Spontaneous Human Combustion

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Dr. Weis's academic interests include: intermediary metabolism, the use of NMR spectroscopy in the study of in vivo metabolism, hospitalist-based patient care, the training of medical students and housestaff officers, and the effects of heavy metal music on long-term cognitive function.

This is to acknowledge that Dr. Weis has disclosed any financial interests or other relationships with commercial concerns relating directly to this program. He has relinquished all stocks in corporations making asbestos undergarments. Dr. Weis will be discussing off-label uses in his presentation.

A Brief History of Spontaneous Human Combustion

Man has been long plagued by the fear of spontaneously bursting into flames, more or less. The paranormal phenomenon of "spontaneous human combustion", or SHC as referred to by those in the know, has been largely relegated to the realm of UFO abductions, ghost sightings, and out-of-body experiences. Yet, nonetheless, it has remained a fascination on both literary pages of old and internet websites today. The legendary British novelist, Charles Dickens (1812-1870), was particularly intrigued by SHC. In his work *Bleak House*, he describes the gruesome discovery of the demise of Mr. Krook, a gin-sodden, illiterate, old man as follows:

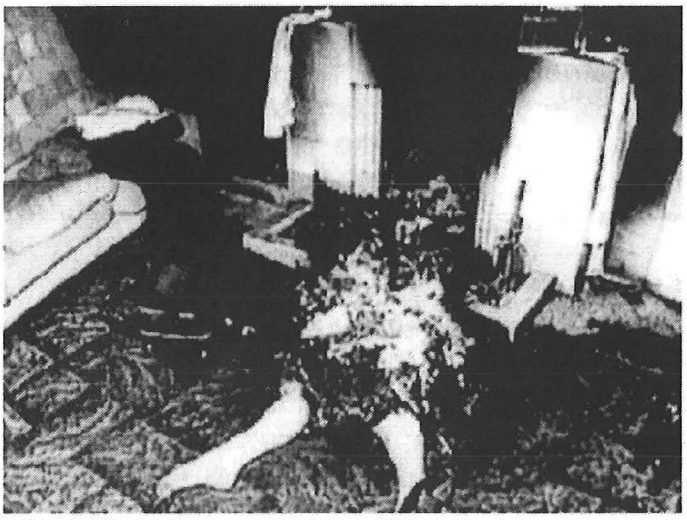
> "And the burning smell is there - and the soot is there, and the oil is there - and he is not there!"
>
> There is a smoldering, suffocating vapour in the room, and a dark greasy *coating* on the walls and ceiling....
>
> Here is a small burnt patch of flooring; here is the tinder from a little bundle of burnt paper, but not so light as usual, seeming to be steeped in something; and here is – is the cinder of a small charred and broken log of wood sprinkled with white ashes, or is it coal? O Horror, he is here! (1)

Charles Dickens was well versed in the details of spontaneous combustion known at the time. He not only alluded to SHC in his other works, but he openly debated with physicians and scientists at the time in the press over the reality of its occurrence.

The first written record of human combustion dates from the sixteenth century. Thomas Bartholin, the Danish anatomist who discovered the lymphatics and the glands that bear his name, published a report in 1663 describing the spontaneous combustion of an old Parisian woman who abused brandy. Reports of human combustion continued into the nineteenth century, similar to the 1832 paper in the *London Medical and Surgical Journal* by C.L. Devouard, concerning

the combustion of a drunken sailor whose friends held a lighted candle too close to his body. The influential *Cyclopaedia of Practical Medicine* (1833) contained a section on spontaneous combustion written by chemistry professor James Apjohn(2). In all, between the first report and 1869 seventy instances of the event were reported from northern Europe and North America(3). The incidence of this phenomenon continues into modernity. Just in recent years, the third drummer for England's loudest band, Spinal Tap, was said to have "exploded on stage"(4).

The concept of human combustion did not seem unreasonable to nineteenth-century physicians, in part because of the confusion over the origin of animal heat. Two theories were advanced to explain the physiology of warmbloodedness. One theory held that chemical reactions in the body, similar to reactions in the inorganic world, caused the heat; the other proposed that body heat was due to the friction of the small particles in the circulation. Irrespective of their theoretical preference, physicians knew that the human body contained flammable gases. Physicians also knew that the human body could get very hot during a febrile illness. It did not take a great leap of imagination to conclude that the organs could reach such a temperature that the body would burst into flames. The concept of spontaneous combustion was reinforced by preachers of the temperance movement, who embellished sermons with the horrors of spontaneous combustion as an example of the hellish torment that awaits those who sin by drinking alcohol(2).

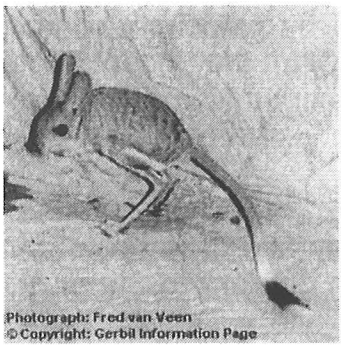


From the reports, the epidemiology and case definition of SHC can be derived. In most instances the person was addicted to the use of alcoholic beverages. The victim was usually an elderly woman, but occasionally men and younger subjects succumbed. Most often, involved victims were corpulent and smoked a pipe. Nearly all deaths from SHC are unwitnessed. The body itself is nearly completely incinerated, including bone and teeth. If there are remains, they usually amount to the extremities distal to the elbow and knees, normally with the clothing still intact. The room in which the event occurred normally contains a stifling heat at the time of discovery. All of the walls and furnishings are coated with an oily, orange film,

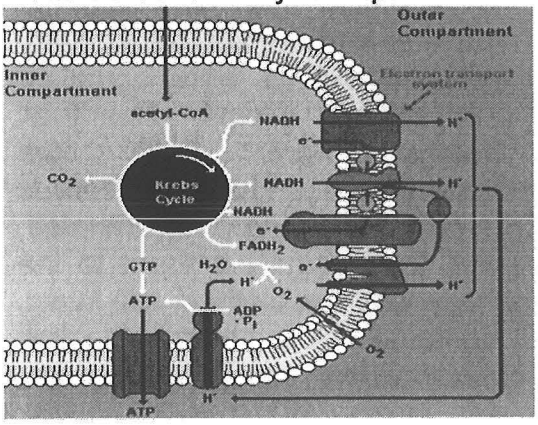
yet nothing in the room except the body has been burned. In modern examples any plastic appliance or fixture is melted or deformed by heat. Most importantly, a source of ignition is not always apparent. Because of the complete consumption of the body without damage to its immediate surroundings, it had been proposed that the fire came from within. In essence, it appears that the person underwent spontaneous combustion.

There are examples of organic systems reaching combustible temperatures. Anyone who has tended a compost pile has firsthand experience of the significant heat that biological entities can generate from uncontrolled metabolism. The ignition of piles of discarded tires has been blamed on bacterial fermentation. While SHC may not be another example of a biological system combusting, it does raise the question as to why we simply do not burst into flames. Several new frontiers in the field of basic metabolism are providing insight into the control of substrate utilization in humans. These observations not only relate to the maintenance of body temperature, but they have implications on the regulation of body weight and habitus. As we uncover these mechanisms of metabolic regulation, it is clear that therapeutic interventions already used in the clinical setting can have significant impact on these processes.

Uncoupling a Mystery



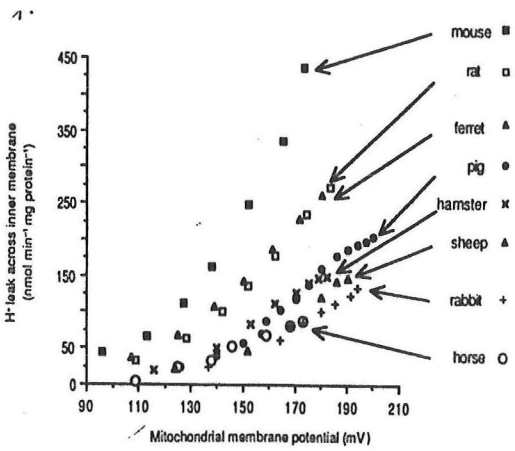
Shown in the picture is a Jerboa, a small jumping rodent indigenous to Asia, North Africa, and Southeast Europe. When this guy is not busy scurrying across arid wasteland, he is hibernating. The question as to how he, and all of his hibernating comrades, maintain their body temperature while steeped in slumber was an unsolved scientific mystery until the last two decades. The answer to this puzzle came not only with the recognition of a specialized tissue known as brown fat associated with thermogenesis, but also with the identification of the mitochondrial protein that gives this tissue its unique function. In order to fully understand the mechanism behind this heat-generating fat, a brief review of basic biochemistry is required.

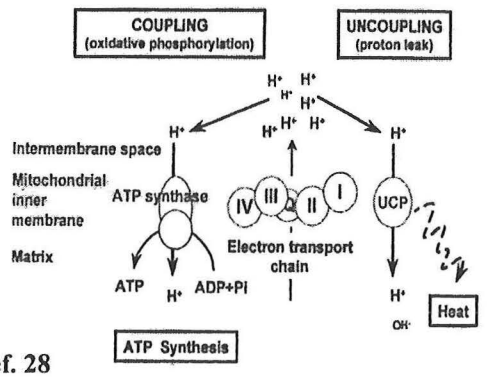


Peter Mitchell received the Nobel Prize in Chemistry in 1978 for his chemiosmotic hypothesis(5), a theory that continues to hold water (or at least protons) today. His model focused on the events at the inner mitochondrial membrane where the electron transport chain is localized. In his proposal, the oxidation of substrates in the mitochondrial matrix (the innermost compartment) results in the reduction of

electon carriers such as NAD^+ and FAD^+ to form NADH and $FADH_2$, respectively. The subsequent flow of electrons derived from these carriers down the electron transport chain results in the translocation of protons from the mitochondrial matrix to the space between the inner and outer mitochondrial membranes. This produces a concentration gradient of protons as well as a charge gradient across the inner membrane. The subsequent flow of these protons down these gradients through a pore-like protein complex in the inner membrane designated the ATP synthase results in the phosphorylation of ADP to the ATP. Through the aforementioned process, the oxidation of substrates resulting in the pumping of protons by the electron transport chain is said to be "coupled" to ATP production. ATP then serves as the energy source for cellular functions.

The system is clever, but far from efficient. If protons are able to traverse the inner membrane without passing through the ATP synthase complex, no ATP is generated. In this circumstance, no energy equivalents are generated and the oxidation of food sources results purely in the generation of heat. Oxidative phosphorylation is thus said to be "uncoupled". The mitochondrial inner membrane is not completely impermeable to protons, and proton leak has been estimated to account for 20-50% of cellular energy expenditure, and roughly 20% of the standard metabolic rate(6). Interestingly, the rate of proton leak in a given organism is inversely proportional to its body size(7, graph at right ,8). In other words, the smaller the critter, the greater the expenditure of energy as heat from uncoupled mitochondrial respiration. The implications of this energy waste for regulation of body size has certainly not escaped the attention of the diet and weight loss community. The toxic compound dinitrophenol, or DNP, is a tissue non-specific uncoupler of mitochondria. Its use was advocated in the past for rapid weight loss without dietary changes. Predictable from its mechanism of action, DNP has resulted in deaths from malignant hyperthermia secondary to unfettered uncoupling. Nonetheless, it remains available today and is openly espoused by the bodybuilding community as a powerful tool for weight control and muscle definition.



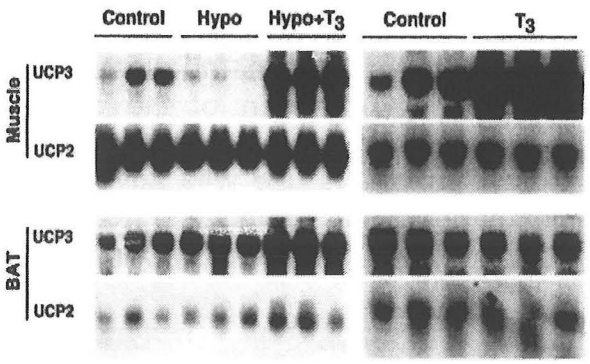


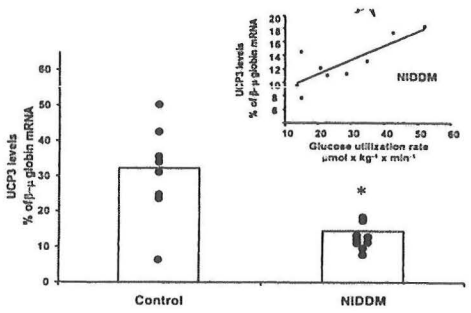
Ref. 28

Uncoupling is now recognized as the mechanism by which brown adipose tissue generates heat for thermogenesis. The specific

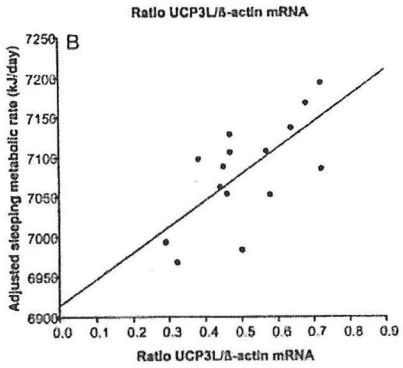
mechanism by which this is accomplished was identified in 1983 with the discovery of the protein thermogenin, or uncoupling protein 1 (UCP 1)(9). This inner membrane protein, found only in brown adipose tissue, allows the passage of protons across the membrane, thus circumventing the ATP synthase. The precise molecular mechanism remains elusive. Two current hypotheses are that UCP 1 acts simply as a proton pore, or that it effects uncoupling by protonating fatty acids and then transporting them along with the protons across the inner membrane(10). While hibernating animals as well as human infants have brown adipose tissue, it was believed that adult humans did not. Since the cloning of UCP 1 molecular biology techniques have resulted in the identification of four more polypeptides that share greater than 50% identity at the amino acid level with the uncoupler. These have now been deemed UCP 2 through 5(11,12). Expression of UCP 2 and 3 in yeast results in a decreased membrane potential, indicating that these proteins can dissipate the proton gradient as uncouplers(13). Analyses at the mRNA and protein level have demonstrated definitively that UCP 2 is ubiquitously expressed in all tissues in adult humans whereas UCP 3 expression is limited to skeletal muscle(14). Thus, with the recognition of uncoupling protein expression in human adults, the search began for the physiological role of these proteins and their impact on resting metabolic rate with the intent of pharmacologic manipulation.

The evidence for UCP 2 and 3 playing significant roles in the maintenance of body temperature and weight are severalfold. First, mice in which UCP 3 was overexpressed showed a 44% and 57% decrease in the ratio of adipose tissue volume to total animal volume in males and female, respectively(15). Second, measurement of the respiratory control ratio (state 3/state 4) in mitochondria from mice with UCP 3 genetically "knocked out" showed a significant decrease in state 4 respiration, the metabolic state in which ADP is unavailable(16). This suggests a tighter coupling of mitochondrial respiration to ADP availability. Third, treatment of rats with thyroid hormone produced UCP 3 levels of greater than 600% of the euthyroid controls(17,18). To the right is shown a Northern blot depicting mRNA levels for UCP 2 and UCP 3 in control animals, hypothyroid animals, and hypothyroid animals following treatment with T3. (17) The authors speculate that the dramatic increase in the uncoupler results in the elevated body temperature associated with a hyperthyroid state. Finally, the expression of UCP 2 and 3 in humans appears to be inversely correlated with the development of obesity and diabetes. In

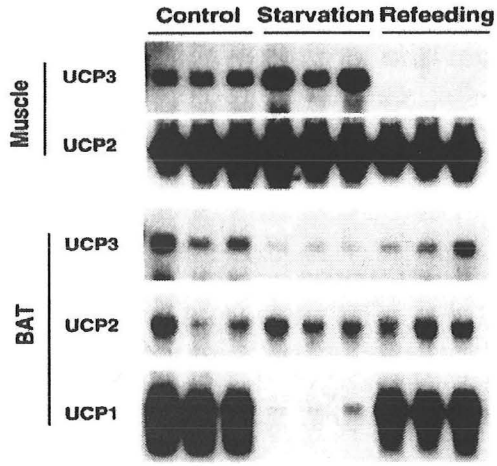


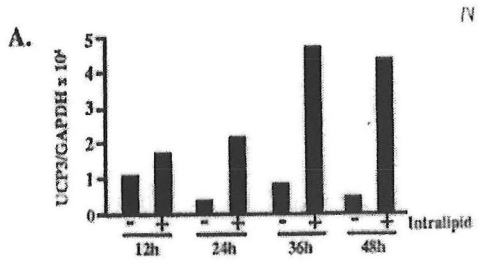


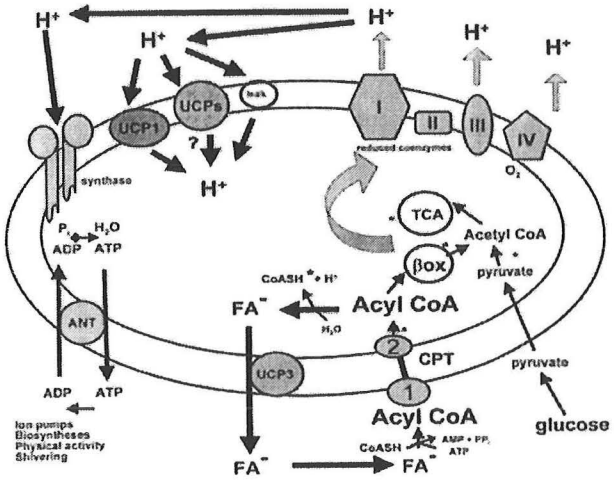
particular, Type 2 diabetics (data shown above at left) have decreased mRNA levels for UCP 3 in their skeletal muscles(19) while Pima Indians with higher UCP 3 expression have higher sleeping metabolic rates and lower body mass indices(20, data shown at right). Consistent with the UCP 3 data, strong genetic linkage has also been identified between markers in the vicinity of the gene for UCP 2 and resting metabolic rate in humans(21).



Despite the initial promise of a system that would be ideal for pharmaceutical intervention in the war on obesity, other data suggests that the UCPs' primary role may not be uncoupling of mitochondria. The proverbial "fly in the ointment" came with the recognition that the expression of both UCP 2 and 3 is upregulated in a fasting state, and then suppressed upon refeeding(22, 23, data shown at left as mRNA expression for UCP 2 and 3). It is obviously counter-intuitive that one would increase the expression and function of an energy-wasting protein at a time when energy stores are in jeopardy, as is the case with fasting. Related to this observation is the fact that fatty acid infusions, mimicking serum levels of these found during a fast, stimulate the expression of these proteins(24, data shown at right). Thus, the hypothesis has arisen that these proteins may have more to do with regulation of fatty acid metabolism than with the translocation of protons across the mitochondrial membrane. This theory is consistent with the proposed mechanism of UCP 1 shuttling protons by acting as a fatty-acyl transporter. Himms-Hagen and Harper(10) have proposed an elegant model (diagram at left) for the function of the UCPs based on the above observations. They note that the mitochondrion contains a thioesterase enzyme that can

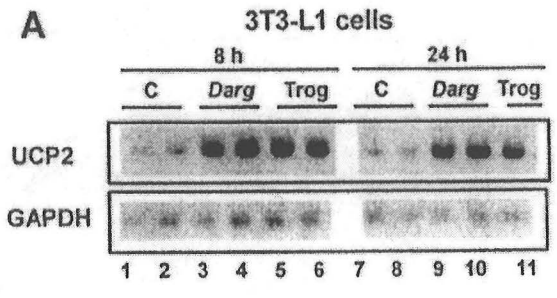






remove the CoA group from activated fatty acids in the mitochondrial matrix, the site of beta oxidation of the fats. If this CoA group is lost, the fatty acid is effectively trapped within the mitochondrion, unable to undergo further metabolism. It has always been believed that the thioesterase activity serves the function of recycling the limited pool of CoA in the matrix, but no consideration has been given to the fate of the "unactivated" fatty acids that have had their CoA removed. In the Himms-Hagen model, the UCPs act as shuttles to remove the CoA-less fatty acids from the matrix, thus preventing the congestion of the matrix with substrates that cannot be oxidized. Once moved to the cytoplasm, the fatty acids can again be activated with CoA by an acyl-CoA synthetase and return to the matrix for a second attempted pass at oxidation. As a corollary to this theory, it has been recognized that slowing of electron passage through the electron transport chain secondary to such "substrate congestion" as would be created by the thioesterase leads to an increased production of reactive oxygen species (ROS) in the mitochondria that can endanger the organelle's integrity. By improving the metabolic efficiency of the matrix and inner membrane of the mitochondrion, the UCPs limit the appearance of ROS. Data has been published that clearly shows the reduction in ROS associated with enhanced UCP 2 and 3 expression(16).

On initial consideration, the above hypothesis would appear disappointing with regard to the hope that the UCPs might prove a simple target for achieving the goal of increased uncoupling, and thus, increased energy wasting with the objective of weight loss. However, the proposal suggests that UCPs may improve the efficiency of fatty acid oxidation by preventing the accumulation of unactivated fatty acids in the mitochondrial matrix. As we come to recognize that the deposition of fats in tissues other than adipose tissue results in cellular dysfunction and insulin resistance in the case of skeletal muscle, then increasing the efficiency of fatty acid oxidation would certainly benefit those who suffer from the morbidities associated with ectopic fat deposition. With this in mind, the thiazolidinediones(TZDs), acting through the PPAR-γ receptor, have proven to be powerful activators of UCP expression in muscle cells(25,26). Shown to the right is the mRNA induction of UCP 2 associated with the TZDs darglitazone and troglitazone (26). Thus, their insulin-sensitizing effect may derive from the enhanced breakdown of fatty acids in the muscle bed, thus leading to improved insulin responsiveness. Other interventions that increase the expression of UCPs may prove useful in the struggle against obesity and insulin resistance by removing any restraints on the efficient oxidation of fatty acids in non-adipose tissues. While this may not lead to the loss of weight associated with uncouplers in the past, it may help prevent the deleterious effects of ectopic fat deposition in tissues such as the pancreas, skeletal muscle, liver, and heart.

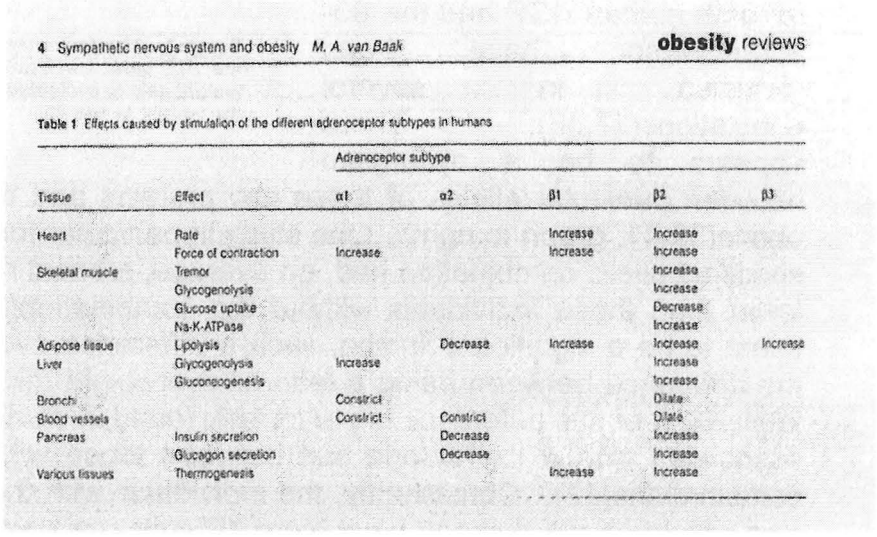


Research and development continue on agents that selectively modify the tissue expression of the UCP proteins.

Fight, Flight, or Fire?

Thermogenesis can be roughly divided into two broad categories: obligatory and facultative. Obligatory thermogenic processes are essential for the life of all cells of the body and include those that support normal and consistent body temperatures. The largest component of obligatory thermogenesis is provided by the basal metabolic rate. Also considered an obligatory thermogenic process is the portion of diet-induced thermogenesis that results from the digestion, absorption, and metabolism of dietary nutrients. The most important of the endocrine factors governing obligatory thermogenesis are the thyroid hormones. By contrast, facultative thermogenesis can be rapidly switched on or off and occurs mainly in two tissues: skeletal muscle and brown adipose tissue. It is in skeletal muscle and brown adipose tissue that heat is produced when endothermic organisms are in a cold environment. Shivering thermogenesis takes place in muscle, and nonshivering thermogenesis occurs in brown adipose tissue. While obligatory thermogenesis is under tonic control by the thyroid, facultative processes can be rapidly mobilized through the actions of the sympathetic nervous system. Elevated circulating catecholamines certainly contribute to the regulation. However, the bulk of metabolic control lies with the rich sympathetic innervation of the liver, adipose tissue, and skeletal muscle that modulates tissue metabolism at the local level.

The paradigm originally held that sympathetic effects in tissues were mediated by four different adrenergic receptors: α1, α2, B1, and B2(27, chart at right). The differential expression and stimulation of these receptors in tissues produce the effects associated with different adrenergic agonists. Investigations into the regulation of UCP 1 in brown adipose tissue revealed that UCP expression was also under the control of the sympathetic system(28), but the specific adrenergic receptor was unidentified. Responses were observed upon adrenergic stimulation with "non-classical" B1 or B2 ligands that suggested a unique receptor existed in this tissue. In 1989, the first report of a novel receptor subtype, the B3-adrenoceptor, was published(29). Subsequent



4 Sympathetic nervous system and obesity *M. A. van Baak* **obesity** reviews

Table 1 Effects caused by stimulation of the different adrenoceptor subtypes in humans

		Adrenoceptor subtype				
Tissue	Effect	α1	α2	β1	β2	β3
Heart	Rate			Increase	Increase	
	Force of contraction	Increase		Increase	Increase	
Skeletal muscle	Tremor				Increase	
	Glycogenolysis				Increase	
	Glucose uptake				Decrease	
	Na-K-ATPase				Increase	
Adipose tissue	Lipolysis		Decrease	Increase	Increase	Increase
Liver	Glycogenolysis	Increase			Increase	
	Gluconeogenesis				Increase	
Bronchi		Constrict			Dilate	
Blood vessels		Constrict	Constrict		Dilate	
Pancreas	Insulin secretion		Decrease		Increase	
	Glucagon secretion		Decrease		Increase	
Various tissues	Thermogenesis			Increase	Increase	

studies have clearly shown that this receptor plays a pivotal role in the regulation of brown adipose tissue-related thermogenesis. These reports have also demonstrated that ever-more-selective B3 agonists have potent anti-obesity and antihyperglycemic properties in animal models(28). Since human adults are believed not to have significant brown adipose depots, the presence of the B3 receptor in humans has been in question(30). Though the levels of protein expression are unknown, the mRNA for the B3-adrenoceptor has been identified in human adipose tissue, gallbladder, stomach, small intestine, colon, prostate gland, and in brain. It is absent in skeletal muscle, heart, liver, lung, kidney, thyroid, and lymphocytes(31). The question as to its contribution to human adrenergically-mediated thermogenesis has been more difficult to assess due to the co-expression of other adrenoceptors in these tissues and their overlapping responses to sympathetic ligands(32). Targeted stimulation of the B3 receptor clearly results in lipolysis in human white adipose tissue, greater in omental fat than subcutaneous fat(33,34). However, unlike animals that utilize brown adipose tissue to maintain body temperature, muscle is clearly the dominant thermogenic organ in man, and it does not contain the B3-adrenoceptor. Some authors have suggested that the B2-adrenoceptor, the form that primarily mediates adrenergic stimuli to muscle, should be the focus of studies on thermogenic control in humans(35,36). Despite the absence of significant brown adipose depots in human adults, different alleles for both human UCP and the B3-adrenoceptor have been identified in several populations(37,38). There appears to be a synergism between particular alleles of these two proteins and the propensity to become obese(39-41, graph to right). One study in particular found that individuals with a specified allelic combination had, on average, a basal metabolic rate 80 kcal/day lower than those individuals without the combination(38). While this may not seem to be a significant finding, such a difference over many years may make the difference between being a lean or overweight middle-aged individual. The implication of this difference is particularly found in studies comparing weight loss associated with a low calorie diet between those with- and without the allelic combinations(42). Consistently, the individuals with the allelic combination lose less weight on the diet and have more difficulty maintaining their new weight than those with the "wild-type" alleles of UCP 1 and the B3-adrenoceptor.

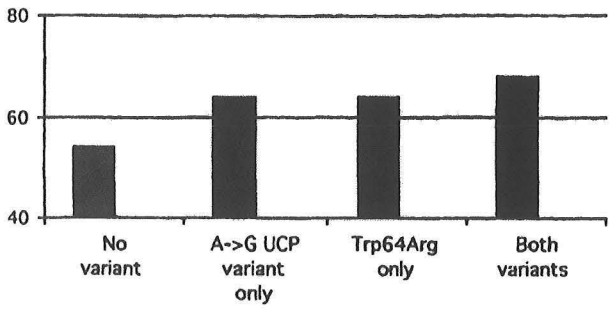
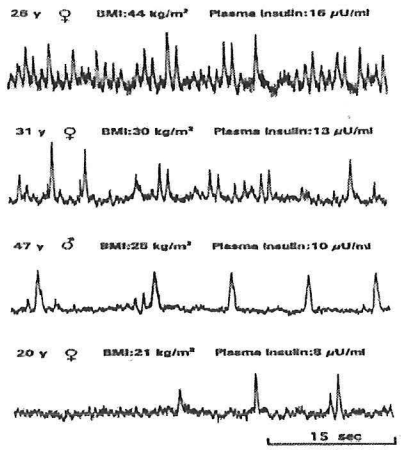


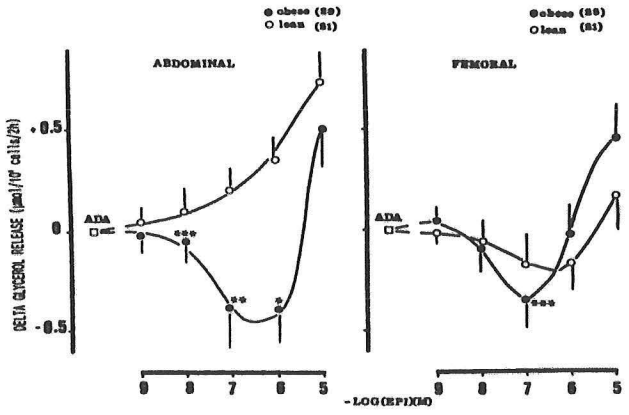
Figure 1 Maximal weight gain associated with A→G variant of the UCP gene and Trp64Arg of the β3-AR gene. The maximal weight gain is evaluated by the maximal reached weight minus the weight at age 20.

The human body uses the sympathetic system to regulate the level of adipose stores. Increased sympathetic tone results in elevated rates of fat breakdown, or lipolysis, and metabolism. Short term regulation is seen after a

meal at which time elevated serum insulin levels enhance adrenergic tone, resulting in increased metabolic rate and thermogenesis. Long term control relies on signaling from the body's fat depots through the actions of leptin, a recently described hormone secreted exclusively by adipose tissue(43). Leptin, the serum levels of which correlate with total body fat stores, acts on the hypothalamus and stimulates sympathetic output from the central nervous system. Increased adrenergic tone in adipose tissue effects lipolysis. This leptin-sympathetic system feedback loop appears to be one mechanism by which the brain monitors and regulates the amount of total body adiposity(44). Understandably, there has been an active search for defects in this system to explain the difference between individuals who are obese and those who maintain normal body weights. Serum catecholamine levels have been examined, and no significant difference has been observed between obese and normal weight subjects(27). Tissue-specific measurements of adrenergic tone, as depicted in the tracings at the right, have shown that, as predicted, increased sympathetic discharge directly correlates with increases in the body-mass index (BMI)(45). Thus, it appears that, if there is a defect in the sympathetic regulation of adiposity in obese individuals, it must be found at the tissue level. The evidence supports that this is indeed the case.

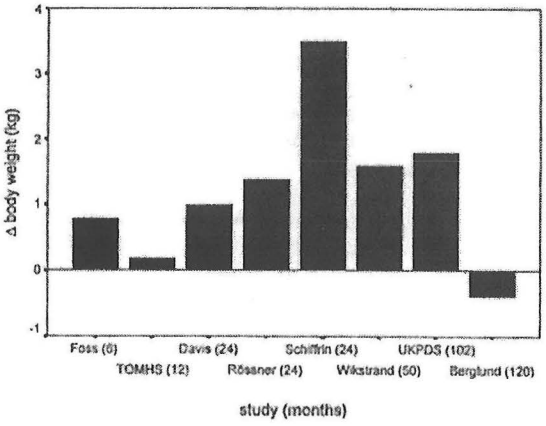


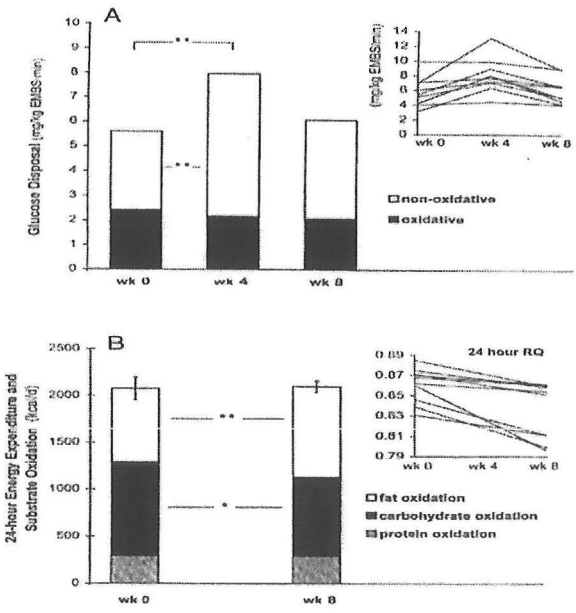
A number of studies have examined markers of sympathetic stimulation on lipolysis in obese and lean individuals(33,34,46). As an example, Mauriege *et al.*(34, data shown below) isolated adipocytes from the femoral and abdominal region of lean and obese volunteers. They then measured the release of glycerol as a marker for triglyceride breakdown under the influence of different adrenergic stimuli. Their findings showed that, not only was there a diminished lipolytic response in the adipocytes from obese individuals, but the adrenergic response also varied depending on the site of adipocyte isolation. In the obese subjects, the effect of epinephrine on fat breakdown in abdominal adipocytes was markedly blunted in comparison to lean controls. Similar findings have been observed when comparing metabolic changes with adrenergic stimulation in older and younger individuals, suggesting that the weight gain associated with aging may be partially due to an acquired defect in the lipolytic response by fat tissue(47).



While the extent to which the sympathetic system determines the basal metabolic rate overall remains controversial, clear differences exist in the specific response of tissue beds to local adrenergic stimulation. The observation that the tissues from obese individuals do not show the same catabolic effects of catecholamine stimulation as those from lean counterparts suggests that subtle variations in cellular metabolism may be partially responsible for the predisposition to weight gain, particularly if considered over the duration of a lifetime.

Are there clinical implications for the sympathetic control of metabolism? Beta blockers have become the cornerstone of treatment for both congestive heart failure and hypertension. One might predict that by blocking the adrenergic stimulation of B-adrenoceptors, the catabolic effects of catecholamines would be reduced. Studies examining the long-term effects of beta-blockers have shown that weight gain is associated with the use of these drugs. A systematic analysis by Sharma *et al.*(48) showed that in 7048 clinical trial patients, 3205 of which were on beta-blockers, there was a 1 to 3.5 kg weight gain in the medication group relative to the controls within the first three years of treatment. This finding has been confirmed with other studies(49, weight changes in studies analyzed shown at right). While, overall, this effect may seem like nothing to write home about, what is not known is the individual susceptibility of different patient populations, particularly those who may already have impaired responses to adrenergic stimulation of metabolic rate. On the flip side, there is interest in the development of pharmaceutical agents that may act as selective agonists for the B3-adrenoceptor with the goal of stimulating lipolysis in adipose tissue. A report examining the effects of the partial B3 agonist, CL 316,243(50), in patients who were treated for eight weeks with the drug demonstrated both increased fat oxidation and improved glucose disposal. This result is encouraging for future development of medications that modulate the metabolic effects of the sympathetic system as agents in the war against obesity.





Some Inflammatory Comments on Obesity

Fat has not always been an interesting tissue. For a long time it was considered simply a passive storage depot for excess energy in the form of triglycerides. Likewise, all adipocytes were believed to be created equal. Thus, fat in the central portion of the body was likely similar to that found in the periphery. However, several observations were clearly indicating that our understanding was too simple. First, people come in different shapes. Some individuals store more fat in the peripheral subcutaneous tissue while others stash it more centrally in the abdominal and omental fat compartments. These latter folks were the ones who appeared to experience more of the obesity-related morbidities including hypertension, lipid derangements, and cardiovascular disease, a clinical scenario known as the metabolic syndrome, suggesting that central adiposity differs from that in the periphery. Second, individuals appear to have a "set point" for adiposity. There are those who seem to be able to eat whatever they wish and remain lean while others continuously battle the bulge despite all dietary and lifestyle modifications. Observations made on rodents, particularly genetically obese strains such as the *ob/ob* mouse or Zucker fatty diabetic rat, suggested the existence of an "adipostat". This concept referred to the putative existence of a marker of adiposity that was used by the body to monitor and regulate the total amount of adipose tissue. The discovery of leptin in 1994(43) as the first candidate for the adipostat marked a revolution in our understanding of the fat cell. Adipose tissue is now recognized as the most active endocrine tissue in the body. A partial list of fat-secreted products is shown to the right (51). Likewise, it is clear that not all fat depots are equal with different adipose compartments giving rise to different metabolic and endocrine profiles.

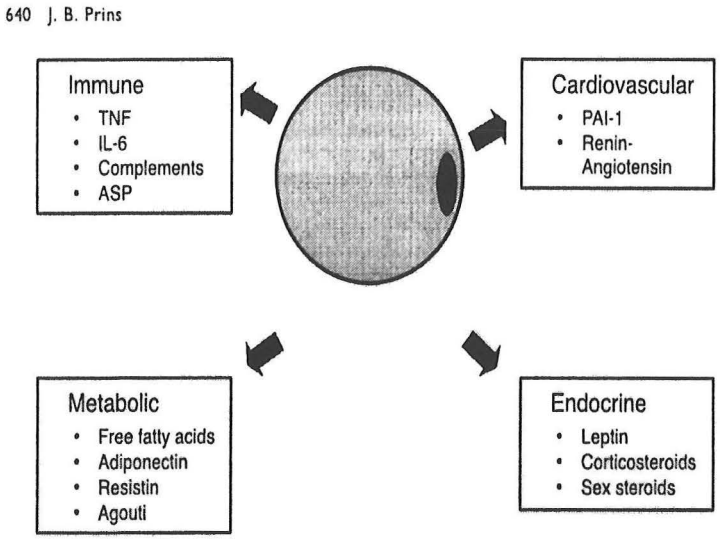
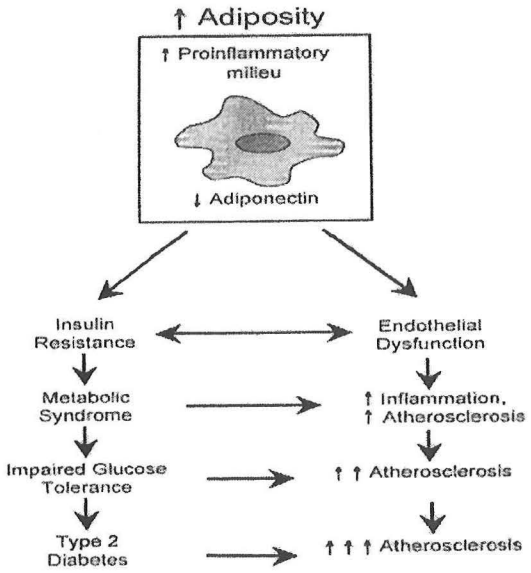


Figure 1. Schematic of the major endocrine products of fat cells. TNF=tumour necrosis factor; IL-6=interleukin-6; ASP=acylation-stimulating protein; PAI-1=plasminogen activator inhibitor.

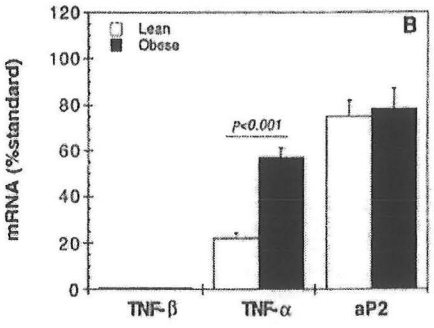
Since the discovery of leptin, little time passes between announcements of yet another secretory product identified from adipose tissue. The list of fat-related endocrine agents includes, but is not limited to, the metabolic modulators

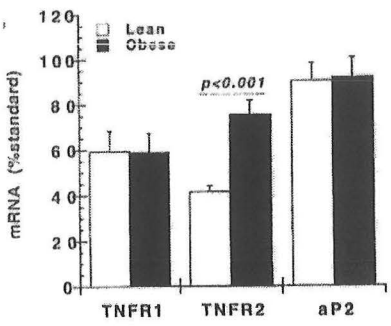
adiponectin, resistin, agouti, and free fatty acids; the cardiovascular peptides plasminogen activator inhibitor 1 (PAI-1), and angiotensin; the endocrine hormones leptin, visfatin, corticosteroids, and sex steroids; and the immune system cytokines tumor necrosis factor α (TNFα), interleukin-6 (IL-6), complement, and acylation-stimulating protein (ASP)(51,52). I would like to focus on this last group of "adipocytokines" with particular emphasis on TNFα and IL-6.

Physicians often refer to areas of inflammation as being "hot". It is no small coincidence that in a discussion of spontaneous human combustion, the inflammatory cytokines are of interest. The role of inflammation in the body is taking on new significance as we realize that pathologic states other than those associated with infections or autoimmune processes are at least in part due to the interplay of inflammatory cytokines. A recent example is the recognition that acute coronary events such as unstable angina or myocardial infarctions involve the inflammation of atherosclerotic plaques(53). The inflammatory marker C-reactive peptide is proving to be as sensitive a marker for an unstable coronary lesion as the more traditional cardiac markers Troponin I and creatine kinase (CK). As with vascular disease, obesity and its related insulin resistance should now be considered an inflammatory state.



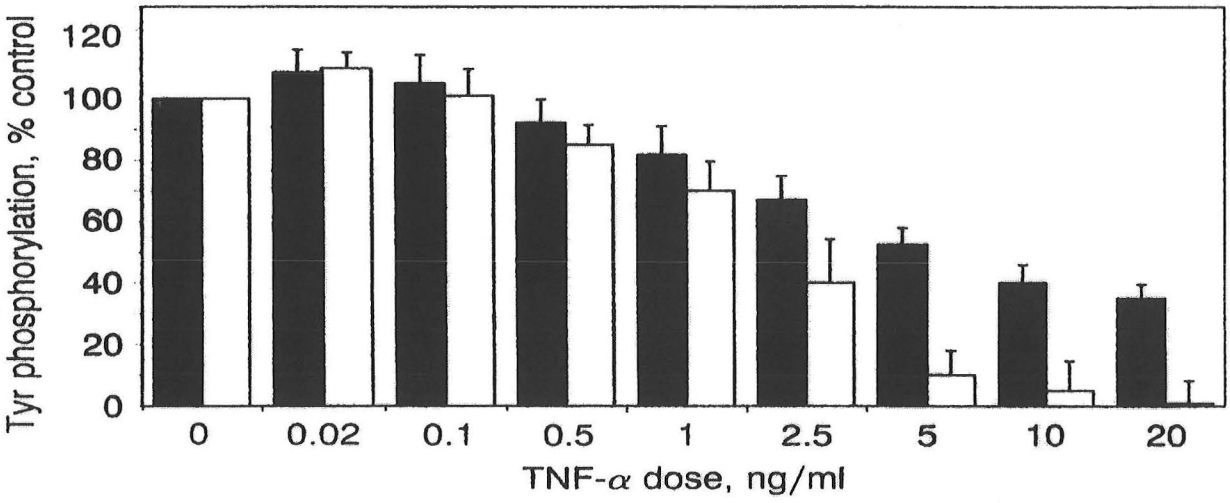
In 1993, Hotamisligil *et al.*(54) published a paper in the journal *Science* in which they demonstrated the specific expression of TNFα by adipocytes. Since that time, numerous other publications have shown that the level of expression of this cytokine is directly proportional to the degree of adiposity when expressed as either the BMI or total body fat mass(55,56, graph shown at right). The actions of TNF*a* are mediated by two different receptors known as TNFR1 and TNFR2. TNFR2 is overexpressed in adipose tissue of obese humans and correlates strongly with BMI, hyperinsulinemia, and TNF mRNA levels in the adipose tissue(57, graph shown at left). The search for other inflammatory cytokines from fat has also revealed the secretion of

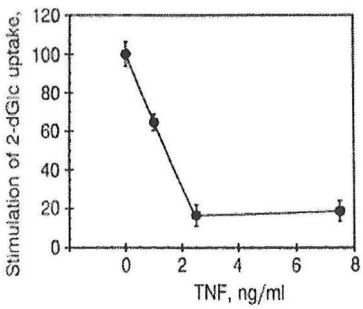




IL-6 from this tissue(58,59). With regards to fat's contribution to serum levels of these inflammatory products, TNF levels in the blood appear to be little affected by the TNF produced in the adipose beds(60). By contrast, the IL-6 produced by fat can make significant contributions to the total serum level(61,62). It is believed that TNFα plays more of an autocrine or paracrine role in adipose tissue whereas IL-6 may modulate other systemic functions. Consistent with this hypothesis is the finding that omental fat releases two to three times more IL-6 than subcutaneous stores. The IL-6 from this source is likely to act directly on the liver in altering hepatic carbohydrate and lipid metabolism(63).

But what role might these inflammatory cytokines play in adipose tissue? One clue comes from the clinical realm of infectious disease. The state of sepsis associated with systemic infection is characterized by the overwhelming expression of inflammatory cytokines. Metabolically, sepsis is characterized by cachexia and insulin resistance(64). This same insulin resistance, presumably driven by the cytokine milieu, may relate to the metabolic role of TNFα and IL-6 in fat. One might speculate that as adipose stores enlarge, the development of insulin resistance would protect the adipocytes from uncontrolled growth by limiting insulin's lipogenic signal and slowing the influx of glucose to the cells. Indeed, TNFα has been specifically shown to be a mediator of insulin resistance through two distinct mechanisms. First, TNFα effects the serine phosphorylation of the insulin receptor substrate 1 (IRS-1), the first intermediate in the insulin signaling cascade(65). Phosphorylated as such, IRS-1 effectively blocks tyrosine phosphorylation of the insulin receptor, the initial step upon the binding of insulin



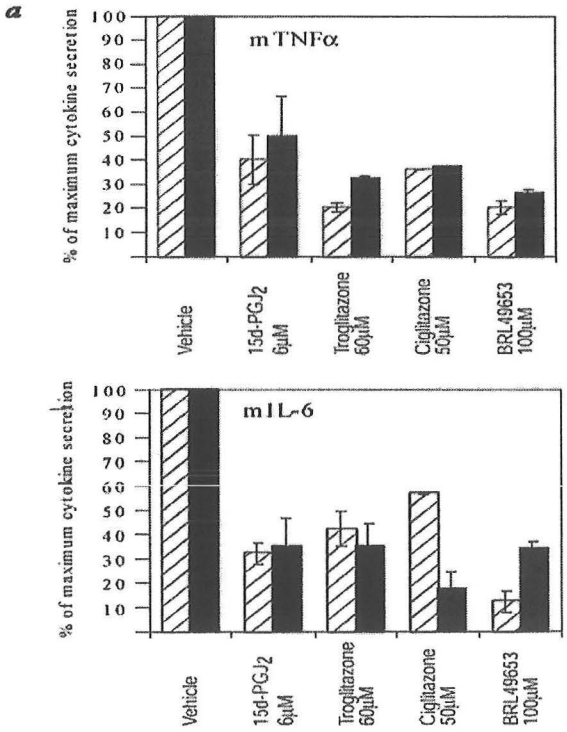


to its receptor. This effect has been demonstrated to be dose dependent, as depicted in the graph above showing phosphorylation of the insulin receptor against increasing concentrations of TNFα. Thus, insulin's binding to its receptor on the fat cell surface does not stimulate the synthesis of fatty acids in the presence of TNFα. Second, TNFα blocks the expression on the fat cell

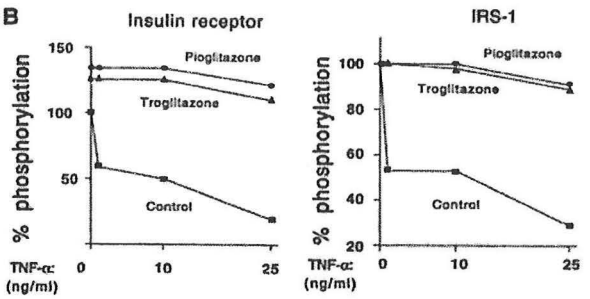
surface of Glut 4, the recruitable glucose transporter necessary for the entrance of glucose into the cell. This impairs glucose uptake as depicted in the graph above(66). For both reasons, adipocytes, under the influence of the inflammatory cytokines, and TNFα in particular, become insulin resistant.

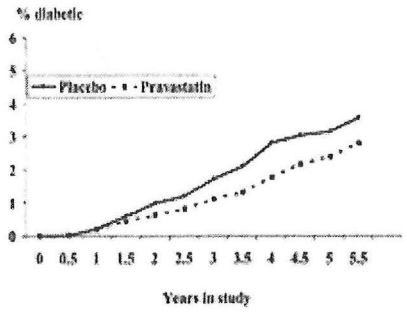
Interesting teleological questions are why adipose tissue expresses inflammatory cytokines in the first place, suggesting a crosstalk between the adipose and immune systems, and what advantage does the insulin resistant state offer. The immune system is a major user of energy, estimated at about 15% of the total metabolic rate. This is about the same percentage of the U.S. gross national product spent on defense. When the immune system is stressed, it needs to call on energy stores, hence cytokines such as TNFα have anti-adipogenic actions. This explains the wasting and insulin resistance associated with sepsis as noted above. Conversely, when the adipose tissue stores are undesirably small, signals that would reduce immunological preparedness and reduce energy expenditure would be appropriate. A relative deficiency of IL-6 expression might restrict the activity of the immune system in times of adipose depletion(58).

If a significant aspect of insulin resistance in the periphery is due to inflammatory cytokines acting in adipose tissue, what clinical interventions available currently might alter this dynamic? The latest medications on the market to treat diabetes mellitus are the thiazolidinediones (TZDs)(67). These agents act on the peroxisome proliferator activated receptor (PPAR) on the cell surface. There are three isoforms of this receptor: α– found in the liver, kidney, and cardiac and skeletal muscle; γ– found in adipose tissue; and δ– expressed ubiquitously in all tissues of adult mammals(68). The TZD's show the highest specificity for the PPAR-γ, thus their effects are most pronounced in the adipocytes. One effect is clearly the upregulation of oxidative pathways including those for fatty acids. However, another effect is the suppression of inflammatory cytokines in adipose tissue. Multiple studies (representative data in the graph at the left) have now shown that levels of both TNFα and IL-6 are decreased in adipocytes upon treatment with the TZDs or other PPAR-γ agonists(69-71). Thus, part of the "insulin



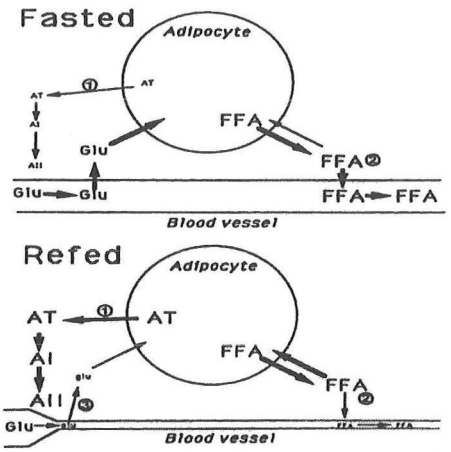
sensitizing" activity of the TZDs derives from reducing the effects of the inflammatory cytokines on the insulin receptor and Glut 4. The TZD's effect on maintaining phosphorylation of the insulin receptor despite increasing amounts of TNFa is shown at the left(70). More traditional anti-inflammatory's such as indomethacin are known to also activate the PPAR-γ pathway. If reduction of the inflammatory state can reduce insulin resistance, then anti-inflammatory's might be useful in the treatment of diabetes. Data was presented this year at the American Diabetes Association meeting in which a cohort of type 2 diabetics were treated with four grams of salsalate per day. By the end of the study, more than half of the subjects were able to discontinue their oral glycemic agents. The trade-off was the tinnitus associated with the salicylate treatment. The trial is currently being repeated with a dose of two grams per day of salsalate. Lastly, the HMG-CoA reductase inhibitors, or statins, have pleotropic effects outside of their designed inhibition on cholesterol synthesis. One of these characteristics is an anti-inflammatory effect. Similar to the findings with the TZD's, pravastatin has been shown to decrease circulating levels of IL-6 and TNFα. This has clear benefit for the inflammatory milieu associated with acute coronary syndromes. In addition, a revisiting of the data from the WOSCOPS cohort data has shown that treatment with pravastatin reduced the risk of developing diabetes mellitus(72,73, Kaplan-Meier plot at left). In all, reduction in the expression of the adipose-related inflammatory cytokines clearly benefits the sensitivity of the peripheral tissues to insulin.





A rather interesting aspect of the adipocytokine story is developing around the expression of angiotensinogen(AT) by fat tissue. The liver is the dominant source of this protein in the body, so its production by fat tissue is believed to play a paracrine role as with TNFα(74). Studies examining the regulation of AT expression in adipose tissue reveal that it is upregulated with feeding and inhibited with fasting(75). Under fasting conditions, adipocyte AT and thus angiotensin II are markedly reduced. This results in increased fat pad perfusion in association with vascular dilatation, resulting in fatty acid efflux into the systemic circulation. Under conditions of refeeding and genetic obesity, the increased adipocyte AT production leads to increased angiotensin II production, arterial constriction, and thus decreased fat pad perfusion. This leads to opposing effects on the lipid economy of the fat pad: 1) decreased fatty acid efflux, facilitating a glucose-based intermediary metabolism in other tissues and

reduced fat pad depletion, and 2) a decreased glucose uptake, an effect that would tend to inhibit further lipid accumulation and increased obesity (model shown in cartoon at right). The significance of this finding is that some studies in humans have shown significant weight loss in association with the use of ACE inhibitors(75). ACE inhibitors might prevent the effect of enhanced AT production by overnutrition, leading to increased adipose tissue blood flow under these conditions, and thus, enhanced efflux of fatty acids from the adipose stores. The tissue penetration and specificity of the different ACE inhibitors remain to be defined.



Back to Spontaneous Human Combustion

Given the aforementioned discussion, what mechanism might be proposed for the phenomenon of spontaneous human combustion? Could it be out-of-control uncoupling? Possibly unfettered sympathetic stimulation of metabolism? Or did an overwhelming inflammatory response simply make things too hot? SHC was scientifically investigated and the findings documented on the British television series, *Q.E.D.* The observation critical to the unraveling of the mystery was that in not one of the reported cases of SHC were the body remains found outdoors. The explanation offered by *Q.E.D.* is as follows: In a majority of the cases examined, a source of ignition was identified. It appears that the victims are rendered unresponsive by a catastrophic event (heart attack, stroke, etc.) or intoxication as was possible with alcohol at the time of Charles Dickens. Thus, when the person's clothing is ignited, they are unable to respond to the development. As the burning proceeds, the fire consumes the oxygen in the room to the point where open flame can no longer be sustained. The body simply begins to smolder. Because there is no open flame at this point, nothing surrounding the body is burned. As the smoldering proceeds, the fat of the body melts, feeding the process much like the wax of a candle feeds the burning wick. The orange, oily film covering the furnishings in the room is actually residue from the smoldering fat aerosolized in the process. Because the fat surrounding the joint extremities such as the elbows or knees is limited, the process normally burns out before it advances past these joints, thus giving rise to the gruesome finding of two preserved legs below the knee as the only trace of the consumed body. The complete incineration of bone is the most impressive testament as to the heat generated in this process. Literature from the cremation field states that complete consumption of bone by fire requires temperatures of 1800-2100°F for 1-2 hours(76). It is no surprise that plastic within the vicinity of the smoldering body succumbs to the heat. Because the phenomenon requires insufficient oxygen to sustain flame in order to produce the characteristic remains, the phenomenon cannot occur in the open air. Thus, no reports of SHC outside. As

with all great scientific endeavors, there are alternative hypotheses. The possibility of the spontaneous ignition of intestinal gas is still discussed among SHC aficionados. However, as an insightful Oxford investigator notes, if this is the explanation for SHC, then one might predict a higher incidence of spontaneous cow combustion. Reports of this are sparse. Based on this explanation, I do believe that it is safe to reassure friends, family, and patients that concern over spontaneously bursting into flames is not a worthwhile source of anxiety.

Dedicated to Dr. J. Denis McGarry, Ph.D.
Scientist, Mentor, and Friend

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