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LYMPHSPIRATION

ADIPOSE TISSUE AND LYMPHATIC FUNCTION: IS THERE MORE TO THIS STORY ESPECIALLY FOR TROPICAL DISEASES ?

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Two decades ago, it seemed timely to capture the interest of Dermatologists in adipose tissue. The functions of adipose tissue were summarized at that time (*Table 1*).

Of special interest was the role of blood supply and lymphatic drainage. Sergio Curri in Milan was showing a similar interest as was the cosmetic industry, gripped by the marketing potential of cellulite. L'Oreal brought us together, and the result was a monograph on "Cutaneous Adipose Tissue" (1). This publication and a later update (2) emphasized the special features of the cutaneous organ.

Some of the points reviewed were as follows:

Fat cells, in the embryo and in the rabbit ear chamber studies of the Clarks in the US, develop at sites distant from where the lymphatics remove lipid but where a slow flowing capillary bed is rich in vasculature.

Unlike blood vessels, which form a rich capillary network within the fat lobules, lymphatics are not found within these fat lobules.

Lymphatics travel through the tough connective tissue that surrounds the neurovascular complexes of cutaneous nerve, artery, vein, and lymphatic in the septa that support the subcutaneous fat lobules.

Macromolecules cleared more slowly in these Oxford studies when inoculated into adipose tissue in the human and in the pig.

The literature on lipoma with its occasional origin from hematomas was also reviewed by Ryan and Curri (1) as an interesting acquired local phenomenon of adipose excess.

Some other organs acquiring fat deposits are without lymphatics, e.g., bone marrow and the brain.

In lymphedema, the tissues accumulate fat, a feature well illustrated by both Brorson and by Cluzan in the 20th International Congress of Lymphology symposium in September 2005. The latter presentation emphasized how little we know about this relationship because it is unpredictable and poorly correlated with swelling. In a few patients it responds to removal of edema and compression. Ryan and Curri (1) also referred to its local disappearance in response to pressure from garments and even from short-term pressure following leaning on a cold railing.

The link was thus emphasized between fat accumulation and impaired lymphatic function.

Since that time new studies have shed fresh light on this relationship. These involved deposition of subcutaneous fat in edematous regions in a mouse model with an inactivating mutation of VEGFR-3 (3) as well as in other animal models of congenital and acquired lymphedema. Furthermore,

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TABLE 1
Functions of Adipose Tissue

Energy provision
Thermoregulation and insulation
Pressure dispersion
Body contour and display of shape
Endocrine and cytokine production
Stem cells

TABLE 2
Features of HIV Adipose Tissue Redistribution

Breast hypertrophy and thinning of thighs and buttocks
Accumulation of visceral abdominal fat
Buffalo hump
Lipodystrophy induced by protease inhibitors

prominent obesity has been associated with abnormal lymphatic patterning and function in adult mice haploinsufficient for *Prox1*, a key transcription factor in lymphatic development (4).

Moreover, a long-standing theme in the literature on new vessel growth, resurrected by studies of Vascular Endothelial Growth Factor (VEGF), is the role of hypoxia. One way hypoxia leads to improved sources of energy is to induce adipose tissue. Inflamed and repairing skin demands high oxygen levels. Its vasculature exceeds its needs when intact and at rest but injury switches on dilation of the vascular bed, which then meets these demands in the short term. Long-term needs require a new vascular organ, which is granulation tissue. The latter is partially replaced by adipose tissue when oxygen demands recede. One mechanism of control through hypoxia was described by Yun et al (5).

Pond and her team of workers (6,7) on adipose tissue have repeatedly recorded that fat metabolism differs from one adipose organ to another. It would seem, therefore, that cytokine, adrenergic receptor control, and endocrine control are also tissue-specific. Their hypothesis is that organs requiring certain specific fatty acids develop the means to control that delivery from local fat depots. Her work with Mattocks and others has opened up new perspectives on fat utilization. In particular, this group has shown in a series of studies a dependence of lymph nodes on local fat metabolism: "Chronic inflammation can, over 6 weeks, induce the formation of more mature adipocytes around the experimentally stimulated lymph node, which can lead to local hypertrophy of the adipose tissue, especially in animals fed on high fat diets" (8).

Obesity is a state of chronic inflammation in which a significant number of lymphocytes can be detected in the stroma of white adipose tissue. In one study of epididymal fat, the lymphocytes were 70% natural killer gamma-deltaT and NKT cells, while in inguinal fat there were high levels of α/β T and B cells (9).

In certain diseases such as Crohn's disease in which lymphoid tissue and adipose tissue are in excess and in patients and in experimental animals with lymphatic functional impairment, the induction of adipose tissue by cytokines from lymphoid tissue has been postulated (10). Other examples may have a definable site-specific relationship contributing to disease by either excess or deficiency of certain fatty acids, including human immunodeficiency virus (HIV)-associated adipose redistribution (*Table 2*) and the periorbital fat in the exophthalmos of Graves disease (as discussed

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by Brorson in this Symposium). The modification of lipogenesis and lipolysis in HIV/AIDS and its therapy with protease inhibitors is due in part to the effect of tumor necrosis factor α and to interleukins 1 and 6 (11,12). The loss of adipose tissue in cachexia has also been attributed to an altered cytokine profile involving TNFα.

Tropical Diseases

Ryan (13) has suggested that tropical diseases may prove to be a resource for fat cell research and has asked, "Does the filarial worm, or its symbiotic bacterium *Wolbachia*, need those fatty acids normally generated only for the lymph nodes of the groin and genital region, and is the adipose tissue therein more than a passive filler space occupying the flexures?" One cannot ignore the TNF and interleukin profile of different adipocyte sites in researching the cytokine profile of the response to and secretion by many tropical infections.

Does *Mycobacterium* ulcerans or the inflammatory response which causes *Buruli* ulcer (14) need or lack specific fatty acids found only in adipose tissue? Does the periadnexal (hair and sweat gland) site of the initial lesion use, or fail to use, its periadnexal fat as a resource for the bacteria in the initial inoculation from biting insects? Is it relevant to the Lymphologist that the affected limb often shows brawny edema?

The low temperature needs of many types of *Mycobacterium* are reminiscent of hibernating animals and of the adaptation of skin adipose tissue and skin dendritic cells to a lower temperature than in core organs. Research into localizing factors in leprosy, and in many other skin diseases that are immunologically induced, has often emphasized cooling as a determining factor of skin pathology (15). Pond points out the importance of the melting point of fat in its availability for cell metabolism and how, by incorporation of different fatty acids, this property may be altered (8).

The concept that tropical disease research should examine the adipocyte has received a boost from recent studies of Chagas disease in which the cardiac muscle has a special relationship with adipocytes as a source of fatty acids, and this feature may be used to advantage by the trypanosome (16)?

It is concluded that the accumulation of fat cells in lymphedema deserves further study along the lines that it may be a response to the needs of improved local immunosurveillance when flow to lymph nodes is impaired. Hypoxia and cooling may be determinants. The role of growth factors and cytokines as mediators of this interaction is likely.

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