

LIPIDOCTOR™

Physiology Simplified

Your body is programmed to make you fat!

I love to eat, so it's easy for me to create scientific justifications. But truly, eating serves a number of useful and very necessary functions:

- It satisfies the urgent, unrelenting internal demands of hunger and appetite.
- It meets basic neurological needs, activating brain centers responsible for pleasure and reward.
- It meets one central psychological need: the repeated acting out and satisfying of your first and most unbreakable habit: putting food in your mouth.
- Most important of all, the consumption of food meets two of the necessary conditions for life: providing the building blocks for growth and the energy for metabolism.

At the cellular level, these 'building blocks' comprise protein and carbohydrate. 'Energy' comes from fat and carbohydrate. The unit of energy is the 'calorie'.

Caloric energy is required by your body every second you're alive for many reasons:

- to fuel life itself, keeping every cell in your body operational.
- for growth, providing the energy to produce the proteins that become your enzymes, muscle and connective tissues.
- to heat your body and to maintain your body temperature at 98.6 degrees Fahrenheit (thermogenesis).
- to provide the energy for muscle contraction, allowing you to move.

Overeating results in your body receiving more caloric energy than it needs. This has one dire consequence: fat storage. To make matters worse, it is irrelevant whether the calories are in the form of fat or carbohydrate. Both sources are converted into fat! In fact, glucose, the building block of carbohydrate, is required to create glycerol, the backbone of the fat molecule. This is why junk food, chock-full of extra sugar and fat calories, is absolute poison.

You may think that your body has the option of either converting excess caloric energy to fat and storing it, or burning the excess calories and releasing them as heat. Excess heat is eliminated from the body by the processes of conduction, convection, radiation and evaporation. That person we all know, who can eat and eat and never get fat, probably has the innate ability to readily burn excess calories. However, the reality for you and me is different. Evolution made the genetic choice for most of us eons ago: accumulate and store excess caloric energy as fat; no options!

Here are three good, physiological reasons for Nature's choice. First, humans have always needed fat stores in case of famine. Second, women require fat reserves for

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child-bearing and particularly for nursing. Third, the practice of covering of our bodies with clothing makes the option of excess heat generation and elimination very problematical.

Are you doomed to a life of pudginess, unless you count calories indefinitely, and meet me in the gym thrice weekly? Good News! The fate of your fat is no longer exclusively determined by the interplay of your genes, food intake and activity level. Medical science has finally created a safe and effective way to intervene. In order to understand the power of Lipidoctor™ Infusion Lipolysis™, you will require some knowledge of the workings of the adipose cell.

Fat is Important!

A molecule of fat is made up of three molecules of fatty acids attached to one backbone molecule of glycerol. Fat is stored in adipose cells.

Fat has many important functions.

- It is the body's most powerful fuel (remember from your calorie-counting days: there are almost as twice as many calories per gram of fat as there are per gram of carbohydrate).
- Fat provides insulation.
- It serves as cushioning.
- It is the reservoir of fatty acids required for the construction of phospholipids, the key component of cell membranes.

Your Competing Fat Factories

Fatty tissue is composed of adipose cells. First and foremost, they continuously manufacture and break down fat, but they also have many unexpected roles. They manufacture estrogens and other hormones; they produce substances that send messages to other cells in the body. Each of these varied functions requires a separate 'factory' within the cell. These factories contain production lines for both assembly and disassembly, but instead of using robotic machinery, they employ individual proteins, called enzymes, to perform the processing steps. Each of your adipose cells houses two competing, permanently-operational, fat factories. One creates fat (lipogenesis); the other breaks down fat (lipolysis). Because your adipose cells are programmed to preferentially accumulate and store excess caloric energy as fat, the fat creation factory is usually working harder than the fat breakdown factory. This is definitely the case when your intake of food exceeds your body's energy requirements, and surprisingly, also if you starve yourself. Here's a bird's eye view of the two fat factories at work.

Additional scientific detail is in fine print.

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Lipogenesis (fat creation)

The manufacture of fat commences with a meal. In your gut, you digest food into carbohydrate, fat and protein. Carbohydrate is then further broken down into glucose molecules; fat is broken down into fatty acids. These molecules are transported to your adipose cells, where new fat is formed and stored as enlarging fat droplets. Adipose cells will swell until they can hold no more fat, then they trigger production of more adipose cells. Your body therefore has an unlimited capacity for fat storage!

(Part of the fat you eat is broken down into fatty acid molecules, which attach to the blood carrier protein albumin. The rest of the fat attaches intact to various blood carrier proteins called lipoproteins. Molecules of glucose, albumin-bound fatty acids and lipoprotein-bound fat are delivered to your adipose tissue by the bloodstream. Fat is too large a molecule to enter the cell directly, so the adipose cell sends out an enzyme, lipoprotein lipase, to detach the fat from its carrier and break it down into fatty acids. Glucose and these fatty acids, plus those freed from albumin, enter the adipose cell. Glucose is converted into glycerol-3-phosphate.

Then, one fatty acid at a time is attached to the phosphorylated glycerol by separate glycerol acyltransferase enzymes. Up to one microlitre of fat can be stored in each adipose cell).

Lipolysis (fat breakdown)

At the same time as fat creation is occurring, fat stored within the adipose cell enters the lipolysis factory, and is broken down to fatty acids and glycerol. These molecules are then flushed out into your bloodstream. The combination of fat breakdown into fatty acids and the release of these fatty acids from the adipose cell into the bloodstream is called 'fat mobilization'. Mobilized fatty acids have a variety of fates.

They can be taken up:

- by muscle cells and burned as fuel for muscle movement and for body warming;
- by liver cells and burned as fuel for daily metabolism;
- by other adipose cells downstream and reconverted into fat.

(The last enzyme in the fat disassembly line, 'hormone-sensitive lipase', breaks down fat by removing the three fatty acids from glycerol. Although the fatty acids created by lipolysis can immediately be recycled by the lipogenesis factory, the glycerol created by lipolysis cannot. It must first leave the adipose cell, be broken down into glucose, then be taken up by another adipose cell and finally be resynthesized into glycerol-3-phosphate, before it can be incorporated into another fat molecule. This means that lipogenesis is more dependent on the new supply of glucose to the adipose cell than it

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is on fatty acids. Insulin controls glucose supply to cells. In Type 2 diabetes, muscle cells become resistant to insulin and insulin levels in the bloodstream must rise to deliver the same amount of glucose into muscle cells as previously. Chronic production of excess insulin has an unavoidable, deleterious impact on adipose cells. It drives in glucose and stimulates lipogenesis. This may explain the relationship between Type 2 diabetes and excess fat).

Who Runs the Factories and Why Should You Care?

Your fat factories operate 24 hours a day, 7 days a week. The net result of the two processes: you are either accumulating fat under your skin and getting thicker, or depleting fat and becoming thinner. In rare instances, the two are in perfect balance and your body contour is stable. The daily balance sheet is determined primarily by your sex hormones, stress hormones, metabolic hormones, other cellular messengers, and even your brain (via the autonomic nervous system). Your balance sheet is actually the sum of a number of mini-balance sheets, because the output from the two competing fat factories differs in various anatomical areas of your body. Each person has a unique, daily fat balance sheet, which depends on age, life stage, and sex. You'll learn more about this when I explain the distinctions between fat and cellulite.

We don't have the complete picture yet about what controls fat metabolism, but a fair bit is known. Let's focus on the fat breakdown factory and its 'disassembly' line, noting that the same principle holds true for lipogenesis and its assembly line. What turns on a fat factory? The adipose cell membrane contains a number of different receptor sites. These receptors respond to specific molecular triggers. When a trigger substance attaches to its specific receptor, it is as if a key turns in a lock, and then acts as a throttle, accelerating the disassembly line in the fat breakdown factory. The more receptors of the same type you activate, the faster the disassembly line moves.

(As an example, there is a unique receptor for noradrenaline, the Beta adrenergic receptor. The more noradrenaline molecules attach to Beta receptors, the more the lipolysis factory cranks up its activity for several hours. During this time, extra hormone-sensitive lipase is activated within the cell and more fatty acids and glycerol are released into the bloodstream. There are four practical and related applications of this example, which explain why young men are usually leaner than older men. First, they have the highest levels of testosterone. The more testosterone, the greater the number and the greater the sensitivity of noradrenaline (Beta adrenergic) receptors per adipose cell. Second, young men tend to be more physically active, releasing even

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greater quantities of testosterone. Exercise also increases noradrenaline levels, further accelerating the fat disassembly line.

Third, exercise increases blood flow, flushing away the resultant glycerol and fatty acids, delivering them to muscle. Fourth, exercise, ie. muscle movement, burns the newly-delivered glycerol and fatty acids to fuel muscle contraction).

There are molecular triggers which fit into adipose cell membrane receptors that accelerate (throttle up) the fat disassembly line and speed up the fat breakdown factory. There are also triggers which fit into receptors that decelerate (throttle down) the line, and slow down the fat breakdown factory. Some receptor trigger molecules (as well as some hormones) not only can stimulate their cell membrane receptors, they also have the amazing ability to increase the number and sensitivity of these receptors. They act as amplifiers. Thus, fat breakdown can go into 'double-time' or greater, depending on the degree of amplification. 'Lean and mean' has been associated with high testosterone levels. It's likely that testosterone is a receptor amplifier for fat breakdown.

(For instance, adrenaline will trigger the Alpha 2 adrenergic receptor at the same time it triggers the Beta receptor. The Alpha 2 receptor slows down the disassembly line. It follows that the ultimate speed of the disassembly line acted upon by two competing trigger molecules depends on the relative numbers and sensitivities of Alpha 2 and Beta receptors on the adipose cell membrane; ie the amplification effect. Amplification is dependent not only on blood levels of testosterone and other hormones., but also on the anatomical location of the adipose cell. An understanding of these dynamics helps one appreciate the difference between cellulite and fat).

Before we leave the topic of receptors, interestingly, another class of receptor has recently been discovered. In the presence of nicotine, a unique nicotine receptor initiates fat breakdown all on its own.

(It has always been assumed that the reason for the relatively lower weight of smokers is that tobacco kills appetite and taste sensation. This does not explain why taste buds remain insensitive for some time after smoking cessation; however, people immediately begin laying down new fat upon quitting. The key reason that smokers invariably gain weight when they quit is that their adipose cell nicotine receptors are no longer being activated).

Your cell membrane receptors can also recognize substances that are not produced by your body. The pharmaceutical industry designs drugs with structures sufficiently

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similar to adrenaline and noradrenaline to trigger the adrenergic receptors. There are also drugs which can attach to receptors but not trigger them. They block the action of trigger molecules. These medications constitute some of the tools of the Lipidoctor™ Infusion Lipolysis™ procedure.

(Trigger substances are called “agonists”, regardless of whether they accelerate or decelerate an intracellular production line. Blocker substances are called “antagonists” or “blockers”. A Beta adrenergic agonist fits into a Beta adrenergic receptor and triggers lipolysis. A Beta adrenergic antagonist fits into the same receptor, but has no triggering effect. It just occupies the receptor, blocking a trigger molecule such as noradrenaline from attaching).

Examples of cell membrane receptor triggers

- Insulin is the prime fat creation trigger. It is so powerful because it has a multiplicity of actions.

(Insulin is the pancreatic hormone that moves glucose into every cell in your body. It also triggers a receptor which accelerates the lipogenesis assembly line by stimulating lipoprotein lipase. It simultaneously stimulates the movement of glucose into your adipose cells and its conversion into glycerol-3-phosphate. Insulin also stimulates another receptor which decelerates the lipolysis disassembly line by decreasing the activity of hormone-sensitive lipase. Because it acts both as an accelerator of lipogenesis and as a decelerator of lipolysis, insulin is a key controller of fat metabolism).

- Adrenaline and noradrenaline are the key hormones that promote fat breakdown over fat creation (at least from the waist up).

(Adrenaline is released from your adrenal glands as a result of the famous ‘fight/flight’ response. Noradrenaline is released from sympathetic nervous system nerve endings, primarily in response to physical activity. Exercise-induced noradrenaline release is the way your muscles tell your fat cells: “We need more fuel to keep contracting”. Fear-induced adrenaline release is the way your muscles tell your fat cells: “We need more fuel to run or fight”).

- Testosterone favours fat breakdown and burning in both sexes.
- Estrogens favour fat creation in some areas of the body and fat breakdown in others. As estrogen levels drop, fat deposits in the abdomen.

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- Growth hormone increases the rate of fat breakdown and decreases the rate of fat creation.
- Thyroid hormone is the central regulator of metabolic rate. It promotes fat breakdown.

(T3 is a trigger which accelerates lipolysis. It favours fat breakdown over fat creation. Why? T3 increases the metabolic rate of all types of cells, as well as increasing thermogenesis. This requires more fuel; ie. fatty acids. Increased fat breakdown provides the fatty acids).

The Lipolysis Cascade

Just as science has discovered natural and man-made substances which can duplicate the activity of adrenaline/noradrenaline and stimulate adipose cell membrane receptors, so it has also identified substances which can modulate intracellular production line machinery. One critical production line in the fat breakdown process is called the “lipolysis cascade”. It is responsible for making the special fuel that drives the fat disassembly line.

(It's probably now apparent to you that fat breakdown is a complex process. What goes on within the cell once the Beta adrenergic or nicotinic receptors are activated involves an added level of complexity. The message “Speed up lipolysis. Make more hormone-sensitive lipase!” must be delivered. How? The receptor releases a ‘G-protein’, which then activates a separate production line called the ‘lipolysis cascade’. This makes the special fuel required for hormone-sensitive lipase to do its job.

Step 1 in the cascade: G-protein activates the enzyme adenylate cyclase.

Step 2: adenylate cyclase assembles cyclic adenosine monophosphate (cAMP) from pre-existing adenosine.

Step 3: cAMP donates its energy-rich phosphate to hormone-sensitive lipase, to help it strip a fatty acid from the glycerol backbone of fat. Confused yet? Here is another complicating factor. Simultaneous with cAMP formation, competing processes are occurring. The enzyme ‘phosphodiesterase’ is trying to break down cAMP as it is formed. Again, it is the balance between enzyme concentrations which determines the end result. For the purist: “The activation of hormone-sensitive lipase is ultimately controlled by phosphorylation-dephosphorylation events, which are regulated, to a large extent, by the respective activities of protein kinase A (via adenylate cyclase-generated cAMP) and an insulin-activated protein phosphatase). [See Reference 4]

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Lipidoctor™ technology is uniquely able to shift the balance between fat creation and fat breakdown in favor of lipolysis, both by modulating cell surface receptors and also by intervening at every step of lipolysis cascade.

Fat and Cellulite: Mars and Venus

Generally, women carry both cellulite and fat. Men just carry fat. Women carry cellulite primarily below the waist. The first difference between cellulite and fat is in the packaging. When we look at a piece of fatty tissue from the buttock of an adult female under the optical microscope, we see a structure that looks like overstuffed mattress ticking. There are vertical fibrous bands, between which are adipose cells. There is no clear boundary between the fatty tissue and the dermis of the skin. Adipose cells protrude into the dermis, raising it so that from the outside, it looks like lumps of cottage cheese pushing through the skin. In contrast, the fatty tissue from the buttock of a male appears smooth. There is a distinct, regular boundary between fat and dermis. (This anatomical difference is probably the result of the different testosterone/estrogen ratio ranges of the two sexes).

The second difference is the female buttock adipose cells' predisposition to fat creation. As a result, there are fewer adipose cells in the butt tissue of a male and those cells are smaller. The fat creation factories are more active in female butt adipose cells compared to male (due primarily to higher lipoprotein lipase activity in female butt adipose cells). In addition, the fat breakdown factories are less active in female butt adipose cells compared to male (due to greater Alpha 2 receptor number and sensitivity in the former). So even if a woman does everything right, in terms of exercise and nutrition, she is at a disadvantage with respect to fat reduction below the waist!

Just as men and women handle stored fat differently below the waist, so there are sex differences in fat storage in the abdomen. Between puberty and menopause, females preferentially lay down fat in the buttocks and hips (except when they are lactating). Males preferentially lay down fat in the abdomen (directly under the skin and also around their internal organs).

(Factor one: Males have greater Alpha 2 receptor activity in abdominal adipose cells than do females who are not menopausal, ie. males have more deceleration of lipolysis in the abdomen than females. Factor two: In females, adipose cells in the hips and thighs have a preponderance of Alpha 2 receptors, whereas in the waist and above,

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there is a preponderance of Beta receptors. In non-lactating females prior to menopause, there is a difference in the activity of their two factories in the butt vs. the abdomen. There is decreased lipolysis and increased lipogenesis in butt adipose cells, so fat is preferentially laid down below the waist. In males, although their abdominal adipose cells are the same size as female abdominal adipose cells, there are many more of them).

This makes it easier to understand why fat is so much more readily depleted by exercise than is cellulite. It also indicates that the most effective time for women to exercise to reduce fat or protect against cellulite is during the nursing period following childbirth.

(Adrenaline and noradrenaline are released in response to exercise. In men, they trigger fat breakdown all over the body via Beta receptor stimulation. In women, net fat breakdown is triggered only in the waist and above by Beta stimulation. Below the waist, the relative preponderance of Alpha 2 receptors means that any increase in fat breakdown as a result of Beta stimulation will be countered by the new fat creation from Alpha 2 stimulation. This is one key reason for the existence of cellulite only in women and primarily below the waist).

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Glossary

Lipolysis: The breakdown of fat into fatty acids and glycerol.

Lipogenesis: The manufacture of fat from fatty acids and glycerol-3-phosphate.

Fat Mobilization: The combination of fat breakdown into fatty acids (lipolysis) and the release of these fatty acids from adipose cells into the bloodstream.

Fat Burning: The burning of fatty acids from broken down fat, to release energy for cell metabolism, heat, and movement.

Thermogenesis: the burning of fatty acids and/or glucose to heat your body.

Infusion Lipolysis™: the proprietary percutaneous/transdermal procedure developed by Lipidoctor™ Medical Slimming Clinics, to promote fat mobilization, fat burning and thermogenesis.