# Research on adipose tissue and the first 25 years of the Journal of Lipid Research

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When publication of the first issue of the *Journal of Lipid Research* was still in the planning stage, a small group (Ahrens, Bragdon, Zilversmit, and myself) had repeated discussions, debating the issues that surround the formation of a new journal. Was a new journal needed? If needed, what format should be followed? How should it be funded? One nightmare was that after a few years, there would be no need for the journal. We all realized that the 1950s had been an exciting time for the development of lipid chemistry and lipid metabolism. There had been important developments due in large measure to the availability of new separation methods by chromatography, ultracentrifugation, and electrophoresis. The most pessimistic among us predicted that after some flurry of activity, the field of lipid metabolism would "die out" and we would then bear the blame for having fractionated research reporting by having a special journal devoted to lipids, away from its natural home in biological chemistry. This glum foreboding was not realized; a vigorous field of lipid research has continued to grow for 25 years. It appears that the *Journal* will live on; however, the subdivisions that make up lipid research come and go, often depending on the appearance of new methods and how quickly they are exploited. Thus, I was curious to determine whether the study of adipose tissue represented some transient fad within lipid metabolism or whether it was also being sustained throughout the 25 year history of the journal.

I learned by examining all issues of the *Journal* that the nature of research on adipose tissue as reported in the *Journal* has varied over time, but the popularity of this subdivision of lipid metabolism is intact. Eight percent of *Journal* articles deal with adipose tissue now and this has been the case throughout most of the *Journal's* history. Dealing with such small numbers of publications, there is considerable year-to-year variation, but an average across any collection of several years, shows that the 8% is well maintained. It was of interest to me to note how representative of the field, and often pace-setting, the publications on adipose tissue in the *Journal of Lipid Research* have been. The "micro" review that follows describes the growth of research on adipose tissue from 1960–1985 with nearly all of the references from the *Journal of Lipid Research*. Highlights are reviewed and new areas are suggested for further research utilizing adipose tissue.

## Adipose tissue and the *Journal of Lipid Research*

In 1959, the first issue of the newly founded *Journal of Lipid Research* carried an article with these words: "Adipose tissue is now considered to be a metabolically active tissue containing most of the enzymes required to carry on reactions common to other mammalian tissues" (1). This speaks for a pre-history in which adipose tissue was thought to be less than a complete mammalian tissue and that was indeed the case. Adipose tissue was of course known to be the site for the storage of triglyceride, but it was believed to be metabolically quite inert and to serve as a cushion, insulator, or as a substance of great cosmetic importance, rounding out the skin to protect one from unsightly wrinkles. It was not until the decade just prior to the birth of the *Journal of Lipid Research* that adipose tissue was credited with more fundamental functions. Some of the most significant observations in the development of adipose tissue research since that time are found in the pages of the *Journal* between 1959 and 1985.

## Adipose histogenesis

At the dawn of scientific interest in adipose tissue, nearly 100 years before the publication of the first issue, there was a lively debate as to the cellular origin of adipocytes. Details are given elsewhere in an excellent review by Wasserman (2). Flemming was quite convinced that the precursor to the adipocyte is a connective tissue cell, no different from the common fibroblast occurring throughout the organism. On the other hand, Toldt, accumulated evidence in favor of the precursor being a special cell occurring in separate collections even in the embryo. Work in this area utilized light microscopy and by this technique, the disagreements could not be fully settled. The pages of the *Journal of Lipid Research* were not a central arena for these debates. Since the work began so long before the *Journal* appeared, other journals

had become the more usual place for publication of morphological observations. Recent advances in the culture of adipocytes have provided new knowledge on adipose histogenesis. This work has been abundantly documented in the *Journal of Lipid Research.*

It is now clear that the stromal-vascular compartment of adipose tissue (the entire tissue minus mature lipid-laden adipocytes) contains cells which are indistinguishable from fibroblasts by any known morphologic criterion, yet these cells will differentiate into mature adipocytes. The methods used for such studies have been presented in the *Journal* (3–5) although the most detailed current failure to find morphological differences between the precursor adipocytes and the fibroblast appeared elsewhere (6). Fibroblasts originating from the rat tail will always grow to fibroblasts in tissue culture. However, fibroblasts harvested from the stromal-vascular compartment, which have exactly the same appearance as tail fibroblasts, will in some instances grow into mature adipocytes with insulin receptors and will produce lipoprotein lipase; in short, they are cells that fulfill any reasonable criteria that one would wish to establish for adipocytes. It would seem as though the Flemming-Toldt disagreement cannot be solved on morphologic grounds alone. There is truth in the contention of each side—adipocytes do come from cells that are morphologically indistinguishable from fibroblasts, but not every fibroblast can, even under the most favorable circumstances, develop into an adipocyte. The distinguishing features or markers are subtle and yet to be discovered.

### Adipose composition for nutritional evaluation

Adipose tissue is the larget lipid depot and although some components of the tissue may turn over quickly, most of the depot is in very slow exchange with dietary lipids (7). When this was shown to be the case, it became evident that triglyceride fatty acids or other lipid-soluble components of adipose lipid may give information on the state of body storage of these substances and hence nutritional status. In particular, the fatty acid composition of adipose tissue reflects dietary practices with considerable fidelity. Key articles in the *Journal of Lipid Research* (8–11) substantiated this observation.

Lipid-soluble agents such as insecticides or drugs may also find their way to adipose lipid. There has been continued interest in the use of adipose tissue needle aspiration or biopsy to sample the body storage of these substances. A recent issue of the *Journal* carries new information on adipose tocopherol in normal and in abetalipoproteinemic subjects (12). Since various polyunsaturated acids present in dietary fat may play important roles in prostaglandin synthesis as well as in the promotion or inhibition of atherogenesis, the technique of adipose aspiration for lipid analysis will most likely be of continuing interest to epidemiologists as well as to laboratory investigators.

### Metabolism of adipose tissue

The history of the *Journal* has been coincident with a period rich in investigations of the metabolism of adipose tissue in man and animals. It is now well recognized that the control of fatty acid release by the modulation of carbohydrate metabolism is "fine-tuned" in adipose tissue. Insulin action, for a time early in the *Journal's* history best measured by bioassay with adipose tissue, is a control mechanism of central importance. The study of hormone-mediated lipolysis in adipose tissue has excited the interest of many investigators and the pages of the *Journal* attest to their productivity. Indeed a very early and also a very recent volume carry comprehensive, expertly documented reviews of this subject (13, 14). Between the two reviews are dozens of significant contributions to the development of our present understanding of how adipose tissue operates to store energy and to control the flow of substrate for energy-consuming tissues. One is hard pressed to pick the "most significant" contributions to this area; hopefully, a few reminders will convince the reader of the pre-eminence of the *Journal of Lipid Research* in this field.

The first volume of the *Journal* carried a paper which demonstrated that lipoprotein lipase was released from adipose tissue when heparin was included in the incubation medium (15). Convincing evidence was provided some years later for the existence of major metabolic pathways in human adipose tissue, as had been found in various experimental animals (16). The second messenger hypothesis found support and was extended to adipose tissue by demonstrating the importance of adenylate cyclase activity in adipocytes (17, 18). The findings on adenylate cyclase in animal tissues were extended to human tissue in the *Journal* (19). More recently, a special regulatory role for nucleotides was shown when the action of GTP in modifying lipolysis in human tissue was clearly demonstrated (20). A landmark study for those interested in experimental obesity was the observation that deranged storage of lipid in adipose tissue was present in the first week of postnatal life of the Zucker obese rat, before hyperphagia had occurred (21).

### Cellularity of adipose tissue

I was pleased to have my work on methods for determining adipocyte size and number in man and animals published in the *Journal of Lipid Research* in 1968 (22). Previous work utilizing histologic methods or the determination of DNA had not been in wide use. Following the development of new methods, the measurement of cellularity became an important addition

to the tools available for the study of adipose tissue. A variety of new methods and useful alterations of older methods were published in the *Journal* (23–27). The new methods were used to examine the effect of growth and development on adipose cellularity (28) and the cellular changes found in various types of experimental obesity (29, 30). A particularly active area of investigation has been the influence of cell size on metabolism and hormone action. This has been examined in several species under different conditions. It is clear that nutrition as well as age or cell size can have important effects (31), and there are specific effects of age separate from nutrition or cell size (32). But cellularity measures can add another important dimension to the analysis of adipose function, inasmuch as one can demonstrate independent effects of cell size that are not related to the age or the nutritional status of the animal (33). In many studies published in the *Journal,* the variations in these effects under the influence of different hormones have been explored. It is now certain that cell size can have some modulating influence on adipocyte metabolism. In general, larger cells are more likely to have brisk lipolysis, but sluggish lipogenesis and esterification. This combination of effects acts as a brake on further lipid accumulation. The details of these findings along with possible mechanistic explanations have filled many pages of the *Journal.* As further information is obtained, the transduction of the signal from receptor to second messenger to final site of action and the tangled skein of effects related to cell size, age, and nutritional status will undoubtedly be unravelled. Adipose tissue will most likely remain a prime target for these investigations, since so much is already known about the interrelations of these phenomena in this tissue.

In recent years, a number of articles in the *Journal* have stressed the importance of alpha adrenoreceptors in adipose tissue which although stimulated by catecholamines, are anti-lipolytic (34–36). Because excess storage of fat in different sites may carry greater or lesser risks for cardiovascular disease and diabetes, depending on which site is favored, investigators have been particularly interested in regional differences in cellular function. It has been shown that catecholamine receptors may differ depending upon the site from which the adipose tissue was removed. There would seem to be no end to the possibilities of studying important physiologic and health-related issues by exploring the metabolism of adipose tissue and the *Journal of Lipid Research* continues to be a prime journal for the reporting of these findings.

**The next twenty five years**

It is fruitless to predict the directions of research; the most enduring contributions are likely to be totally unforeseen. What may be of more interest is to note some major questions that confront investigators at this time. The search for answers will surely occupy our attention in the immediate future.

*1. Is adipose tissue an active or passive participant in the control of energy metabolism?* Adipose tissue has a remarkable set of adaptations which make it compliant, even subservient, to nutritional demands. It can either be drained of calories or store an enormous surfeit of triglyceride. A casual examination of the behavior of the adipose depot makes one convinced that it plays only a *passive* role in energy metabolism. The most telling argument for an *active* role comes from consideration of the cellularity of the tissue. Whatever arguments may be made for or against the importance of cell size and cell number in the development of obesity, there is general agreement that once adipocytes store triglyceride, they rarely, if ever, de-differentiate or disappear. Even with prolonged, severe starvation, the unfilled cells persist (37). The absence of a turnover of cells under these circumstances suggests that the enduring presence of empty cells may be an important factor in the inevitable re-accumulation of fat when calories become freely available. Whether this idea is the poetic license of one who has dealt with the tissue over many years or whether some mechanism will be uncovered which demonstrates how this might occur is still under debate. If a mechanism exists whereby adipose tissue autoregulates size and thereby contributes to energy metabolism, then a study of this mechanism will be of central interest to those who attempt to understand why so many individuals readily become obese and why dietary treatment is rarely successful in removing this hazard to health.

*2. What factors control adipocyte replication?* Since adipocytes do not disappear and it may be, as conjectured above, that they have more than a passive role in energy metabolism, it becomes a matter of considerable moment to elucidate the factors or events that lead to the achievement of a particular cell number. It is relevant to note that there are marked regional differences in the replication of adipose cells, a phenomenon most extensively studied in the rodent. Thus, lipectomy of portions of the epididymal pad will not lead to regrowth of the lost tissue (38), but lipectomy in the inguinal subcutaneous aera leads to a slow, yet precise regrowth of all that is lost (39). High-fat feeding in some rat strains produces a marked increase in food intake and it is abundantly clear that this leads to the development of new adipocytes, most particularly in the perirenal, retroperitoneal depots (40). In man, the data now seem incontrovertible that obesity in one site is more hazardous to health than in another. Abdominal fat enlargment makes for a far greater risk for cardiovascular disease

and stroke than fat enlargement in other depots (41). These observations speak for sharp regional differences in histogenesis, metabolism, and disease consequences of different fatty depots.

The explanation for such differences is not at hand. There is some evidence in rodents for true clonal differences in adipocytes from different sites (42). Whether a clonal difference or regional growth-promoting differences external to the cell will be found most significant is yet to be learned. The new methods for adipocyte tissue culture will assist in the search by permitting the study of cells from different sites grown in culture under a variety of conditions. This approach is an obvious next for the "drawing boards" and thence into the hands of the editor of the *Journal of Lipid Research*. Whatever new directions are followed in forthcoming work on adipose tissue, I am quite convinced that future issues of the *Journal of Lipid Research* will carry a major share of the new findings, published as always in a convenient format and with a high standard of editing.

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