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Editorial

Adipose tissue, the anatomists' Cinderella, goes to the ball at last, and meets some influential partners

When serving as demonstrator at the Veterinary School of the University of Pennsylvania during the 1970s, I was frequently required to remove all that nasty, messy adipose tissue to enable the students to see the "real" structures beneath. The anatomy textbooks devoted only a few lines to what was sometimes the most abundant tissue in the body. Many readers are probably familiar with the attitudes thus embodied. Lipids and adipose tissue are seen as at best superfluous or ugly, often indicative of an indolent or intemperate lifestyle, and sometimes positively harmful. They are the agents of retribution for the modern lifestyle, turning self-indulgence and sloth into debility and death, and above all, compared with the mathematical sophistication of genes and proteins, adipose tissue is dull. All adipocytes look alike and respond mindlessly to blood borne orders such as insulin, cortisol, and glucagon. The ideal adipocytes know their duties and their place: they should mop up excess lipids in the blood and mould themselves into gaps and smooth contours to form rounded breasts, thighs and cheeks, perhaps fill a few internal spaces not required by more important tissues, but otherwise keep quiet and make themselves as small as possible until starvation calls them to attention.

The immune system is seen as diverse, sophisticated and noble, its cells sacrificing themselves for the benefit of the whole body. The cardiovascular system is the crowning achievement of vertebrates, ingeniously accommodating abrupt changes in the pressure and composition of blood, sealing off wounds, maintaining water balance, etc. For these intricate and important tissues, forming permanent liaisons with adipose tissue is surely to marry beneath them, yet several independent lines of research during the 1990s suggest that such improbable alliances are widespread, ancient, and essential.

Adipocytes' progress from obscurity began in 1987 with the isolation of their first known secreted protein, adipsin.[1] When first discovered, adipsin was hailed as the key to controlling obesity, but enthusiasm for it quickly waned, and its exact physiological role is still not clearly established. Its successor, leptin, discovered in the early 1990s in a spontaneously obese mutant strain of mice,[2] has held the limelight for longer. During the last five years, it has become by far the most thoroughly studied of the many proteins now known to be synthesised in adipocytes. Leptin was first identified as a secretion of adipocytes that curtails appetite by binding to receptors in the hypothalamus, thus linking energy stores to appetite. But like adipsin, the protein was soon found to be produced in, and have effects upon, several different tissues, including the immune and reproductive systems.[3] Alas, attempts to manipulate body composition with leptin work much better in mice than in people,[4] and its multiple effects, especially those on fertility, may severely restrict its use on those patients most likely to complain of obesity: young, otherwise healthy adults.

Advances in the separation and identification of proteins and messenger RNAs have greatly extended the list of adipocyte secretions. Many (including leptin itself) turn out to be cytokines, identical to those produced by lymphocytes and other immune cells.[5] Their discovery has, in barely a decade, raised the status of adipose tissue from passive repository for excess lipids, to active player in the physiological orchestra.[6 7] Information about the molecular biology of adipocyte secretions may be found elsewhere[8 9]; in keeping with all good romances, this article concentrates on why, where, and above all, with whom, messages and materials are exchanged.

Obesity is a serious, and rapidly increasing, medical problem, which by definition involves large adipose depots. In small animals such as mice, only the largest depots contain enough tissue for biochemical analysis. Biochemists choose adipose tissue that is not "contaminated" with other cell types. For all these reasons, much more is known about the large, "pure adipose" depots. However, cytokines typically act in a paracrine or autocrine fashion, usually conveying short term, short range signals between contiguous cells and tissues. Interesting physiological interactions mediated by cytokines are most likely to take place in the many scruffy fragments of "impure" adipose tissue that are usually consigned to the waste bin after the "real", "typical" depots have been excised for study.

Adipose tissues associated with the heart, pericardium, and large blood vessels are among the most familiar but least understood depots. Since comparative anatomy is no longer taught to medical students (or indeed at A-level), most surgeons obliged to rummage through them in search of coronary arteries and their replacements are unaware that these depots are not confined to sedentary, overfed people, and domestic animals. On the contrary, in lean specimens of wild mammals and birds, especially species adapted to sustained exercise such as wolves, deer, rabbits

and swans, visible adipose tissue is *mainly* associated with the heart, pericardium, and great vessels.[6 10] Far from being merely structural, these tiny depots are, at least in guinea pigs, more metabolically active than many larger ones.[11] Perivascular adipose tissue in rats seems to be essential for normal responses to the agonists that control vascoconstriction.[12] These properties should be investigated further, as they may help to explain why perivascular and epicardial adipose tissues are so firmly attached to their associated tissues; it is often very difficult to dissect them off neatly. Renal physicians have held the ubiquitous perirenal adipose tissue in similar contempt, so were surprised when at least some adipocytes turned out to express genes and secrete proteins of the complement pathway,[13] and some of those more directly involved in renal function.[14]

The bone marrow has long been known as a site of intimacy between adipocytes and a variety of other cell types including osteoblasts and haematopoietic cells, but such associations were discretely out of sight to all but the most invasive surgery, so attracted little attention. Techniques for extracting and culturing such cells have improved so much that their interactions can now take place under bright laboratory lights.[15] Marrow adipocytes, until very recently regarded as mere space fillers,[16] now prove to share properties with several other cell types, and probably contribute to processes as important and diverse as myelopoiesis, erythropoiesis, and the deposition of bone and its loss in osteoporosis.[17] Cytokines of the interleukin family are central to the reciprocal relationship between osteoblastogenesis and adipogenesis[18] that may explain the association between the decreased bone formation and the resulting osteopenia and the increased adiposity seen with advancing age in laboratory animals and humans. These roles may explain why marrow adipocytes are not depleted even in severe starvation in rabbits[19] (and probably other non-ruminant mammals) or barn owls.[20] "Knock-out" mice, in which particular genes are eliminated to order, have been powerful tools in demonstrating that, in addition to its role in regulating appetite and fatness, leptin may also control aspects of haematopoiesis and macrophage function.[21 22]

Another place where adipose tissue can always be found, even in the leanest animals, is around major lymph nodes. Under the microscope, such adipocytes are indistinguishable from those of the larger, more conveniently studied depots. We began to investigate perinodal adipocytes experimentally when our studies of the comparative anatomy of adipose tissue raised the simple question: Why is mammalian adipose tissue—and only that of mammals—always split into a few large depots and many small ones, widely scattered around the body? Many small depots contain lymph nodes, and nearly all large nodes, and their connecting lymph ducts, are embedded in adipose tissue.

In vitro and in vivo investigations show that perinodal adipose tissue participates in immune responses, and has special properties that equip it to interact locally with lymphoid cells.[23] Cultured lymphoid cells stimulate lipolysis by up to threefold in explants of adipose tissue from around lymph nodes, much more than in similarly treated samples from elsewhere in the same animals.[24] Adipocytes isolated from adipose tissue from around mesenteric, omental, and popliteal lymph nodes have lower rates of spontaneous lipolysis, but release more glycerol in the presence of combinations of noradrenalin, tumor necrosis factor-α (TNF-α) and interleukins than those from elsewhere in the same depots.[25] Perinodal adipose tissue can be activated via its lymph node early in local immune response,[26] but fails to respond strongly to the endocrine conditions of fasting. Triacylglycerols in all perinodal adipose tissue studied contain more polyunsaturated fatty acids and fewer saturates than those in adipose tissue remote from nodes.[27] These properties are consistent with the hypothesis that perinodal adipose tissue provisions lymphoid cells and intervenes in the relationship between dietary lipids and immune activity by sequestering necessary fatty acids and releasing them where and when required. The interactions may be mediated by the itinerant dendritic cells (S C Knight, personal communication),[28] which frequent lymph nodes and ducts, and sometimes inexplicably acquire quite large droplets of triacylglycerols.

This intimate relationship between perinodal adipocytes and lymphoid tissue may underlie the hitherto unexplained redistribution of adipose tissue that becomes noticeable after months or years of chronic inflammation including autoimmune disease. The cytokine TNF-α seems to be involved in the selective accumulation of intra-abdominal fat and the unusual arrangement of mesenteric adipose tissue often noticed in patients with Crohn's disease.[29] The recent suggestion that obesity may sometimes be caused, or at least exacerbated, by a transmissible virus,[30] could also be rooted in the response of adipose tissue to immune stimulation.

Local interactions between adipocytes and lymphocytes may help to explain one of medicine's newest and most baffling problems: in patients who have been infected with HIV for several years, particularly if they have been treated with one or more of the drugs developed to curtail the proliferation of the virus, some adipose depots shrink to almost nothing while others expand enormously. Among the depots that enlarge are the mesentery, omentum, and "buffalo hump" around the back of the neck, all rich in lymphoid tissue, while adipose tissue not associated with lymph nodes tends to atrophy.[31] The resulting changes in body conformation, facial appearance and skin texture are very distressing, not least because HIV positive people become instantly recognisable.[32] Does the abnormally high turnover of lymphocytes associated with HIV infection[33] release signals that prompt more and more adipocytes to dance to their tune, leaving fewer to fuel other tissues in response to the endocrine conditions of fasting? If so, adipocytes controlled by the immune system would grow abnormally at the expense of "normal" adipose tissue, slowly depleting the large nodeless depots including the buttocks and thigh, then the subcutaneous layers on the arms and calves, and eventually the Bichat's pad in the cheeks and adipose tissue in the eye sockets, which are usually metabolically inert. Consistent with this hypothesis are the observations that HIV is much influenced by its hosts' cytokines,[34] retroviral infection makes dendritic cells alter their secretion of some of the cytokines to which perinodal adipocytes respond,[35] and changes the pattern of cell differentiation in bone marrow.[36]

With her newly discovered gown of many different cytokine receptors, and accomplished enough to respond with apt and varied secretions, adipose tissue is well equipped to be the belle of the ball, and may indeed attract even more partners than listed here. Meanwhile, physicians might look more favourably on conspicuous adipose tissue, and surgeons may wish to ponder the implications of putting asunder what nature has joined together.

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1 Cook KS, Min HY, Johnson D, *et al*. Adipsin: a circulating semi protease homologue secreted by adipose tissue and sciatic nerve. *Science* 1987;**237**:402–95.
2 Caro JF, Scutia, MK, Kalaczynsk, JW, *et al.* Leptin, the tale of an obesity gene. *Diabetes* 1996;**45**:1455–62.

3 Trayhurn P, Hoggard N, Mercer JG, *et al*. Leptin: fundamental aspects. *Int J Obesity* 1999;**23**(suppl 1):22–8.
4 Himms-Hagen J. Physiological roles of the leptin endocrine system: differences between mice and humans. *Crit Rev Clin Lab Sci* 1999;**36**:575–655.
5 Kelso A. Cytokines: principles and prospects. *Immunol Cell Biol* 1998;**76**: 300–17.
6 Pond CM. *The fats of life*. Cambridge: Cambridge University Press, 1998.
7 Plata-Salaman CR. Cytokines and feeding. *News in Physiological Sciences* 1998;**13**:298–304.
8 Dusserre E, Moulin P, Vidal H. Differences in mRNA expression of the proteins secreted by the adipocytes in human subcutaneous and visceral adipose tissues. *Biochim Biophys Acta—Mol Basis Disease* 2000;**1500**:88–96.
9 Mohamed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. *Int J Obesity* 1998;**22**:1145–58.
10 Marchington JM, Mattacks CA, Pond CM. Adipose tissue in the mammalian heart and pericardium: structure, foetal development and biochemical properties. *Comp Biochem Physiol* 1989;**94B**:225–32.
11 Marchington JM, Pond CM. Site-specific properties of pericardial and epicardial adipose tissue: the effects of insulin and high-fat feeding on lipogenesis and the incorporation of fatty acids in vitro. *Int J Obesity* 1990;**14**:1013–22.
12 Soltis EE, Cassis LA. Influence of perivascular adipose tissue on rat aortic smooth muscle responsiveness. *Clin Exp Hypertens Theor Pract* 1991;**A13**: 277–96.
13 Mathieson PW, Peters DK. Complement, adipocytes and the kidney. *Nephrology* 1996;**2**:S22–6.
14 Engeli S, Gorzelniak K, Kreutz R, *et al*. Co-expression of renin-angiotensin system genes in human adipose tissue. *J. Hypertens* 1999;**17**:555–60.
15 Bennett JH, Joyner CJ, Triffitt JT, *et al*. Adipocytic cells cultured from marrow have osteogenic potential. *J Cell Sci* 1991;**99**:131–9.
16 Grimble JM, Robinson CE, Wu X, *et al*. The function of adipocytes in the bone marrow stroma: an update. *Bone* 1996;**19**:421–8.
17 Beresford JN, Bennett JH, Devlin C, *et al*. Evidence for an inverse relationship between the differentiation of adipocytic and osteogenic cells in rat marrow stromal cell-cultures. *J Cell Sci* 1992;**102**:341–51.
18 Kajkenova O, Lecka-Czernik B, Gubrij I, *et al*. Increased adipogenesis and myelopoiesis in the bone marrow of SAMP6, a murine model of defective osteoblastogenesis and low turnover osteopenia. *J Bone Min Res* 1997;**12**: 1772–9.
19 Bathija A, Davis S, Trubowitz S. Bone marrow adipose tissue: response to acute starvation. *Am J Haematol* 1979;**6**:191–8.
20 Thouzeau C, Massemin S, Handrich Y. Bone marrow fat mobilization in relation to lipid and protein catabolism during prolonged fasting in barn owls. *J Comp Physiol [B]* 1997;**167**:17–24.
21 Bennett BD, Solar GP, Yuan JQ, *et al*. A role for leptin and its cognate receptor in hematopoiesis. *Curr Biol* 1996;**9**:1170–80.
22 Gainsford T, Willson TA, Metcalf D, *et al*. Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells. *Proc Natl Acad Sci U S A* 1996;**93**:14564–8.
23 Pond CM. Physiological specialisation of adipose tissue. *Prog Lipid Res* 1999;**38**:225–48.
24 Pond CM, Mattacks CA. Interactions between adipose tissue around lymph nodes and lymphoid cells in vitro. *J Lipid Res* 1995;**36**:2219–31.
25 Mattacks CA, Pond CM. Interactions of noradrenalin and tumour necrosis factor-α, interleukin-4 and interleukin-6 in the control of lipolysis from adipocytes around lymph nodes. *Cytokine* 1999;**11**:334–46.
26 Pond CM, Mattacks CA. In vivo evidence for the involvement of the adipose tissue surrounding lymph nodes in immune responses. *Immunol Lett 1998;63:159–67*.
27 Mattacks CA, Pond CM. The effects of feeding suet-enriched chow on site-specific differences in the composition of triacylglycerol fatty acids in adipose tissue and its interactions in vitro with lymphoid cells. *Br J Nutr* 1997;**77**:621–43.
28 Hill S, Edwards AJ, Kimber I, *et al*. Systemic migration of dendritic cells during contact sensitization. *Immunology* 1990;**71**:277–281.
29 Desreumaux P, Ernst O, Geboes K, *et al*. Inflammatory alterations in mesenteric adipose tissue in Crohn's disease. *Gastroenterology* 1999;**117**:73–81.
30 Dhurandhar N, Kulkarni PR, Ajinkya SM, *et al*. Association of adenovirus infection with human obesity. *Obesity Res* 1997;**5**:464–9.
31 Safrin S, Grunfeld C. Fat distribution and metabolic changes in patients with HIV infection. *AIDS* 1999;**13**:2493–505.
32 Wanke C. Epidemiological and clinical aspects of the metabolic complications of HIV infection: the fat redistribution syndrome. *AIDS* 1999;**13**: 1287–93.
33 Kaur A, Rosenzweig M, Johnson RP. Immunological memory and acquired immunodeficiency syndrome pathogenesis. *Philos Trans R Soc Lond B* 2000; **355**:381–90.
34 Poli G. Cytokines and the human immunodeficiency virus: from bench to bedside. *Eur J Clin Invest 1999;29:723–32*.
35 Kelleher P, Maroof A, Knight SC. Retrovirally induced switch from production of IL-12 to IL-4 in dendritic cells. *Eur J Immunol* 1999;**29**:2309–18.
36 Kelleher P, Williams NJ, Knight SC. Interleukin-12 administration in retroviral infection of mice increases the potential to produce functional dendritic cells from bone marrow stem cells. *Immunol Lett* 1999;**65**:51–4.