess fatty acids *in vivo* (Park et al. 2004) are consistent with this concept. Fatty acids exchanged between the contiguous tissues may be accompanied by lipid-soluble pollutants that may be toxic to the heart (Bergkvist et al. 2015).

Comparing human epicardial adipocytes and myocardium with the developmental origins and maturation of homologous tissues in mice explains its appearance early in life and much of the contrasts between species (Yamaguchi et al. 2015). Transcriptome data from human biopsy samples indicate site-specific properties within epicardial adipose depot (Gaborit et al. 2015), another example of structural complexity within apparently amorphous adipose masses. Thermogenesis is now recognised as an important property of epicardial adipose tissue. Brown adipose tissue is clearly visible in these depots in neonates and hibernators (Nedergaard et al. 1986; Cannon and Nedergaard 2008) and in some adult humans (Cypess et al. 2009). In epicardial adipose tissue of Americans undergoing cardiac bypass surgery, particularly younger patients, the mRNA for the mitochondrial uncoupling protein (UCP1) is detectable (Sacks et al. 2009). Further examination of human biopsy samples indicates that the epicardial depots include some beige adipocytes (Sacks et al. 2013).

These and other aspects of recent research into these small, idiosyncratic but medically important adipose depots are thoroughly reviewed elsewhere (Iacobellis 2015).

1.6.8 Perivascular Adipose Tissue

Twenty years ago, the study of neurohumoral activity of perivascular adipose tissue around rat aorta was prompted by the observation that 'virtually every blood vessel in the (human) body is surrounded to some degree by adipose tissue' (Soltis and Cassis 1991). Like the epicardial adipocytes and those around lymph vessels, perivascular adipocytes are not separated by a fascia from the underlying tissue (Ouwens et al. 2010), an anatomical arrangement that facilitates paracrine interactions. These specialised white adipocytes are widespread and heterogeneous, with many site-specific differences (Gil-Ortega et al. 2015). They receive and secrete a wide range of signals (Fitzgibbons and Czech 2014; Ozen et al. 2015) and contribute to paracrine control of vascular smooth muscle (Ozen et al. 2015), tissue repair (Takaoka et al. 2010), immune processes (Omar et al. 2014), inflammation and thermogenesis (Brown et al. 2014; Fitzgibbons and Czech 2014). Defects in these interactions are implicated in various human pathologies, including atherosclerosis, blood pressure abnormalities and type II diabetes (Fitzgibbons and Czech 2014).

Aided by the development of animal models and *in vitro* systems (Brown et al. 2014), the physiology and medical implications of these small but active adipose depots is progressing rapidly (Fitzgibbons and Czech 2014), including adipokine secretion and paracrine control of vascular tone (Ozen et al. 2015). Gene expression and some physiological properties of murine perivascular adipose tissue resemble that of brown as well as adipocytes (Fitzgibbons et al. 2011). Thermal imaging combined with CT scanning reveals the presence of thermogenic adipose tissue around major blood vessels, as well as the oesophagus, upper regions of the spinal cord and vital organs of the thorax (Sacks and Symonds 2013).

1.7 Adipose Tissues for Mammalian Habits and Habitats

Several distinctive features of mammalian adipose tissues are described above: distributed anatomical arrangement, site-specific properties, fatty acid sorting, participation in multiple signalling pathways and paracrine as well as endocrine interactions. These properties can be related to some of the most fundamental features of mammals: herbivory, thermogenesis, variable, often high body temperature, lactation, allometric growth and sociality.

1.7.1 Diet

Selective foraging for foods that together form a balanced diet is essential for herbivores, but becomes less important if predator and prey have similar body composition (Kohl et al. 2015). Most extant reptiles are snakes, the great majority of which

prey on other vertebrates that they eat whole and within minutes of death (i.e. before rancidity and putrefaction impair its nutritional quality). Thus the chemical composition of the prey is unusually similar to that of the predator. All adult crocodiles and most large lizards are also predators on other vertebrates and they eat at least some of it very fresh. Such prey may be intermittently available and demanding to obtain but a single meal is close to supplying a 'balanced diet'.

Large herbivorous reptiles became extinct at the end of the Mesozoic and failed to re-establish themselves in the face of competition from mammals and birds. The only reptilian herbivores to survive into the modern era are the tortoises and the adult stages of a few tropical lizards (the juveniles eat small prey, as do the chicks of most herbivorous birds). Flight and climbing enable birds to access a varied diet of highly nutritious, energy-dense foods that may be widely dispersed. In all extant species, the teeth are entirely replaced by a beak, digestion is quick and water requirements usually low.

In contrast, the great majority of mammals are and have been throughout the Tertiary specialist consumers of fruit, seeds, grasses and other vegetation, abundant but nutritionally imbalanced foods that can be successfully exploited with good teeth, efficient digestion and means of detoxifying plant anti-herbivory compounds. Many mammals have highly specialized dentition and/or digestion and restricted ranges so at least at certain seasons, their diets are more homogeneous than those of similar-sized birds. From a nutritional point of view, such diets are far from ideal, often low in minerals and essential amino and fatty acids, though efficient chewing and digestion greatly improve absorption (Langer 2002). Small mammals, particularly the large ubiquitous groups such as rodents and bats (Chiroptera), owe their abundance and diversity to the ability to breed prolifically on monotonous, nutrient-poor diets. Eating more of poor quality but abundant forage to obtain these components generates too much energy, which may be stored in white adipocytes or dissipated by diet-induced thermogenesis (Cannon and Nedergaard 2004). In other words, 'burning off' excess energy can help to correct nutritional imbalances in monotonous or barely adequate diets, distilling out scarce nutrients including amino acids, essential fatty acids, vitamins and minerals from energy-rich but nutrient-poor foods.

The principal mediator of such facultative thermogenesis is probably mitochondrial uncoupling, but especially in large mammals that have little brown adipose tissue, other substrate cycles in muscle or liver (Dulloo et al. 2004; Wijers et al. 2009; Rowland et al. 2015) and thermogenic processes demonstrated in subcutaneous white adipose tissue of UCP1-knock-outs (Meyer et al. 2010) may contribute. Such processes may underlie the finding that lipodystrophic but not 'healthy normal' humans also respond to excess fat intake by substantially increasing their total daily energy expenditure (Savage et al. 2005). Those familiar only with lab animals and people on modern, nutritionally balanced diets fail to recognise the central role of such processes (Kozak 2010).

The presence of brown adipose tissue in superficial depots on the back and neck of adult mammals, including humans (Nedergaard et al. 2007), is also consistent with heat dissipation. Thermogenic adipose tissue in internal depots inside the

abdomen and thorax works best for heat retention, as required for rewarming after birth, and for hibernation and torpor. Diet-induced thermogenesis was among the first roles of brown adipose tissue to be investigated in adults (Stirling and Stock 1968; Rothwell and Stock 1979), but proved less convenient than cold exposure for studying the cellular and molecular mechanisms in laboratory rodents (Cannon and Nedergaard 2004; Xue et al. 2009). Spectacular physiological feats such as rewarming of adult mammals following hibernation and tiny neonates achieving euthermy attracted more thorough investigation, leading to the notion that these functions may be the original roles of brown adipose tissue. This conclusion overlooks the importance of adjusting metabolism to diet and digestion in conferring many of the ecological advantages of mammals over reptiles and birds. Nonetheless, facultative thermogenesis is now seen as central to maintaining energy balance (Wu et al. 2013) and recent accounts of thermogenesis in brown and beige adipocytes recognise control from 'other stimuli' as well as cold exposure (Cohen and Spiegelman 2015) (Fig. 1.1). Feeding has been shown to increase non-shivering thermogenesis involving several different pathways in sheep skeletal muscles (Clarke et al. 2013).

The capacity to deal with imbalanced or nutrient-poor diets may be transferred to offspring, probably through epigenetic mechanisms, as 'fetal programming' (Barker 2002; Mostyn and Symonds 2009; Symonds et al. 2009). Brown as well as white adipose tissues are particularly susceptible to such maternal influences (Symonds et al. 2003).

1.7.2 Controlled Heterothermy and Thermogenesis

Endothermy has long been regarded as the principal physiological advance of mammals over ancestral mammal-like reptiles, but it evolved slowly and is far from 'perfect' in some living species.

Many living reptiles are poikilothermic, warmed by solar radiation and by heat generated by exercise, protein synthesis and digestion, suggesting the same of the extinct ancestors of mammals and birds including dinosaurs, for which the term 'meosthermy' has been coined (Grady et al. 2014). Implanted probes reveal deep-body temperatures in the large South American tegu lizards (*Salvator merianae*) that cannot be fully explained by these processes alone but arise from seasonal changes in metabolic rate and in whole-body thermal conductance (Tattersall et al. 2016). The highest temperatures were found in breeding females, as is also true of primitive eutherian mammals (Levesque and Lovegrove 2014).

Although many different biochemical processes contribute to body heat, mammals and birds maintain core body temperature very precisely during euthermic periods (Silva 2006).

Controlled heterothermy (i.e. hibernation, torpor) takes several distinct forms in mammals (Ruf and Geiser 2015) but some general principles emerge. Hypothermia entails selective gene activation and dedicated neural pathways that set minimum body temperature which protects body tissues and maintains adequate but low

energy expenditure during fasting, followed by rewarming by BAT and muscle-based thermogenesis. At maximum, thermogenesis is among the most energy-demanding of all biological activities (Cannon and Nedergaard 2004) and entails rapid mobilization and transport of lipids from cool tissues.

Although mammals can oxidise almost all animal-derived (and most plant-derived) fatty acids when euthermic, efficient hibernation depends upon appropriate fatty acid composition of storage lipids. Experimental feeding of captive mammals and observations on diet selection in free-ranging specimens show that some hibernators can achieve low body temperatures, and hence minimal energy expenditure, only if they have access to adequate quantities of lipids containing low melting-point fatty acids (Dark 2005; Frank et al. 2008). The functional bases of this relationship are not fully explored but optimizing membrane fluidity and lipid transport in cold, slow-moving blood are among the possibilities.

Such experiments demonstrate the importance of different fatty acids for various aspects of metabolic well-being. While diet selection is the principal mechanism by which blood-borne lipids acquire compositions appropriate to the tissues' requirements, the adipose tissues can help. During the fattening period preceding hibernation, the adipose tissue of Alpine marmots (*Marmota marmota*), a strictly herbivorous rodent, selectively retains unsaturated fatty acids (Cochet et al. 1999). The echidna (*Tachyglossus aculeatus*), one of the most primitive extant mammals, also selectively utilises monounsaturated fatty acids during prolonged hibernation (Falkenstein et al. 2001). Fatty acid sorting ensures that saturates are oxidised while the body is euthermic, reserving the lower melting-point fatty acids to support metabolism at low temperature. The capacity partially emancipates mammals from the necessity of ingesting a diet containing a large proportion of monounsaturated and polyunsaturated fatty acids just before hibernation and thus extends the range of foods that hibernators can exploit.

Immune responses to pathogens acquired during or just before hibernation are fully effective only after arousal and rewarming (Prendergast et al. 2002). The slow transport of nutrients in the blood and lymph that delay immune responses at low temperatures would be alleviated by paracrine provision of lipids from perinodal described above (Sect. 1.6.4).

Thus fatty acid sorting in adipose tissue, even if slow and only partially efficient, enables mammals to adapt to ecological fluctuations and species to diversify into new niches. Many students of physiological evolution believed that 'constitutional eurythermy' was the norm for primitive Mesozoic mammals i.e. torpor and hibernation are very ancient habits (Grigg et al. 2004). If so, more efficient fatty acid sorting and paracrine provision may be early and fundamental properties of mammalian white adipose tissue, and indeed do occur in prototherians (Falkenstein et al. 2001). Hibernation implies both controlled cooling and active warming; shivering and activation of brown adipose tissue, both fuelled by lipolytic products released from white adipose tissue, are the main mechanisms of additional thermogenesis in mammals. Palaeontological perspectives on the evolution of endothermy recognise a role for more abundant and leakier mitochondria (Kemp 2006), but not of the adipose tissues that manage the physiologically risky process of thermogenesis (normal body is perilously close to dangerous hyperthermia) as well as hold and dispense the fuel.

1.7.3 Pregnancy and Lactation

Birds are endothermic and the majority provision their hatchlings, mostly by gathering appropriate foods that may differ significantly from those of the parents, but a few, notably pigeons and doves, produce 'crop-milk', a mixture of deciduous tissue and secretions from the upper digestive tract. Thus comparisons between these two advanced groups can reveal something of the origins and physiological relationships of these traits (Farmer 2003), both predicated on properties of mammalian adipose tissues.

Comparative anatomists and physiologists have long emphasised that lactation is an ancient and fundamental habit of mammals (Pond 1977; Farmer 2000), a conclusion consistent with modern genomics (Lefèvre et al. 2010) and evo-devo analysis (Oftedal and Dhouailly 2013). Lactation enables mammals to breed efficiently on any diet that can support the adults, supplemented as necessary by body reserves, in contrast to birds and reptiles, especially large species, that need access to foods suitable for all growth stages (Pond 1983). Ecological modelling of this reproductive strategy (Dall and Boyd 2004; Kunz and Hosken 2009) fail to recognise the importance of lipids, proteins and minerals reclaimed from adipose tissue, bone etc. to supporting lactation and thus rapid growth of suckling offspring through periods of food shortage. Adipose tissue's role in managing lipid supplies to the mammary gland has been demonstrated in laboratory animals and livestock (Vernon and Pond 1997) and in wild mammals (Fowler et al. 2016).

Reliable supplies of nutritionally balanced milk support rapid post-natal growth and remove the need for diet-induced thermogenesis, thus releasing brown adipose tissue in suckling mammals for cooling-induced thermogenesis. By transferring the physiological demands of obtaining and digesting food from neonates to mother, functionality of some systems, notably the teeth, can be postponed until the body has grown large enough to support them. Figure 1.2 summarizes the causal relationships of these apparently disparate features and habits to thermogenic adipocytes and those involved in storage, fatty acid sorting and signalling.

Milk synthesis and secretion have long been recognized as energetically demanding processes, especially for small mammals that have large litters and/or nutrient-poor diets (Langer 2003). The mother's gut, liver and pancreas enlarge during lactation to meet the additional metabolic requirements but the composition of the food does not usually change: the mother just needs more of her usual foods, thus permitting the evolution of specializations of teeth, digestion and metabolism to particular diets and largely eliminating the need for seasonal migration to habitats that can support breeding. Energy and nutrients from body stores and greatly increased food intake contribute to milk synthesis but competing metabolic demands, including some immune processes, may be compromised (McClellan et al. 2008; Speakman 2008) and human mothers experience extreme tiredness.

The finding that shaving mice increases milk secretion suggests that the capacity to dissipate metabolic heat, not nutrient availability, is limiting, at least for small mammals (Król et al. 2007). The capacity to support such high metabolic rate and

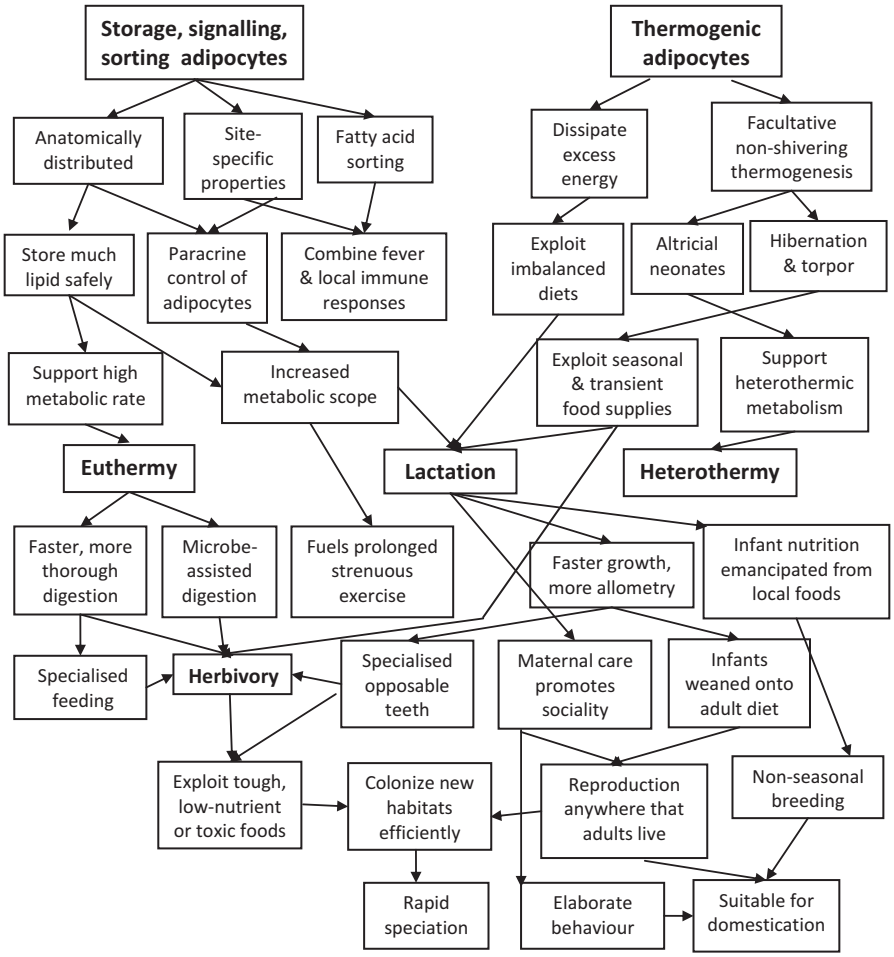

Fig. 1.2 Summary of the contributions of storage, signalling & sorting (*white*) adipocytes and thermogenic (*brown*, *beige*) adipocytes to the evolution of mammalian structure, habits and reproductive strategy

to tolerate high body temperature, at least transiently during lactation, must have evolved alongside the evolution of mammary glands, secretory mechanisms and milk proteins. Genomic data on the latter show that lactation evolved very early in mammalian ancestry and that genes, proteins and cellular processes derived from the immune system make a major contribution (Goldman 2002; McClellan et al. 2008). Milk may have been as important to protection from pathogens (many of them derived from the nest and/or the parents) as to nutrition, as it is modern eutherian mammals (Langer 2008, 2009). In both cases, adipose tissue is strongly implicated.

Many wild mammals fatten during pregnancy with the stored nutrients supporting milk synthesis. Mammals that eat little or nothing during lactation become massively obese before parturition: for example, polar bears give birth to up to four relatively very small offspring in inland dens and suckle them for several months without eating or drinking until the young are mature enough to accompany the mother to the coast where she has access to her normal diet of seals (Ramsay and Stirling 1988). Somehow, females adapted to such reproductive strategies avoid the complications of pregnancy and parturition found in obese women (Davis and Olson 2009).

Thus metabolic adaptations enabling storage of large quantities of lipid during pregnancy can evolve among wild mammals, but are weak or absent in women, suggesting that humans are adapted to support pregnancy and lactation mainly from current diet. The gluteo-femoral depots, that are always extensive in women of reproductive age but regress after menopause (Wells et al. 2010), extract fatty acids from the circulation slightly more slowly than other subcutaneous adipose tissue so may be an adaptation to long-term, more metabolically inert lipid storage (McQuaid et al. 2010). Nonetheless, lactation for a substantial period has clear benefits for women's lipid metabolism and body composition after giving birth (Stuebe and Rich-Edwards 2009). The observation that obese women breast-feed less competently than comparable women of normal body composition (Kitsantas and Pawloski 2010) is also consistent with the conclusion that, from an evolutionary point of view, obesity during human breeding is an aberration not an adaptation.

Metatherian and eutherian mammals produce very small, almost yolk-free eggs and the fetus is supplied entirely by the mother after development begins. Nutrient uptake is continuously regulated by the placenta and by the fetal tissues, processes that, at least in the most primitive eutherians may entail thermogenic adipose tissue. The hedgehog tenrec (*Echinops telfairi*) of tropical Madagascar is among the most phylogenetically ancient extant eutherians in which the unusual anatomical arrangement of brown adipose tissue suggests it may warm the gonads. Like many primitive mammals, its body temperature fluctuates except during pregnancy when non-shivering thermogenesis maintains euthermy, suggesting that thermogenic adipose tissue was fundamental to reproduction in early eutherians (Oelkrug et al. 2013, 2015). In euthermic rodents of similar size, the perigonadal depots are among the last to develop thermogenic adipocytes under experimental conditions (Sanchez-Gurmaches and Guertin 2014).

During gestation, glucose is the main energy source and most fatty acids are incorporated into cell structures, but immediately after birth, the roles reverse. Birth also triggers major changes in the immune system that adapt the neonate to symbiotic and pathogenic microbes, not least those from their own parents (Calder et al. 2006). In contrast to lower vertebrates and birds, the development of adipocytes is delayed until shortly before birth. Even the exceptionally large quantities of white adipose tissue in neonatal humans does not form until the last trimester of gestation (Kuzawa 1998). Lack of involvement in fetal metabolism may have enabled the specialization of adipose tissues to perinatal thermogenesis and paracrine interactions.

1.7.4 Primates and the Origins of Human Obesity

Despite its obvious relevance to humans, primate adipose tissue has only recently been studied from comparative and evolutionary perspectives, mainly to explore the propensity for obesity and its relationship to reproductive biology, including sex differences in its distribution and the demands of gestation and infant care.

The energetic cost of reproduction is lower in primates than in other advanced eutherians (such as rodents and ungulates) and is particularly low in humans (Dufour and Sauther 2002; Prentice et al. 2005). Using evidence from anthropology, reproductive biology and diet, Wells (2010) concluded that in the great apes, encephalisation (disproportionately large brain) and omnivory are among the characteristics closely associated with increased adiposity. More than half of the dry weight of the brain is lipid, a high proportion of which contains long-chain fatty acids derived from dietary essentials. So the metabolic bases of both these features require efficient digestion and internal distribution of dietary and synthesised lipid. Another dimension to the evolutionary relationships between brain and adipose tissue in primates is the hypothesis that physiological flexibility in energy storage is complemented, to varying degrees, by cognitive flexibility that entails reasoning and social organization and thus a large brain (Isler 2014; Heldstab et al. 2015).

For more than 50 years, the evolution of exceptionally high average fatness of humans was attributed to 'thrifty' genes that enable people to cope with food supplies that, until very recently, were irregular and unpredictable (Wells 2009, 2010; Watve 2012). Adaptations to recurrent starvation were claimed for the human genome and patterns of gene imprinting *in utero* (Prentice et al. 2008). Attractive though it is, this hypothesis is inconsistent with much human demographic data and genetic theory (Speakman 2007), and with information from other primates. A recent critique (Higginson et al. 2016) directs attention away from external factors affecting food supplies and towards the evolution of internal factors that regulate body mass, and, by implication, appetite.

The ranges of several other species of long-lived, slow-maturing apes were closely similar to those of *Homo* and its ancestral genera for much of their evolutionary history, so would be similarly affected by prolonged, severe famines caused by climate fluctuations etc. Comparisons of body composition, metabolism and habits can illuminate the origins of human obesity. Even after many years in humane captivity, the average proportion of dissectible adipose tissue in bonobos (*Pan paniscus*) is much greater than the minimum compatible with health found among indigenous peoples following traditional lifestyles, though, as in humans, females are consistently fatter than males (Zihlman and Bolter 2015). Gorillas (*G. G. gorilla*) and orang-utans (*Pongo*) in captivity can become fatter (Zihlman and McFarland 2000) but in the absence of data from free-living specimens, the norms for wild apes are difficult to estimate.

Three metabolically active body constituents, the skin, skeletal muscle, especially of the arms, and the digestive system, are proportionately more massive in these great apes than in modern humans (Zihlman and McFarland 2000; Zihlman

and Bolter 2015). Nonetheless, measurements on healthy young adult orang-utans in a large, semi-natural enclosure in Iowa reveal the lowest daily energy expenditure ever recorded from a higher primate (Pontzer et al. 2010). Their idiosyncratic locomotion through dense forest is unusually efficient (Thorpe et al. 2007). This ape, which evolved under selective pressures similar to those acting on the ancestors of modern humans and chimpanzees (Enard et al. 2010), has responded to unreliable food supplies by improving mechanical and metabolic efficiency and breeding slowly.

The human diet has probably been as diverse as it is throughout the modern world for much hominid evolution (Bellisari 2008). Such adaptability contributes greatly to efficient colonization of new habitats (Wells and Stock 2007) and to coping with rapid fluctuations in climate (Wells 2012c). Hunting animals, especially in large social groups, requires advanced cognition and communication, and prolonged strenuous activity but provides nutrient-dense food. Cooking and manual food preparation increase the efficiency of nutrient extraction, enabling the jaws, teeth and digestive system to become smaller, and to exploit a greater variety, but not quantity, of different foods (Wrangham 2009). Most chimpanzees' diets include some animal food and some actively hunt other mammals. Chimps apparently understand the advantages of cooked food (Warneken and Rosati 2015), thus supporting the hypothesis that cooking evolved earlier among the ancestors of modern people than previously believed (Wrangham 2009).

Such advances in diet and food processing allow for smaller stomach and intestines, contributing, with the radical changes to the pelvis and lumbar region (Warrener et al. 2015), to the distinctively human shape of the abdomen and waist. Smaller abdominal cavity would mean less space for intra-abdominal adipose tissue, thus promoting expansion of the superficial depots without altering overall body composition, as has happened in Carnivora (Pond and Ramsay 1992).

Diet, foraging strategy, food processing and digestion are intimately related to the evolution of hair reduction and hence of superficial adipose tissue. Diurnal pursuit of prey in the tropics generates much body heat, and many unique features of human anatomy, including hair reduction, evolved adaptations to heat dissipation (Wheeler 1991; Lieberman 2015). Body hair became thicker and more extensive in elephants, rhinoceroses and other large mammals as they colonized cooler areas, but not in *Homo*, which exploited fire and animal skins instead. A review of alternative hypotheses for the evolution of hair reduction favoured the theory that it protects against ectoparasites and the diseases they transmit (Rantala 2007).

The human integument not only has greatly reduced hair over most of the body, it is also much less massive than that of other great apes (Zihlman and Bolter 2015). Humans have more white adipose tissue, especially in superficial depots, than other mammals from late gestation onwards (Kuzawa 1998). Even non-obese western adults have about ten times as many white adipocytes as would be expected in a wild mammal of similar size and diet (Pond and Mattacks 1985c). Although similar in general organization and relative thickness to that of other (furred) primates, human superficial adipose tissue is unusually extensive and supports various skin functions (Klein et al. 2007). The unusual thinness of human skin may contribute to

the tendency of adipose tissue to form, sometimes in substantial quantities, on limbs with impaired lymph drainage (Brorson et al. 2008) and perhaps some forms of generalised obesity (Harvey 2008).

Such theories cannot explain why human ancestors evolve thinner, softer skin overlying thicker superficial adipose tissue. The identification of beige adipocytes in subcutaneous adipose tissue under cold-exposed skin (Lidell et al. 2014) suggests that the tissue may be capable of thermogenesis as well as insulation (Alexander et al. 2015). Thermal insulation entails restriction of blood flow, while heat dissipation and active thermogenesis require a rich blood supply. The extensive vasculature and its neural control combined with reduced pigmentation enable the skin to acquire roles in social and sexual signalling, as it has in other higher primates (Street et al. 2016). From about 2.3 My ago, visibility of such indicators of social and sexual status was enhanced by reduction in body hair (Dror and Hopp 2014), contrasted against denser hair on the head and external genitalia. Exposed skin enabled sex and ethnic differences and age-related changes in adipose tissue distribution to evolve under sexual as well as natural selection (Pond 1998).

Adipose tissue is central to such intra-specific communication and its roles in flexible habits and life history strategies in human evolution (Wells 2012b). Sexual dimorphism in the distribution of adipose tissue is not more extensive in macaque monkeys and lemurs (prosimians) than would be expected from differences in body size (Pond and Mattacks 1987; Pereira and Pond 1995), but contributes to the signalling of age and social status in most apes, including the conspicuous fatty cheeks in mature male orang-utans (Caillaud et al. 2008). These small but conspicuous depots on the face and head are species-specific and are presumably composed of adipocytes arising from the neural crest, another example of its plasticity (Billon et al. 2007).

The interpretation of sex differences in the distribution of superficial adipose tissue does not consider the contribution of site-specific properties to whole-body metabolism. The rounded buttocks created by pelvic adaptations to faster, more efficient running are a key evolutionary advance of *Homo sapiens* that in women are emphasised by adipose tissue to create enlarged, rounded buttocks and smooth, thickened thighs. This distribution of adipose tissue, conspicuous and sometimes massive at least since the Palaeolithic, emphasises the sex differences in pelvic anatomy that enable women to combine running fully erect with giving birth to neonates with large heads (Pond 1998; Gruss and Schmitt 2015). The intrinsic metabolic properties of these depots have also contributed to human evolution: enlargement of these lower-body depots entails less risk of metabolic and cardiovascular disease than expansion of intra-abdominal and upper body depots (Karpe and Pinnick 2015). In other words, natural selection has promoted the evolution thick thighs and large buttocks that enable women to maximise energy reserves without compromising longevity. Sexual selection for these depots in younger, reproducing women (Furnham et al. 2004) promotes social bonding that is essential for the role of post-reproductive ‘grandmothers’ in advancing the evolutionary success of their descendents (Wells 2012b), and also entails high post-menopausal life expectancy.

Adipose tissues thus have several important roles in the anatomy and metabolism of modern humans, and have evolved to continuously support more fat than is found in most mammals. Body insulation from clothing during the past 70,000 y would undermine the thermoregulatory importance of superficial adipose tissue, freeing it to evolve under different selection pressures, or none, and producing the observed variations in the modern population (Wells 2012d). A wide range of other habits and social factors contribute to the pathogenicity of large quantities of adipose tissue (Wells 2012a).

The only large-scale, long-term study of spontaneous obesity in large primates is that of macaque monkeys (*Macaca mulatta*) 'ranched' in large enclosures in USA. The resemblances to human populations are striking: not all apparently similar monkeys on similar diets gain weight, and of those that become obviously obese, not all develop metabolic complications (Schwartz et al. 1993; Wells 2009).

1.7.5 Rapid Adaptation to Modern Diets and Lifestyles

In a few taxa, notably whales (Cetacea), large quantities of adipose tissue are widespread and ancient enough for positive selection for 'obesity' to be detected for scores of genes involved in lipid metabolism and its control (Wang et al. 2015). Such studies demonstrated that mammals can evolve adaptations to obesity, but are only obliquely relevant to the current epidemic of human obesity and other metabolic disorders.

Bears, Svalbard reindeer and other mammals too big to hibernate and not subject to heavy predation deal with similar fluctuations in food intake by both long periods of low energy expenditure and by impressive levels of obesity, at least for part of the year. Their total adipocyte complements are only 2–3 times larger than those of related lean species (Pond 1998), mostly in superficial depots (Pond et al. 1993), and there is no evidence that they suffer from the complications of pathological obesity found in modern people and in many apes and large monkeys in captivity. These and other evolutionary and comparative points are among the most persuasive evidence that humans are not naturally and adaptively obese. But the observations on bears show that metabolic adjustments to high-fat or poor quality diets and improved thermogenesis can evolve over many millennia, not decades, and presumably under intense natural selection.

The present rate of change of human diets and habits is apparently the fastest in history and probably in pre-history (Wells 2006, 2010, 2012a; Morin 2012). Arctic mammals may be the only wild animals that have undergone comparably rapid adaptation. Bears (Carnivora, Ursidae) ranged over much of the northern hemisphere during the Pleistocene glaciations when *Homo* was colonizing the temperate regions of Europe and Asia. Several of the species that shared human habitats (sometimes featuring in Palaeolithic art) are now extinct (Morin 2012), but the polar bear (*Ursus maritimus*) and its direct ancestor, the brown bear (*Ursus arctos*) are fortunately still extant, though their ranges are much reduced. Some adaptations

that evolved, probably relatively rapidly, to changes in diet and climate have been recently described and offer some interesting parallels with human metabolic adjustments.

Comparison of the genomes of *U. maritimus* with *U. arctos* shows that adaptations of thermoregulation and thermogenesis in polar bears entail changes to the nuclear and mitochondrial genes fundamental to cellular respiration (Welch et al. 2014). They are also heterothermic to a degree unusual for a large mammal (Whiteman et al. 2015). Very low daily energy expenditure, including reduction in vital organs, adapts another ursid, the giant panda (*Ailuropoda melanoleuca*) to its indigestible, nutritionally poor diet of bamboo (Nie et al. 2015).

Brown bears, like most ursids, are omnivores, selecting diets that supply about 15–20% of the metabolizable energy as protein, much the same as humans, but in choosing far more lipid over carbohydrate, they resemble dogs—and laboratory mice artificially selected for obesity (Erlenbach et al. 2014). This preference is taken to extremes by polar bears, whose basic diet of seal blubber (80% fat, 20% protein) comprises one of the highest in fat known for any mammal (Thiemann et al. 2011). They accumulate enough replete adipose tissue to support up to 8 months of ambulatory fasting (Atkinson et al. 1996) or 4 months suckling twins (sometimes triplets) (Robbins et al. 2012), without detectable impairment of locomotory capacity (they travel huge distances), or nutritional, metabolic and cardiovascular health. Studies of the gut microbiota in wild *U. arctos* during summer fattening and winter fasting suggest that symbiotic microbes may facilitate such nutritional and metabolic feats (Sommer et al. 2016).

Another factor is anatomical distribution of the adipose tissue: depots in the relatively small abdominal cavity enlarge in proportion to the viscera, so up to 85% of the dissectible adipose tissue is superficial. As in healthy women (Karpe and Pinnick 2015), depots over the lower back, pelvis and hind limbs expand most with increasing obesity but, although the metabolic demands of reproduction are far greater for female bears, sex differences in adipose tissue distribution are undetectable (Pond et al. 1992). The partitioning between intra-abdominal and superficial depots is similar to that of other terrestrial carnivores, refuting the hypothesis that it is an adaptation to thermal insulation (Pond and Ramsay 1992).

Woolly mammoths (*Mammuthus primigenius*) are another species of tropical ancestry that colonised northern Eurasia 1–2 million years ago, sharing their cold habitat with Upper Palaeolithic people during the final 10% of that time. Comparisons of mammoth genomes extracted from subfossil tissues preserved in ice with those of Asian elephants reveal differences in 54 genes that directly influence the anatomical distribution, abundance or metabolism of adipose tissues and a similar number acting on hair growth and temperature sensation (Lynch et al. 2015). *Homo sapiens* had much less time in which to evolve similar adaptations to cold climate, and the changes have been abruptly reversed during recent millennia with technological advances in clothing, fire use and shelter. Interestingly, data from native Greenlanders suggest that adaptations to diets high in protein and ω-3 fatty acids have evolved faster than those to the cold climate (Fumagalli et al. 2015).

1.8 Conclusions

Mammalian adipose tissues are physiologically more diverse, have more complex anatomical relations to non-adipose tissues and make a wider range of fundamental contributions to activities at all stages of the life cycle than those of lower vertebrates. Partitioning white adipose into numerous depots, many with site-specific properties, is a fundamental feature of mammals. Paracrine interactions avert competition between tissues and enable adipose tissue to support the specific requirements of contiguous tissues, notably the heart and immune system during hypothermia as well as euthermia. Depots that support lymphoid tissues demonstrate capacities for selective uptake and/or retention of certain fatty acids thus directing scarce essentials to where they are most needed. Paracrine interactions between adipocytes and the immune system have central roles in infectious diseases including HIV/AIDS, digestive disorders such as Crohn's disease and the metabolic complications of obesity. Early-developing adipocytes in avian embryos also sort fatty acids, ensuring that the limited lipid resources in the yolk are efficiently partitioned between oxidation and structural roles (especially in the nervous and immune systems).

Thermogenesis in adipose tissues involves several different biochemical mechanisms some of which resemble non-shivering thermogenesis in muscle. Facultative thermogenesis and its many control systems evolved gradually, starting in reptilian ancestors of mammals and paralleled in birds. Diet-induced thermogenesis enables mammals to dissipate excess energy taken in to obtain scarce proteins, vitamins and minerals. These fundamental metabolic roles of adipose tissue may have appeared early in the evolution of mammals as adaptations to rapid colonization of new habitats, including efficient digestion and utilization of poorer quality diets, and metabolic support of lactation that enables fast-growing young to delay fully functional dentition until after weaning.

Selection for post-menopausal longevity as well as sexual selection and heat dissipation may have contribution to the evolution of sex differences in the distribution of human adipose tissue. Genomic analysis of the evolution of natural obesity in arctic mammals reveals scores of genetic changes that appeared in around a million years ago. Several interspecific comparisons indicate that modern human are not (yet) similarly adapted to obesity and that intermittent famine and cold climate have been at most minor factors in recent evolution.

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