The adipocyte life cycle hypothesis

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ABSTRACT

The adipocyte life cycle hypothesis states that the metabolic properties of an adipocyte vary predictably during its life cycle: that as an adipocyte matures, it accumulates triacylglycerol (triglyceride) and becomes larger; that the rates of triacylglycerol synthesis and lipolysis are matched within adipocytes and that larger adipocytes, in general, have greater rates of triacylglycerol synthesis and, concurrently, greater rates of lipolysis and, therefore, larger adipocytes have greater rates of transmembrane fatty acid flux; and that the secretion of cytokines can also be related to adipocyte size with larger adipocytes having a more unfavourable profile of cytokine secretion than smaller adipocytes. Adipocyte location is an important modifier of this relationship and the favoured sites of adipocyte proliferation are a function of gender and the position within the life cycle of the organism at which proliferation occurs. The adipocyte life cycle hypothesis posits that the metabolic consequences of obesity depend on whether expansion of adipose tissue is achieved primarily by an increase in adipocyte number or adipocyte size. This hypothesis may explain a variety of previously unanswered clinical puzzles such as the vulnerability of many peoples from South East Asia to the adverse metabolic consequences of obesity.

INTRODUCTION

The adipocyte life cycle hypothesis relates adipose tissue function to hepatic triacylglycerol (triglyceride) and apoB (apolipoprotein B) metabolism and so attempts to integrate plasma FA (fatty acid) flux to the pathophysiology of the commonest atherogenic dyslipoproteinaemia: hypertriglyceridaemia hyperapoB. In brief, this hypothesis states that the metabolic properties of an adipocyte are related both to its position within its own life cycle and to its position within the life cycle of the organism. The core insights are that adipocyte size, number and site are key determinants of total hepatic FA flux and, therefore, key determinants of VLDL [very-LDL (low-density lipoprotein)] secretion.

The conventional position is that increased lipolysis due to ‘insulin resistance’ is responsible for the increased release of FAs from adipose tissue. The release from visceral adipose tissue, in particular, is excessive and uncontrolled because the FAs are delivered directly to the liver. Synthesis of triacylglycerol within visceral adipose tissue is almost never mentioned and, to the extent it is insulin dependent and the adipocyte is ‘insulin resistant’, presumably would be diminished. As will be detailed below, we believe this is not a satisfactory answer. On the contrary, we believe that the metabolic consequences of obesity depend on whether it was achieved principally by an increase in adipocyte size or by an increase in adipocyte number and, if by the latter, where and what type of adipocytes were produced?

At the outset, we want to acknowledge that the studies of Jensen and his colleagues [1–3] triggered this reformulation of views we held previously [4]. They, of course, bear no responsibility for the outcome.

Key words: adipose tissue, apolipoprotein B (apoB), fatty acid metabolism, hypertriglyceridaemia, obesity.

Abbreviations: apoB, apolipoprotein B; BMI, body mass index; ER, endoplasmic reticulum; FA, fatty acid; HSL, hormone-sensitive lipase; LDL, low-density lipoprotein; LPL, lipoprotein lipase; TNF-α, tumour necrosis factor-α; VLDL, very-LDL.

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Figure 1  FA delivery to the adipocyte

(1) LPL molecules on the endothelial surface of the capillary bind to a chylomicron and hydrolyse the triacylglycerol (Triglyceride) portion of the particle. (2) FAs released by this process then enter the adipocyte and are esterified into triacylglycerol or bind to albumin with the capillary space becoming part of the albumin–FA complex. These can either enter the adipocyte or systemic circulation. (3) Triacylglycerol within the adipocyte can be hydrolysed to FAs by HSL or triacylglycerol lipase. These FAs are either re-esterified within the adipocyte or released into the capillary to bind with albumin. Because the venous-arterial gradient in the FA–albumin pool is always positive only triacylglycerol-rich lipoproteins, such as chylomicrons, can contribute to a positive influx of FAs into the adipocyte.

THE ADIPOCYTE LIFE CYCLE: THE RELATIONSHIP BETWEEN ADIPOCYTE SIZE, TRANSMEMBRANE FA FLUX AND CYTOKINE SECRETION

As a rule, the life cycle of the adipocyte is mirrored by its size. Adipocytes accumulate triacylglycerols during their life cycle, up to a maximum, after which proliferation is triggered. Accordingly, in general, larger adipocytes are more advanced in their life cycle than smaller ones. Moreover, the metabolic activities of the adipocyte vary predictably during their life cycle and therefore are related to their size. The first and most fundamental of these we will consider is FA flux. FA flux can be described in several ways and it is necessary to disentangle them. We will begin with FA flux into and out of the adipocyte and then consider FA fluxes across adipose tissue in toto.

Transmembrane adipocyte FA flux

Dietary FAs are, by far, the major source of triacylglycerol within adipocytes [5]. They enter the adipocytes either as FAs released from the triacylglycerol-rich lipoproteins or from FAs within the albumin–FA pool. These two routes make up transmembrane FA influx into adipocytes (Figure 1). FAs from the triacylglycerol-rich lipoproteins can either enter adipose tissue directly [6] or enter the albumin–FA pool, some of which will enter the adipocyte and some of which will enter the systemic circulation [5]. The portion that enters the systemic circulation is variable and could constitute an important mechanism of FA delivery to the liver. Moreover, since venous FA concentration always exceeds arterial FA concentration, only entry from the triacylglycerol-rich lipoproteins can produce positive transmembrane FA influx into the adipocyte [7]. Hydrolysis of intracellular triacylglycerols by HSL (hormone-sensitive lipase) and triacylglycerol lipase [8] produces FAs of which a variable number are re-esterified to form triacylglycerol (for review, see [9]). Transmembrane efflux of FA from the adipocyte is, therefore, the difference between the total FA generated by HSL and triacylglycerol lipase minus the portion that is re-esterified into triacylglycerols.

Net FA flux across the adipocyte membrane denotes the absolute change per day in the total mass of FAs within the adipocyte. This may be net positive, if adipose tissue mass is increasing, net negative, if adipose tissue mass is decreasing, or net neutral, if adipose tissue mass is constant. Whichever of these states exists, net FA flux, per day, will always be less than transmembrane FA flux. This is the first key point. Any change in the volume of a single cell can be no more than the difference between influx and efflux and therefore must necessarily be less than the greater of the two. Therefore net change is less than directional transmembrane flux. Furthermore, over the course of any single day, the change in volume of any single cell must be small indeed.

The second point is that, although transmembrane FA influx and efflux must be close in actual amount, they are dissociated in time. In the post-prandial period, there will
be net influx of FA into the adipocyte, whereas in the post-absorptive period there will be a net efflux of FAs out of the adipocyte [10]. It follows that FA flux to the liver as FAs bound to albumin will be maximal in the post-absorptive period.

**Remnant hepatic triacylglycerol flux**

However, there is yet another mode to deliver FA to the liver, namely the FAs still present as triacylglycerol within the chylomicron particle, which were attached to the capillary endothelium and had been acted on by LPL (lipoprotein lipase), but were then released from the endothelium back into the capillary space. These are the remnant particles of the original triacylglycerol-rich lipoproteins.

The veins draining adipose tissue and muscle, therefore, contain chylomicrons that have not been modified by LPL as well as remnant lipoprotein particles that have.

The distinction matters because the particles that are partially depleted in triacylglycerol, the remnant particles, will be rapidly taken up by the liver [11,12] and thus represent an important route of delivery of FAs to the liver. If chylomicron remnants are released prematurely, they will contain more triacylglycerol than normal. Little is known as to the determinants of premature release of triacylglycerol-rich particles except that remnants correlate with plasma triacylglycerol levels, one increasing with the other, suggesting that higher VLDL triacylglycerol levels might occupy increasing amounts of endothelial LPL resulting, perhaps, in less secure attachment of chylomicrons to the available LPL [13,14].

**Relationship of transmembrane adipocyte FA flux with adipocyte size and site**

Studies in a variety of species have demonstrated that, as adipocytes increase in size, both synthesis and lipolysis become more active. Larger adipocytes synthesize triacylglycerols more rapidly than smaller adipocytes, but they also release FAs more rapidly than smaller ones [15–18]. For example, studies in rats have consistently demonstrated that larger adipocytes have a greater rate of basal lipolysis and triacylglycerol synthesis than smaller adipocytes [8]. In humans, Bjorntorp et al. [19] have demonstrated that the larger abdominal adipocytes of obese individuals had greater glucose incorporation into triacylglycerol than did the smaller adipocytes. Thus larger adipocytes are characterized by higher transmembrane FA fluxes across their cell membranes than smaller adipocytes.

The mechanisms connecting input and output have not been elucidated, perhaps because their co-linearity has not been appreciated. All that would be necessary is an increase in the mass and/or activity of the key enzymes and transporters as the cell continues to increase in size. Indeed, key enzymes in lipid synthesis and hydrolysis, such as fatty acid synthase, HSL, LPL and GLUT4, have elevated activity and mRNA levels in larger adipocytes compared with smaller adipocytes [20]. Moreover, microarray analysis has also revealed that the genes required for lipid metabolism and differentiation are up-regulated in larger adipocytes [21].

However, other mechanisms could link influx and efflux. Substrate accessibility could be a major determinant with the newly synthesized triacylglycerol being in closest proximity to the lipase: the more triacylglycerol just synthesized, the greater the presentation of substrate to HSL. Whatever the mechanisms, it is the relationship that matters at the moment: whenever synthesis increases, so does lipolysis; whenever lipolysis increases, so does synthesis.

This formulation differs from the conventional one that characterizes adipocytes solely by the rates at which they release FAs with a greater hydrolytic capacity being associated with greater risk of the metabolic complications of dysglycaemia or dyslipidaemia. However, sustained changes in lipolysis could never occur dissociated from sustained changes in synthesis. Otherwise, the mass of triacylglycerol within the adipocyte would soon be depleted. Subjects in whom increased lipolysis from omental adipocytes is claimed to be the cause of their atherogenic dyslipoproteinaemia are fat not thin. In this instance, common experience contradicts, and should trump, conventional wisdom.

Several studies have related adipocyte size and adverse metabolic profiles. Adipocyte size was the only feature of body composition that distinguished healthy lean men from lean men with type IV or type V hyperlipoproteinaemia in a study by Bernstein et al. [22]. In a similar study, individuals with Type II diabetes or dyslipidaemia had larger subcutaneous adipocytes than control subjects [23]. Perivisceral fat cell size strongly predicted plasma apoB levels in obese men and women ($r = 0.95$ and $0.62$ respectively) [24]. Correlations have also been found in healthy men and women between femoral fat cell size and fasting plasma insulin, triacylglycerols and total cholesterol to HDL (high-density lipoprotein)-cholesterol ratio [25].

To summarize, as more FAs are presented to the adipocyte in the form of higher plasma triacylglycerol levels, the challenge is to try to store more fat per cell. The adipocyte adapts by increasing the potency of its metabolic processes: larger fat cells will take up more FAs, because they synthesize more triacylglycerols more rapidly. They will therefore be able to clear a greater mass of triacylglycerols from the blood in the post-absorptive period. The normal clearance process will be amplified, but so necessarily will release. Excess leads to excess. Increased intake into the organism leads to increased intake into the adipocyte and that leads to increased output from the adipocyte.
Regional variation in the relationship between adipocyte size and triacylglycerol synthetic capacity and triacylglycerol hydrolytic capacity

Smaller adipocytes have a lower triacylglycerol (TG) synthetic capacity and triacylglycerol hydrolytic capacity compared with larger adipocytes. Thus larger adipocytes have a greater daily transmembrane FA flux. This relationship is shifted to the left in upper-body compared with lower-body adipocytes. This results in larger transmembrane FA fluxes at any given adipocyte size.

Because input and output from the adipocyte are dissociated in time, the increase in FA transmembrane cycling leads to increased FA flux to the liver and then to an increase in hepatic apoB secretion [26]. As absolute triacylglycerol clearance by adipose tissue increases, so does triacylglycerol secretion by liver – and so the cycle is created and continues.

Relationship between transmembrane FA flux and adipocyte size

All adipocytes are not the same. Tchkonia and her co-workers [12] have shown that pre-adipocytes produce two functionally different adipocyte prototypes that characteristically predominate at different sites. One displayed greater replicative potential with greater evidence of differentiation and resistance to TNF-α (tumour necrosis factor-α)-induced apoptosis than the other. We presume this first prototype would demonstrate a more favourable relationship between size and function, that is transmembrane FA flux would be less at the same size as the other. In addition, the proportion of the two prototypes differed by site, with more of the more functional prototype produced from pre-adipocytes obtained from abdominal subcutaneous adipose tissue than from omental adipose tissue. We denote proliferation of adipocytes from the first as primary or lower-body adipocyte proliferation and proliferation of adipocytes from the other as secondary or upper-body adipocyte proliferation (Figure 2). At the same size, transmembrane FA flux would be greater in upper-body adipocytes than in lower-body adipocytes.

The findings by Jensen and his co-workers [2] support this division. They showed that upper-body adipocytes were responsible for most triacylglycerol clearance and that triacylglycerol clearance was linked to FA flux. This was the case even in women characterized by lower-body obesity [3]. This dissociation between where triacylglycerols are cleared and where they are primarily accumulated was, in fact, the challenge that initiated our present line of thought. Our hypothesis is that the relationship between size and function differs between these two prototypes with upper-body adipocytes reaching the heights of their metabolic potential earlier than lower-body adipocytes.

Relationship between cytokine secretion and adipocyte size

Adiponectin and TNF-α, two of the multitude of proteins secreted by adipocytes, appear to play key roles in the pathophysiology of insulin resistance and dyslipidaemia (for review, see [27]). In the case of these two peptides, there is also a predictable relationship between their secretion and adipocyte size: younger smaller adipocytes secrete more adiponectin than larger older ones, whereas larger older adipocytes secrete greater amounts of TNF-α [28–30]. Thus adipocyte size also correlates with the pattern of cytokine secretion: more benign for mid-size adipocytes and more adverse for larger ones.

Consequences of increased adipocyte transmembrane flux

Consequences for the liver

FA delivery to liver is directly related to the amount of FA released from adipose tissue. Thus FA flux to liver is a function both of adipocyte transmembrane FA efflux and remnant release. Increased delivery of FA to liver results in increased synthesis of triacylglycerol in liver and increased secretion of triacylglycerol by liver [31], but there is more to take into account. As a nascent VLDL particle is being formed on the ER (endoplasmic reticulum), it is encircled by a molecule of apoB100, which forms its external skeleton, staying with the particle throughout its lifetime and providing the link between plasma apoB and atherogenic particle number [32]. However, more apoB molecules are synthesized than are incorporated into nascent VLDL particles, the proportion incorporated varying directly with the secretion rate, increasing as it increases and decreasing as it decreases. The relationship matters because LDL particle number is a direct function of VLDL secretion rate and increased secretion of VLDL particles is the major cause of increased plasma atherogenic particle number [33,34]. No agreement has been reached as to the determinants of the proportion of apoB molecules that form nascent VLDL particles. One school of thought relates it only to...
The prime regulatory function of the apoB lipoprotein pathway, according to this scheme, is to maintain sterol balance in the ER membrane and its role in triacylglycerol secretion represents evolutionary adaptation, occasioned by the enrichment of dietary intake of FA. The basal rate of the secretion of apoB particles is determined by the balance between cholesterol delivery from chylomicron and VLDL remnants, as well as via LDL and HDL particles plus hepatic synthesis of cholesterol, minus secretion of cholesterol in bile and bile acids per day [31]. The difference must be exported on apoB secretion and therefore variations in the processes that regulate hepatocyte sterol balance are major determinants of plasma apoB.

Increased delivery of FA increases synthesis of cholesterol ester above the basal rate and therefore increases the secretion of VLDL particles [39]. This occurs because FA and cholesterol within the ER membrane are joined by ACAT (acyl CoA:cholesterol acyltransferase) 2 to form cholesterol ester. Evidence from our laboratory and many others indicates that it is the mass of cholesterol ester that is the primary lipid determinant of the rate of secretion of apoB particles by allowing the newly synthesized apoB molecule to achieve an appropriate three-dimensional conformation and thus escape an early death by hydrolysis. Cholesterol synthesis increases to maintain the concentration of cholesterol in the ER membrane and therefore, paradoxically, increased sterol secretion results in increased sterol synthesis [26]. Increased delivery of FA leads to increased synthesis and secretion of triacylglycerol within the increased number of VLDL particles that are secreted. The net result is elevated plasma triacylglycerols and an elevated VLDL particle number, which leads to the generation of increased numbers of LDL particles, more of which are smaller and denser, containing less cholesterol than normal [40].

In this model, conceived in discussion with Dr Jacqueline de Graaf and her colleagues at the Medical Centre of Nijmegen, The Netherlands, increased delivery of FA raises apoB secretion above the basal rate, but the final plasma apoB will be determined both by the basal rate and the incremental rate due to increased delivery of FA. Thus the phenotype of hypertriglyceridaemic normapoB would correspond to a normal basal rate of apoB secretion plus the increment due to increased FA delivery to the liver, whereas the phenotype of hypertriglyceridaemic hyperapoB would correspond generally to an elevated basal apoB secretion rate plus the increment due to increased FA delivery. Obviously, the component of each (basal rate compared with FA incremental rate) is variable and much remains to be learned as to the determinants of each.

**Consequences for adipose tissue**

As we have outlined, events in adipose tissue have consequences for liver. Similarly, events in liver have consequences for adipose tissue. They are connected not just by purpose, but also by consequence. FA uptake by adipose tissue is a function of the rate of transmembrane FA influx. FA uptake by adipose tissue will also be determined by the mass of FAs liberated at the adipose endothelial surface, which will be determined in turn by the rate at which they can be taken up by adipocytes and incorporated into triacylglycerols. In this model, adipose tissue and liver are intricately and intimately interconnected, change in one leading to change in the other.

**Patterns of adipose tissue development during maturation and post-maturation**

This section will compare and contrast expansion of adipose tissue mass in males and females during and following maturation. Adipose tissue mass can increase either by an increase in the size of individual adipocytes – hypertrophy – or by an increase in their number – hyperplasia.

**Adipose tissue development during maturation**

Maturation includes the period from birth through to puberty, that is the period encompassing the full maturation of the human organism. At birth, adipocytes are small. As a percentage of total body mass, adipose tissue declines over the first 2 or 3 years of life, after which there is a gradual increase in total adipose tissue mass. Increase in cell size rather than proliferation is probably the principal mechanism for the normal increase in adipose tissue mass that occurs in the first decade of life [41].

Until puberty, body composition differs little between the two genders [42]. The sex hormones then drive development in different directions. Testosterone drives the development of muscle mass in males, whereas oestrogen spurs an increase in adipose tissue mass in females, particularly in the primary sites of adipose tissue deposition – the adipose tissue depots of the lower body. Given the dramatic change in body composition during puberty in the female, adipocyte proliferation must be the major mechanism by which this occurs (Figure 3). In males,
Development of adipose tissue in women and men

In prepubertal females, adipocytes are small. Increases in both size and number occur as adipose tissue mass expands during puberty. This expansion occurs primarily in the lower body. Thus, overall, there is low transmembrane FA flux. In post-maturation obesity (adult-onset) both lower-body and upper-body adipocytes increase in size in order to accommodate the increased storage requirements. This increases the triacylglycerol synthetic and hydrolytic capacity of the adipose tissue increasing FA flux to the liver and apoB secretion. Adipose tissue in prepubertal males is similar to prepubertal females. During puberty, there is little expansion in adipose tissue mass. With post-maturation obesity, the upper-body adipocytes increase in number and in size, leading to transmembrane FA flux and thus to the increased secretion of apoB.

There is relatively little increase in lower-body adipose tissue mass and, therefore, only very limited proliferation of primary site adipocytes [43] (Figure 3).

The rapid expansion of adipose tissue in females is programmed, driven by oestrogen-induced adipocyte proliferation [44], but the period of expansion lasts only a few years; it represents a burst of proliferation that soon ends. The multiplication of adipocytes in the normal pubertal female is not driven by excess dietary intake. On the contrary, dietary intake must increase in the female to support its development just as dietary intake must increase in the male to support the development of muscle.

In summary, the ‘normal’ pattern of development is that adipose tissue mass expands markedly in females during maturation and only slightly in males. In both genders, if energy balance is maintained, adipose tissue mass then remains stable. The normal expansion of adipose tissue mass during maturation is driven by genes, not by behaviour. Whatever increase in energy intake that occurs is secondary to the primary drive to expand adipose tissue mass. After puberty, the female possesses far more primary adipocytes than the male and this explains, we believe, much of what occurs during the post-maturation phase of life.

Post-maturation expansion of adipose tissue

The post-maturation increase in adipose tissue mass, so characteristic of the peoples of the modern world, is governed by behaviour, not by genes. It is driven by the need to accommodate excess energy intake and this can be accomplished by hypertrophy and/or hyperplasia in either primary or secondary adipose tissue depots.

In adult females, fat tissue does not correlate with adipocyte number [25,45–47]. This suggests that at least the initial stages of post-maturation expansion of adipose tissue mass are accomplished by increase in adipocyte size as well as in adipocyte number. Initially, more small adipocytes are available to store the excess FAs. With more substantial demands to increase FA storage, adipocyte proliferation must take place. However, at least initially, this tends to occur more in the primary than in the secondary adipose tissues zones. If so, transmembrane FA flux remains low and, therefore, so does hepatic FA flux.

In adult males, by contrast, fat mass correlates much more closely with adipocyte number and therefore any substantial increase in fat mass must be achieved principally by proliferation. This proliferation occurs predominantly in the secondary sites of adipose tissue in the upper body, and it is the process that leads to expansion of intra-abdominal adipose tissue mass. Thus post-maturation expansion of adipose tissue in the male produces adipocytes with high transmembrane FA flux and, therefore, high hepatic FA flux and increased plasma atherogenic particle number.

Clinical implications of the adipocyte life cycle hypothesis

We will highlight only a few of the implications of the adipocyte life cycle hypothesis. This hypothesis predicts...
that adipocyte number and site are the major determinants of whether hypertriglyceridaemia and elevated apoB are associated with obesity. We suggest these differences account for the fact that fat mass is much larger in women than in men while, at the same time, plasma triacylglycerols and apoB are lower in women than in men. We also suggest that the appearance of the metabolic complications of obesity in South East Asians at lower BMI (body mass index) than Caucasians might relate to an inherently lower number of adipocytes and therefore larger adipocytes at similar BMI [48]. The impact would be particularly crucial were there primarily a reduction in the number of lower-body adipocytes. Over long periods of time, difference in climate or food availability could have influenced this divergence in body composition among the peoples of the world. Colder climates with less secure and less accessible food sources would favour higher adipocyte numbers during maturation. Warmer climates with more accessible and more secure food sources would favour lower adipocyte numbers. In such peoples, positive energy balance in both males and females will more rapidly produce larger, more metabolically disadvantageous, adipocytes. Thus we suggest that the unstressed gene hypothesis, rather than the thrifty gene hypothesis, may explain the greater proclivity to dyslipidaemia and cardiovascular disease when subjected to conditions of energy overload.

At the other extreme, it is possible that the normal triacylglycerol and apoB levels, so typical of the Pima Indians for example, are the outcomes of an increased adipocyte number occurring during maturation [49,50]. The same might be the case for the morbidly obese in whom excessive adipocyte proliferation might be the metabolic basis of their profound obesity, and there is initial evidence in animal models in favour of this hypothesis [21,51–55]. Moreover, the generally benign lipoprotein profile in the morbidly obese and in the Pima Indians establishes that dyslipidaemia and dysglycaemia are not always concurrent features of obesity – even when abdominal fat masses are markedly increased – and suggests that, although their pathophysiology may share a common theme, the sequence is not identical.

Finally, if the adipocyte life cycle hypothesis is correct, there is no metabolic defect as such to account for the consequences that accompany increasing adipocyte size. Rather, what happens reflects natural adaptation as the adipocyte struggles to cope with the challenge of storing excessive amounts of fat. Yes, the metabolic machinery of the adipocyte accelerates as it strains to keep up – but is that not to be expected? Increase the mass of triacylglycerols presented to the adipocyte and the mass taken in is increased, but action leads to reaction: accelerate input and output is accelerated. This co-ordination between input and output is essential and is dictated by a larger reality: the ability of the adipocyte to get rapidly larger is limited and so, more in, must, almost immediately, be followed by more out. A self-perpetuating cycle is established in which higher plasma triacylglycerols are both cause and consequence. Increased adipocyte size leads to increased adipocyte uptake, which leads to increased hepatic FA flux, which leads to hypertriglyceridaemia, which leads to increased adipocyte uptake (Figure 4).

How can this cycle be broken? If this model is correct, the search for a specific fault in the adipocyte – such as the
precise mechanism of insulin resistance – is futile. Indeed, even the concept of insulin resistance needs to be rethought. Is it a cause or is it only a consequence of excessive energy intake? No doubt, some genetic errors will be identified that will produce the same effects, but we believe they will be the exception rather than the rule in determining who is affected and who is not. For the greatest number who are affected, the best solution, the most practical solution, perhaps the only possible solution, will lie in learning how to limit their energy intakes.

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