Lecture 08- Temperature and Metabolism –Part 2
Guyton Chapters 69 and 74
Formation of Acetoacetic Acid in the liver and its transport in the blood

A large share of the initial degradation of fatty acids occurs in the liver, especially when excessive amounts of lipids are being used for energy.

However, the liver uses only a small proportion of the fatty acids for its own intrinsic metabolic processes.

Instead, when the fatty acid chains have been split into Acetyl-CoA, two molecules of acetyl-CoA condense to form one molecule of acetoacetic acid, which is then transported in the blood to other cells throughout the body, where it is used for energy.

Part of the acetoacetic acid is also converted into β-hydroxybutyric acid, and minute quantities of acetone. These three molecules diffuse freely through the liver membranes and are transported by the blood to the peripheral tissues.

Once at the peripheral tissues, these three molecules again diffuse into the cells, where reverse reactions occur and Acetyl-CoA molecules formed.

These in turn enter the citric acid cycle and are oxidized for energy.

Ketosis in Starvation, Diabetes, and other Diseases.

- Concentrations of acetoacetic acid, β-hydroxybutyric acid, and acetone occasionally rise to levels many times normal in the blood and interstitial fluids.
- This condition is called ketosis, because acetoacetic acid is a keto acid. The three compounds are called ketone bodies. Ketosis occurs especially in starvation, in diabetes mellitus, and sometimes even when a person's diet is composed almost entirely of fat.
- In all these states, essentially no carbohydrates are metabolized: in starvation and with a high-fat diet because carbohydrates are not available, and in diabetes because insulin is not available to cause glucose transport into the cells.
- When carbohydrates are not used for energy, almost all the energy of the body must come from metabolism of fats.
- As a result, tremendous quantities of fatty acids become available 1) to the peripheral tissue cells to be used for energy and 2) to the liver cells, where much of the fatty acids is converted to ketone bodies.

Ketone bodies-2

- The ketone bodies pour out of the liver to be carried to the cells.
- For several reasons, the cells are limited in the amount of ketone bodies that can be oxidized.
- The most important reason is that one of the products of carbohydrate metabolism, oxaloacetate, is required to bind to acetyl-CoA before it can be processed in the TCA cycle.
- Therefore, deficiency in oxaloacetate derived from carbohydrates limits the entry of acetyl-CoA into the TCA cycle, and thus favors production of acetoacetic acid and other ketone bodies from the liver, and this leads to extreme acidosis.
- ***(Remember, 2 Acetyl-CoAs [2 carbons] combine to form one acetoacetic acid [4 carbons])***.
- The acetone that is formed during ketosis is a volatile substance, some of which is blown off in small quantities in the expired air of the lungs.
- This give the breath an acetone smell that is frequently used as a diagnostic criterion of ketosis.

Phospholipids and Cholesterol

- Phospholipids always contain one or more fatty acid molecules and one phosphoric acid radical, and they usually contain a nitrogenous base.
- Although the chemical structures of phospholipids are somewhat variant, their physical properties are similar because they are 1) all lipid soluble,
- 2) transported by in lipoproteins, and
- 3) used throughout the body for various structural purposes, such as in cell membranes and intracellular membranes.

Specific uses of phospholipids.

- Several functions of the phospholipids are the following:
- important constituent of lipoproteins in the blood; in their absence, serious abnormalities of transport of cholesterol and other lipids can occur.
- Initiation of the blood clotting process
- High levels are present in the nervous system, especially in myelin, which acts as an electrical insulator in the myelin sheath around nerve fibers.
- Provide phosphate radicals for different chemical reactions in the tissues.
- (most importantly)—participate in the formation of structural elements-mainly membranes- in cells throughout the body.

Cholesterol

- Cholesterol is present in the diets of all people, and can be absorbed slowly from the GI tract into the intestinal lymph. It is highly fat soluble but only slightly soluble in water.
- Formation of cholesterol:
- Cholesterol absorbed from the GI tract is called exogenous cholesterol; an even greater quantity is formed in the cells of the body, called endogenous cholesterol.
- Essentially all the endogenous cholesterol that circulates in the lipoproteins of the plasma is formed by the liver, but all other cells of the body form at least some cholesterol, which is consistent with the fact that many of the membranous structures of all cells are partially composed of this substance.
- The basic structure of cholesterol is a sterol nucleus.
- This is synthesized entirely from multiple molecules of Acetyl-CoA. In turn, the sterol nucleus can be modified by means of various side chains to form 1) cholesterol,
- 2) cholic acid, which is the basis of the bile acids formed in the liver; and
- 3) many important steroid hormones secreted by the adrenal cortex, the ovaries, and the testes.

Factors that affect the plasma cholesterol concentration-

feedback control of body cholesterol.

- Among the important factors that affect plasma cholesterol concentration are the following:
- 1) an increase in the amount of cholesterol ingested increases the plasma concentration slightly. However, when cholesterol is ingested, the rising concentration of cholesterol inhibits the most essential enzyme for endogenous synthesis of cholesterol, thus providing an ***intrinsic feedback control system*** to prevent an excessive increase in plasma cholesterol concentration. As a result, plasma cholesterol concentration usually is not changed upward or downward more than ±15 per cent by altering the amount of cholesterol in the diet, although the response of individuals differs markedly.
- 2) A *highly saturated* fat diet increases blood cholesterol concentration 15 to 25 per cent. This results from increased fat deposition in the liver, which then provides increased quantities of acetyl-CoA in the liver cells for the production of cholesterol. Therefore, to decrease the blood cholesterol concentration, it is usually just as important, if not more important, to maintain a diet low in saturated fat as to maintain a diet low in cholesterol.
- 3) ingestion of fat containing *highly unsaturated fatty acid*s usually depresses the blood cholesterol concentration a slight to moderate amount. The mechanism of this effect remains unknown, despite the fact that this observation is the basis of much present-day dietary strategy.
- 4) lack of insulin or thyroid hormone increases the blood cholesterol concentration, whereas excess thyroid hormone decreases the concentration, effects most probably caused by changes in the degree of activation of specific enzymes responsible for the metabolism of lipid substances.

Specific uses of cholesterol in the body

- The most abundant nonmembranous use of cholesterol in the body is to form cholic acid in the liver. As much as 80 % of cholesterol is converted into cholic acid, which is conjugated with other substances to form bile salts, which promote digestion and absorption of fats.
- A small quantity of cholesterol is used by
- 1) the adrenal glands to form adrenocortical hormones,
- 2) the ovaries to form progesterone and estrogen, and
- 3) the testes to form testosterone.
- These glands can also synthesize their own sterols and then form hormones from them.
- A large amount of cholesterol is precipitated in the corneum of the skin.
- This along with other lipids, makes the skin highly resistant to the absorption of water-soluble substances and to the action of many chemical agents, because cholesterol and other skin lipids are highly inert to acids and to many solvents that might otherwise easily penetrate the body.
- Also, these lipid substances help prevent water evaporation from the skin. Without this protection, the amount of evaporation can be 5 to 10 liters per day (as occurs in burn patients who have lost their skin), instead of the usual 300 to 400 milliliters.

Cellular structural functions of phospholipids and cholesterol—especially for membranes.

- The major function of cholesterol and the phospholipids is their role in forming specialized structures, mainly membranes, in all cells of the body; this includes both the cell membrane as well as the membranes of the internal organelles of all cells.
- It is also known that the ratio of membrane cholesterol to phospholipids is especially important in determining the fluidity of the cell membranes.
- Another fact that indicates the importance of phospholipids and cholesterol for the formation of structural elements of the cells is the slow turnover rates of these substances in most nonhepatic tissues- turnover rates measured in months or years.

Atherosclerosis

- *Atherosclerosis* is a disease of the large and intermediate-sized arteries in which fatty lesions called plaques develop on the inside surfaces of the arterial walls.
- Arteriosclerosis, in contrast, is a general term that refers to thickened and stiffened blood vessels of all sizes.
- One abnormality that can be measured very early in blood vessels that later become atherosclerotic is damage to the vascular endothelium.
- This is turn increases expression of adhesion molecules on endothelial cells and decreases their ability to release nitric oxide and other substances that help prevent adhesion of macromolecules, platelets, and monocytes to the endothelium.

Atherosclerosis-2

- After damage to the endothelium occurs, circulating monocytes and lipids (mostly low-density lipoproteins) begin to accumulate at the site of the injury (Fig. 68-6A).
- the monocytes cross the endothelium, enter the intima of the vessel wall, and differentiate to become macrophages, which then ingest and oxidize the accumulated lipoproteins, giving the macrophages a foam like appearance. These macrophage foam cells then aggregate on the blood vessel and form a visible fatty streak.

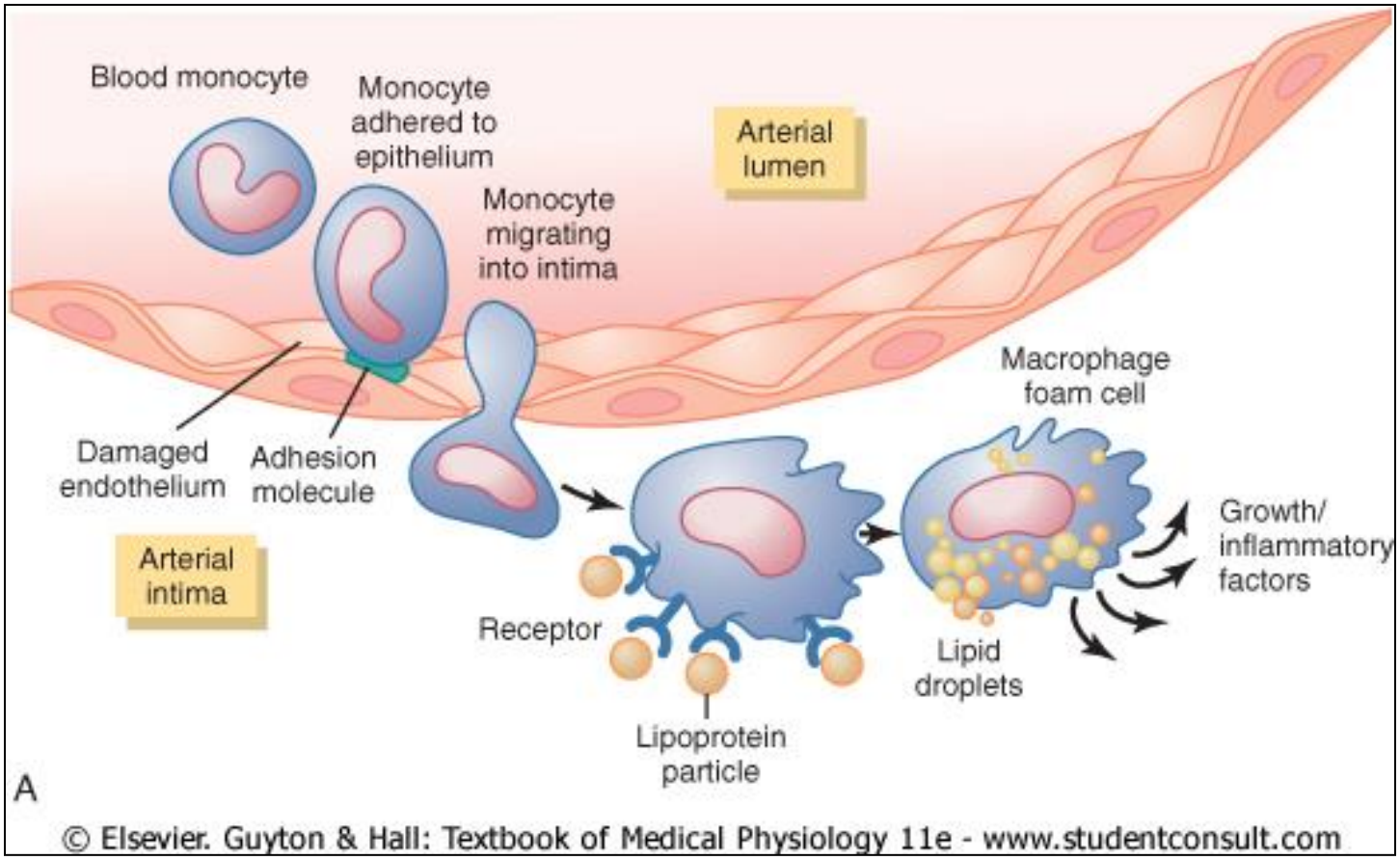

Figure 68-6 Development of atherosclerotic plaque. A, Attachment of a monocyte to an adhesion molecule on a damaged endothelial cell of an artery. The monocyte then migrates through the endothelium into the intimal layer of the arterial wall and is transformed into a macrophage. The macrophage then ingests and oxidizes lipoprotein molecules, becoming a macrophage foam cell. The foam cells release substances that cause inflammation and growth of the intimal layer. (Modified from Libby P: Inflammation in atherosclerosis. Nature 420:868, 2002.)

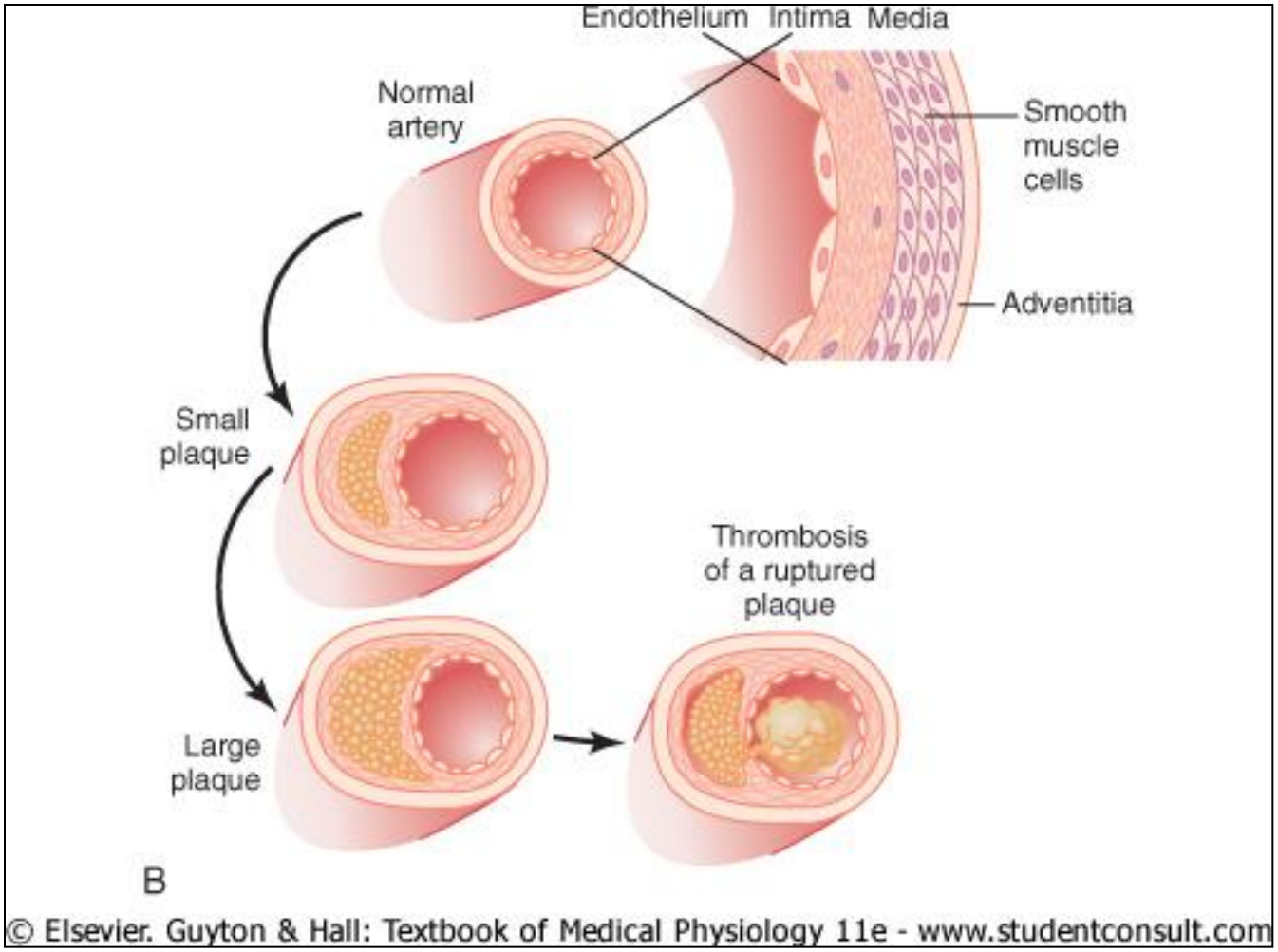

Figure 68-6 B, Additional accumulation of macrophages and growth of the intima cause the plaque to grow larger and accumulate lipids. Eventually, the plaque could occlude the vessel or rupture, causing the blood in the artery to coagulate and form a thrombus. (Modified from Libby P: Inflammation in atherosclerosis. Nature 420:868, 2002.)

With time, the fatty streaks grow larger and coalesce, and the surrounding fibrous and smooth muscle tissues proliferate to form larger and larger plaques (fig. 68-6B). also the macrophages release substances that cause inflammation and further proliferation of smooth muscle and fibrous tissue on the inside surfaces of the arterial wall.

Atherosclerosis-3

- The lipid deposits plus the cellular proliferation can become so large that the plaque bulges into the lumen of the artery and greatly reduces blood flow, sometimes completely occluding the vessel.
- Even without occlusion, the fibroblasts of the plaque eventually deposit extensive amounts of dense connective tissue.
- Sclerosis (fibrosis) becomes so great that the arteries become stiff and unyielding.
- Still later, calcium salts often precipitate with the cholesterol and other lipids of the plaques, leading to hard calcifications that can make the arteries rigid.
- Both of these later stages of the disease are called “hardening of the arteries”.

Atherosclerosis-4

- Atherosclerotic arteries lose most of their distensibility, and because of the degenerative areas in their walls, they are easily ruptured.
- Also, where the plaques protrude into the flowing blood, their rough surfaces can cause blood clots to develop, with resultant thrombus formation, leading to a sudden blockage of all blood flow in the artery.
- Almost half of all deaths in the US and Europe are due to vascular disease.
- About 2/3 of these are caused by thrombosis of one or more coronary arteries; the remaining 1/3 are caused by thrombosis or hemorrhage of vessels in other organs of the body, especially in the brain (causing strokes).

Basic causes of artherosclerosis- the roles of cholesterol and lipoproteins

- Increased low-density lipoproteins (LDL).
- Atherosclerosis can be caused by high plasma concentration of cholesterol in the form of LDL.
- Plasma concentration of these high cholesterol containing LDLs is increased by eating highly saturated fat in the daily diet, obesity, and physical inactivity.
- To a lesser extent, eating excess cholesterol may also raise plasma levels of LDL.
- Familial hypercholesterolemia:
- This is a disease in which the person inherits defective genes for the formulation of LDL receptors on the membrane surface of the body's cells.
- In the absence of these receptors, the liver cannot absorb either intermediate-density or low-density lipoproteins.
- Without this absorption, the liver compensates by producing new cholesterol and is no longer responsive to the feedback inhibition of too much plasma cholesterol.

- Patients with full-blown familial hypercholesterolemia have blood cholesterol concentrations of 600 to 1000 mg/dl, levels that are 4-6 times normal.
- Many of these people may die before age 20 because of myocardial infarction or other events due to atherosclerotic blockage of blood vessels throughout the body.

- Role of high-density lipoproteins (HDL) in preventing atherosclerosis:
- HDLs may actually absorb cholesterol crystals that are beginning to be deposited in arterial walls. When a person has a high ratio of HDL to LDL, the likelihood of developing atherosclerosis is greatly ***reduced***.

Chapter 69 protein metabolism

- Fate of amino acids absorbed from the GI tract.
- Immediately after a meal, the amino acid concentration in a person's blood rises, but the increase is usually only a few milligrams per deciliter for two reasons:
- 1) protein digestion and absorption are usually extended over 2 to 3 hours, which allows only small quantities of amino acids to be absorbed at a time.
- 2) after entering the blood, the excess amino acids are absorbed within 5-10 minutes by cells throughout the body, especially by the liver.
- Therefore, almost never do large concentrations of amino acids accumulate in the blood and tissue fluids.

- Active transport of amino acids into cells.
- Amino acids are too large as molecules to diffuse readily through pores of the cell membranes. Therefore, significant quantities of amino acids can move either inward or outward through membranes only by facilitated transport or active transport using carrier mechanisms.
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- Reversible equilibrium between the proteins in different parts of the body.
- If any particular tissue requires proteins, it can synthesize new proteins from the amino acids of the blood; in turn, the blood amino acids are replenished by degradation of proteins from other cells of the body, especially from liver cells.
- These effects are particularly noticeable in relation to protein synthesis in cancer cells. Cancer cells are often prolific users of amino acids; therefore, the proteins of the other cells can become markedly depleted.

Functional role of the plasma proteins

- The major types of protein present in the plasma are albumin, globulin, and fibrinogen.
- A major function of albumin is to provide colloid osmotic pressure in the plasma, which prevents plasma loss from the capillaries.
- The globulins perform a number of enzymatic functions in the plasma, and also are principally responsible for the body's both natural and acquired immunity against invading organisms.
- Fibrinogen polymerizes to fibrin in blood coagulation.

- Essential and Nonessential amino acids.
- Ten of the twenty amino acids normally present in animal proteins can be synthesized in the cells, whereas the other 10 cannot be or only in small amounts inadequate to the needs of the body. This second group is called the ***essential amino acids***, because they must be taken up in the diet.
- Use of proteins for energy.
- Once the cells are filled to their limit with stored protein, any additional amino acids in the body fluids are degraded and used for energy or are stored mainly as fat or secondarily as glycogen. This degradation occurs almost entirely in the liver, and it begins with deamination.
- Deamination means removal of the amino groups from the amino acids

- Urea formation by the liver.
- The ammonia released during deamination of amino acids is removed from the blood almost entirely by conversion into urea.
- Essentially all urea formed in the human body is synthesized in the liver.
- In the absence of the liver or in serious liver disease, ammonia accumulates in the blood.
- This is extremely toxic, especially to the brain, often leading to a state called hepatic coma.
- After its formation, the urea diffuses from the liver cells into the body fluids and is excreted by the kidneys.

- Effect of starvation on protein degradation.
- Except for the 20 to 30 grams of obligatory protein degradation each day, the body uses almost entirely carbohydrates or fats for energy, as long as they are available.
- After several weeks of starvation, when the quantities of stored carbohydrates and fats begin to run out, the amino acids of the blood are rapidly deaminated and oxidized for energy.
- From this point on, the proteins of the tissues degrade rapidly, as much as 125 grams daily- and as a result, cellular functions deteriorate precipitously

Chapter 74: body temperature, temperature regulation, and fever

- Core temperature and skin temperature
- The temperature of the deep tissues of the body—the core of the body—remains very constant, within ±1 deg. F day in and day out, unless the person is experiencing fever. The skin temperature in contrast, rises and falls with the temperature of the surroundings.

Body temperature is controlled by balancing heat production against heat loss

- Heat production is a principal by-product of metabolism. The most important of the metabolic factors to consider are
- 1) basal rate of metabolism of the cells of the body;
- 2) extra rate of metabolism caused by muscle activity, including muscle contractions caused by shivering;
- 3) extra metabolism caused by growth- and other hormones on cells;
- 4) extra metabolism caused by the effect of epinephrine, norepinephrine, and sympathetic stimulation on cells;
- 5) extra metabolism caused by increased chemical activity in the cells themselves, especially when the cell temperature increases; and
- 6) extra metabolism needed for digestion, absorption, and storage of food (thermogenic effect of food).

Heat loss

- Most of the heat produced in the body is generated in the deep organs, especially in the liver, brain, and heart, and in the skeletal muscles during exercise.
- Then the heat is transferred from the deeper organs and tissues to the skin, where it is lost to the air and other surroundings.
- Therefore, the rate at which heat is lost is determined almost entirely by two factors:
- 1) how rapidly heat can be conducted from where it is produced in the body core to the skin and
- 2) how rapidly heat can then be transferred from the skin to the surroundings.

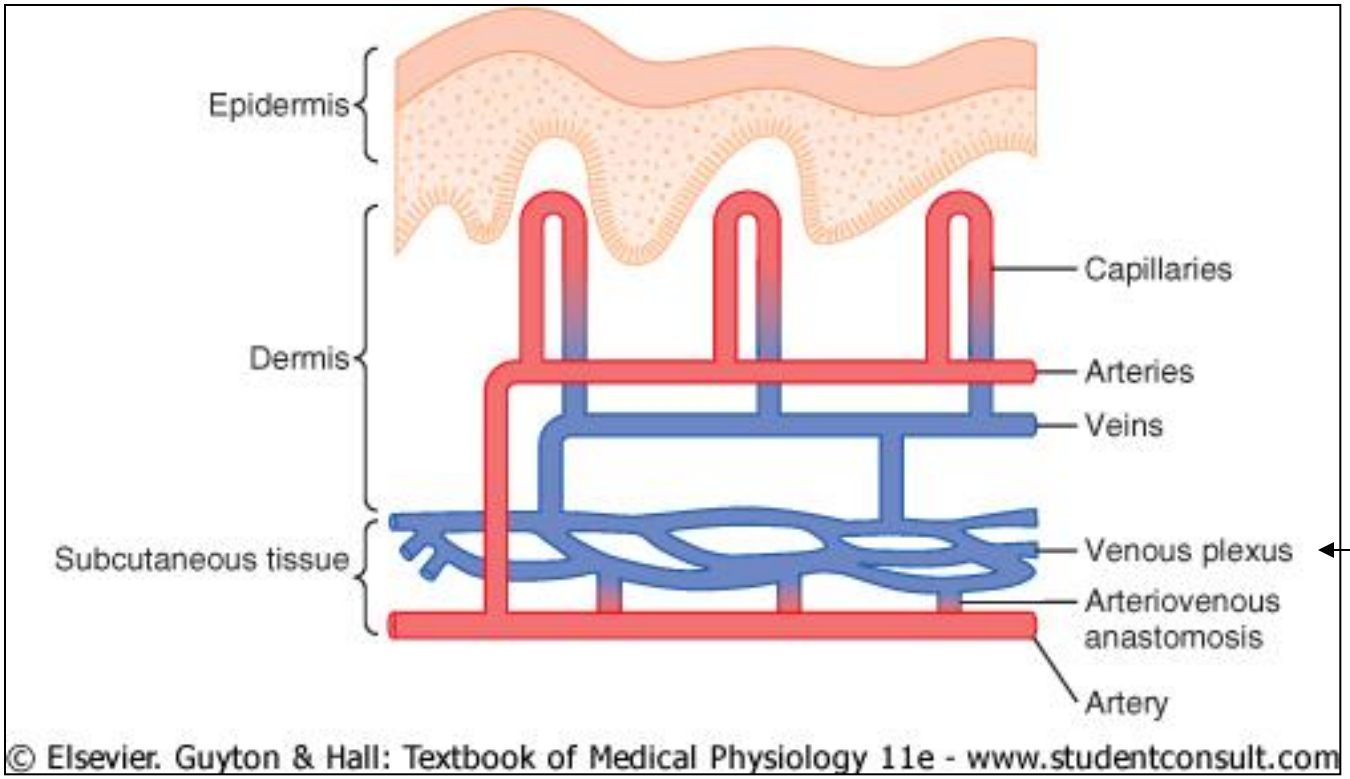

Figure 73-2 Skin circulation.

Blood flow to the skin from the body core provides heat transfer.

Blood vessels are distributed profusely beneath the skin. Especially important is a continuous venous plexus that is supplied by inflow of blood from the skin capillaries, as shown in fig. 73-2.

The rate of blood flow into the skin venous plexus can vary tremendously- from barely above zero to as great as 30 percent of the total cardiac output. A high rate of skin flow causes heat to be conducted from the core of the body to the skin with great efficiency, whereas reduction in the rate of skin flow can decrease the heat conduction from the core to very little.

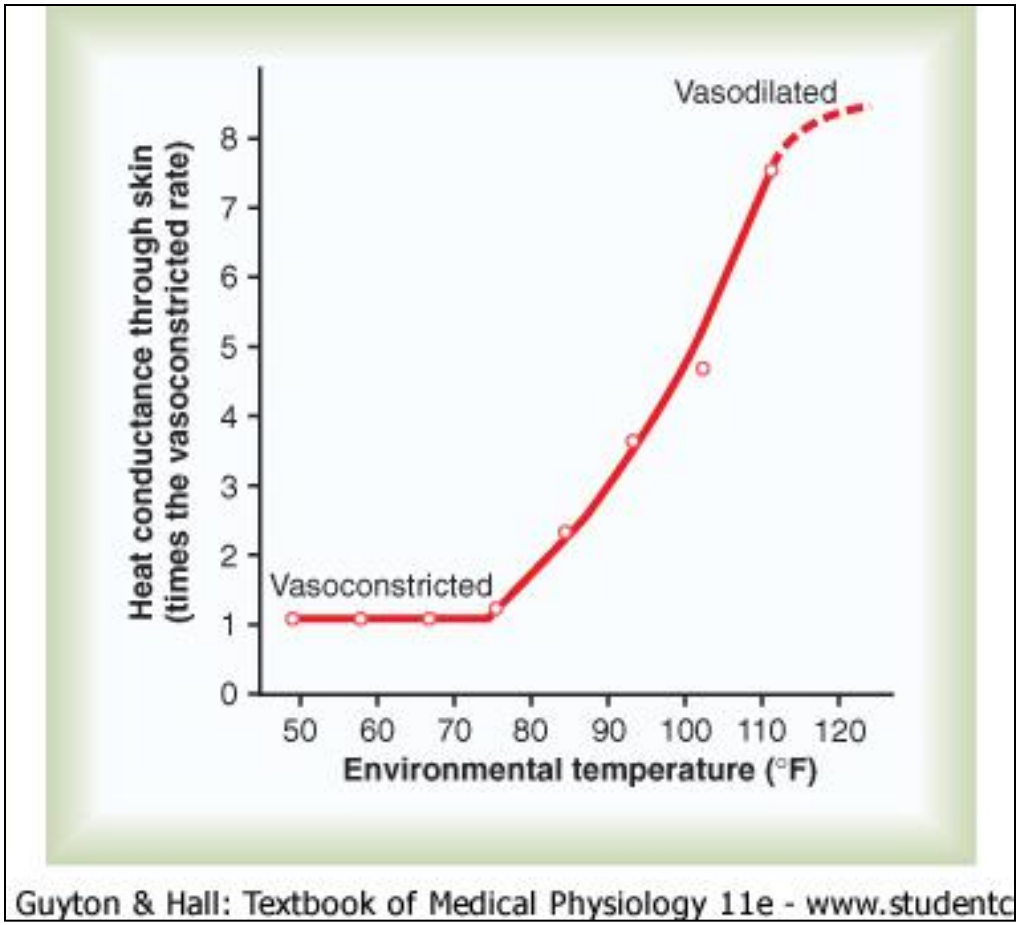

Figure 73-3 shows quantitatively the effect of environmental air temperature on conductance of heat from the core to the skin surface and then conductance in the air, demonstrating an approximate eightfold increase in heat conductance between the fully vasoconstricted state and the fully vasodilated state.

Therefore, the skin is an effective controlled “heat radiator” system, and the flow of blood to the skin is a most effective mechanism for heat transfer from the body core to the skin.

Figure 73-3 Effect of changes in the environmental temperature on heat conductance from the body core to the skin surface. (Modified from Benzinger TH: Heat and Temperature Fundamentals of Medical Physiology. New York: Dowden, Hutchinson & Ross, 1980.)

- Control of heat conduction to the skin by the sympathetic nervous system.
- Heat conduction to the skin by the blood is controlled by the degree of vasoconstriction of the arterioles and the arteriovenous anastomoses that supply blood to the venous plexus of the skin.
- This vasoconstriction is controlled almost entirely by the sympathetic nervous system in response to changes in body core temperature and changes in environmental temperature.

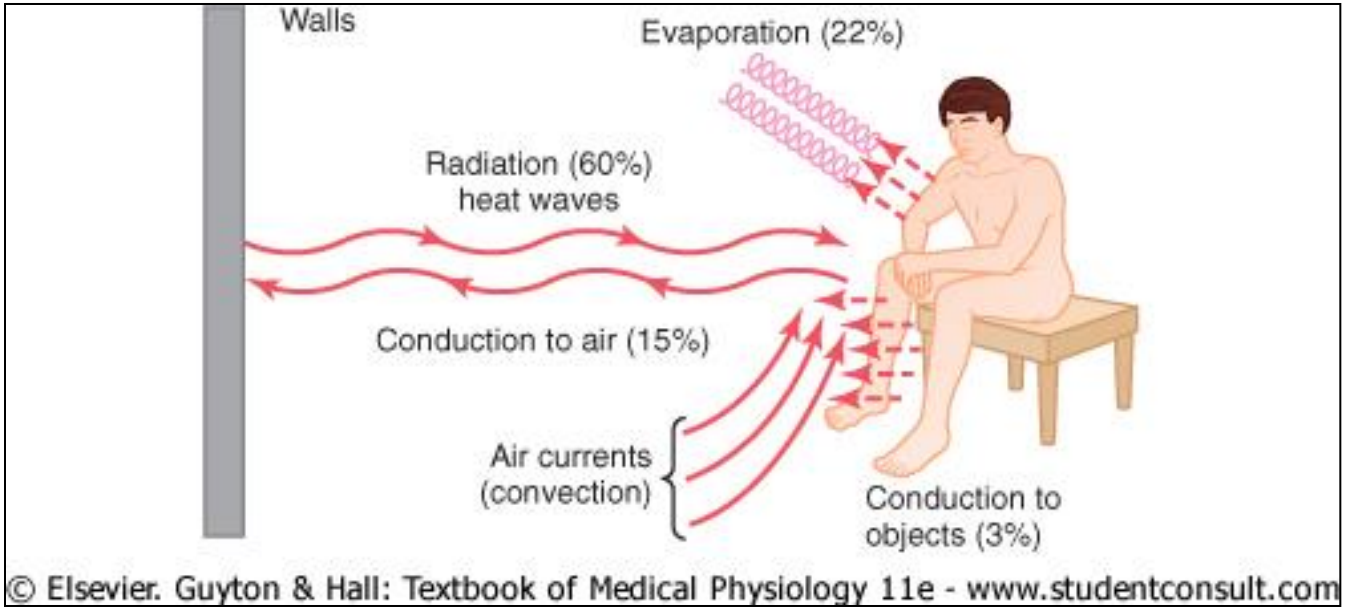

Figure 73-4 Mechanisms of heat loss from the body.

Basic physics of how heat is lost from the skin surface.

The various methods by which heat is lost from the skin to the surroundings are shown in fig. 73-4. these include: radiation, conduction, and evaporation

- Heat Radiation.
- As shown in Fig. 73-4, in a nude person sitting inside a room at normal room temperature, about 60% of total heat loss is by radiation.
- Loss of heat by radiation means loss in the form of infrared heat rays.
- All objects that are not at absolute zero temperature radiate such rays.
- The human body radiates heat rays in all directions. Heat rays are also being radiated from the walls of rooms and other objects toward the body.
- If the temperature of the body is greater than the temperature of surroundings, a greater quantity of heat is radiated from the body than is radiated to the body.

- Conduction of Heat.
- Only a small portion of heat (3%) is usually lost from the body by conduction to solid objects, while more (15%) is lost to air.
- Since heat is kinetic energy of molecular motion, much of the energy of this motion can be transferred to the air if the air is cooler.
- Once the temperature of the air adjacent to the skin equals the temperature of the skin, no further loss of heat occurs in this way, and is therefore self-limiting unless the heated air moves away from the skin so that new, unheated air is brought in contact with the skin, a phenomenon called air convection.

- Convection.
- Effect of wind. When the body is exposed to wind, the layer of air immediately adjacent to the skin is replaced by new air much more rapidly than normal, and heat loss by convection increases accordingly.
- Conduction and convection in water: water has a specific heat several thousand times as great as that of air, so that each unit portion of water adjacent to skin can absorb far greater quantities of heat than air can.
- Also, heat conductivity in water is very great in comparison with that of air.
- Consequently, it is impossible for the body to heat a thin layer of water next to the body to form an insulator zone as occurs in air.

- Evaporation
- When water evaporates from the body surface, 0.58 Calorie of heat is lost for each gram of water that evaporates.
- Even when a person is not sweating, water still evaporates insensibly from the skin and lungs at a rate of about 600 to 700 ml/day.
- This causes continual heat loss at a rate of 16 to 19 Calories per hour. This insensible evaporation through the skin and lungs cannot be controlled.
- However, loss of heat by evaporation of sweat can be controlled by regulating the rate of sweating.

- Evaporation is a necessary cooling mechanism at very high air temperatures.
- As long as skin temperature is greater than the temperature of the surroundings, heat can be lost by radiation and conduction.
- But when the temperature of the surroundings becomes greater than that of the skin, instead of losing heat, the body gains heat by both radiation and conduction.
- Under these conditions, the only means by which the body can rid itself of heat is by evaporation.

- Effect of clothing on conductive heat loss.
- Clothing entraps air next to the skin, consequently the rate of heat loss from the body by conduction and convection is greatly depressed.
- The effectiveness of clothing in maintaining body temperature is almost completely lost when the clothing becomes wet, because the high conductivity of water increases the rate of heat transmission through cloth 20-fold or more.

- Sweating and its regulation by the autonomic nervous system.
- Stimulation of the anterior hypothalamus-preoptic area in the brain either electrically or by excess heat causes sweating.
- Nerve pulses from this area of the brain are transmitted in the autonomic pathways to the spinal cord and then through sympathetic outflow to the skin everywhere in the body.

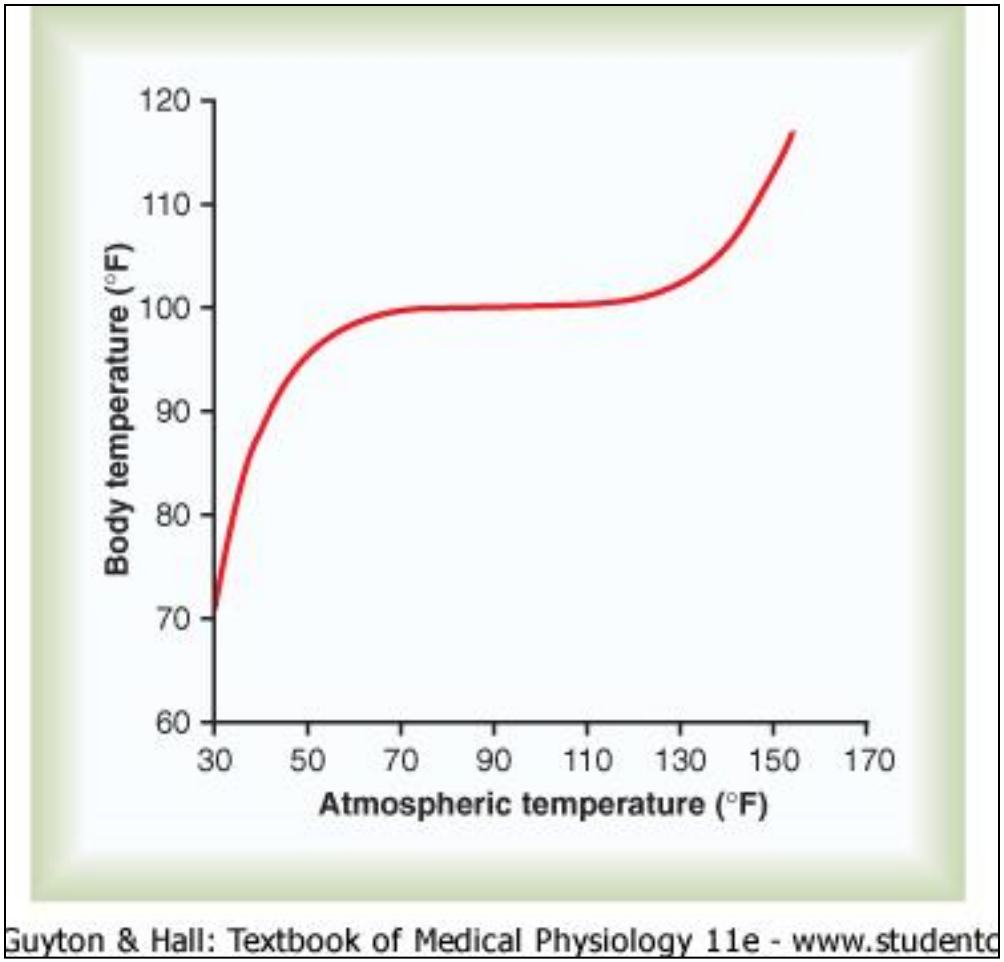

Figure 73-6 Effect of high and low atmospheric temperatures of several hours' duration on the internal body "core" temperature. Note that the internal body temperature remains stable despite wide changes in atmospheric temperature.

Regulation of body temperature-role of the hypothalamus.

Figure 73-6 shows what happens to the body “core” temperature of a nude person after a few hours exposure to dry air at different temperature. In general a nude person in dry air between 55 and 130 deg F is capable of maintaining a normal body temperature somewhere between 97 and 100 deg. F.

The temperature of the body is regulated almost entirely by nervous feedback mechanisms, and almost all these operate through temperature-regulating centers located in the hypothalamus. For these feeback mechanisms to operate, there must also be temperature detectors to determine when the body temperature becomes either too high or too low.

- Role of the anterior hypothalamic-preoptic area of the brain in thermostatic detection of temperature.

- This area of the brain has been found to contain larger numbers of heat-sensitive neurons as well as about one-third as many cold-sensitive neurons.
- The heat sensitive neurons increase their firing rate 2-10 fold in response to a 10 deg. C increase in body temperature.
- The cold-sensitive neurons, by contrast, increase their firing rate when the body temperature falls.
- Thus the hypothalamic-preoptic area of the brain has the capability to serve as a thermostatic body temperature control center.

Detection of temperature by receptors in the skin and deep body tissues

- Receptors in parts of the body other than the brain play additional roles in temperature regulation. This is especially true of temperature receptors in the skin and in a few specific deep tissues of the body.
- Skin for example is endowed with both cold and warmth receptors. When the skin is chilled over the entire body for example, immediate reflex effects are invoked and begin to increase the temperature of the body in several ways:
- 1) by providing a strong stimulus to cause shivering, with a resultant increase in the rate of body heat production.
- 2) inhibition of the process of sweating; and
- 3) by promoting skin vasoconstriction to diminish loss of body heat from the skin.
- Deep body temperature receptors are found mainly in the spinal cord, in the abdominal viscera, and in or around the great veins in the upper abdomen and thorax.
- It is probable that both the skin and the deep body receptors are concerned with preventing hypothermia- that is, preventing low body temperature.

- Neuronal effector mechanisms that decrease or increase body temperature:
- 1) Temperature decreasing mechanisms when the body is too hot:
- vasodilation of skin blood vessels. Full vasodilation can increase the rate of heat transfer to the skin as much as eightfold.
- 2) Sweating
- 3) Decrease in heat production. The mechanisms that cause excess heat production, such as shivering and chemical thermogenesis, are strongly inhibited.

- Temperature increasing mechanisms when the body is too cold:
- 1) Skin vasoconstriction
- 2) Piloerection: this means hair standing on end. Although not important in humans, in lower animals upright projection of the hairs allows them to entrap a thick layer of insulator air next to the skin, so that transfer of heat to the surroundings is greatly depressed.
- 3) Increase in thermogenesis (heat production)- promoted by shivering, for example.

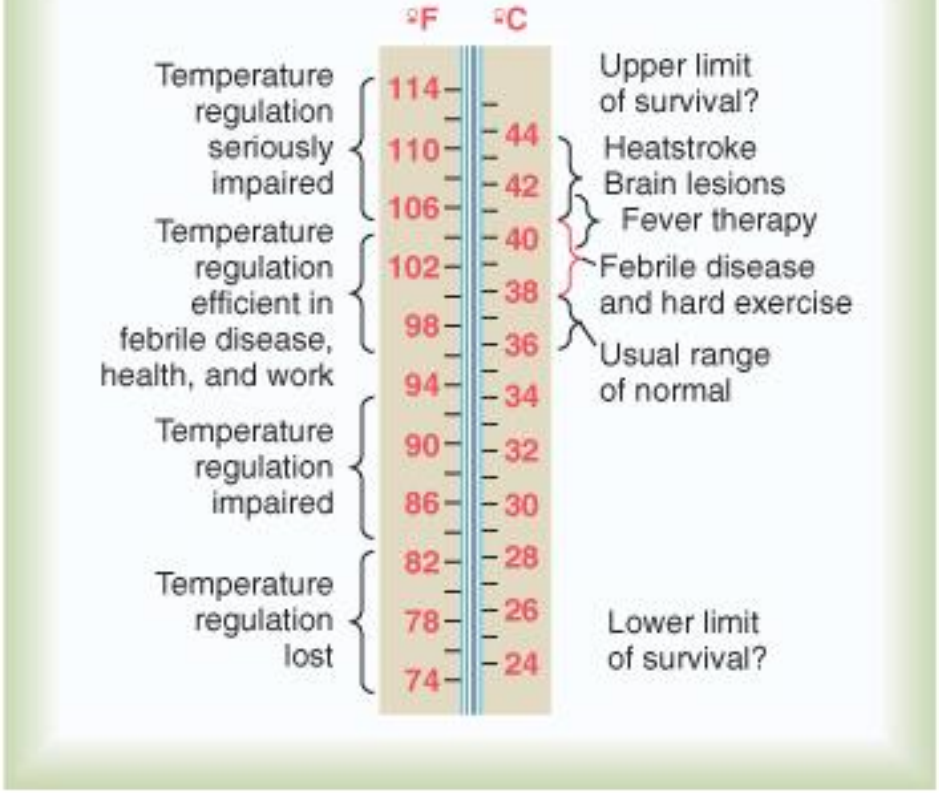

Figure 73-10 Body temperatures under different conditions. (Redrawn from DuBois EF: Fever. Springfield, IL: Charles C Thomas, 1948.)

Abnormalities of body temperature regulation

Fever.

Can be caused by abnormalities in the brain itself or by toxic substances that affect the temperature-regulating centers. Some causes of fever are presented in figure 73-10. They include bacterial disease, brain tumors, and environmental conditions that may terminate in heatstroke.

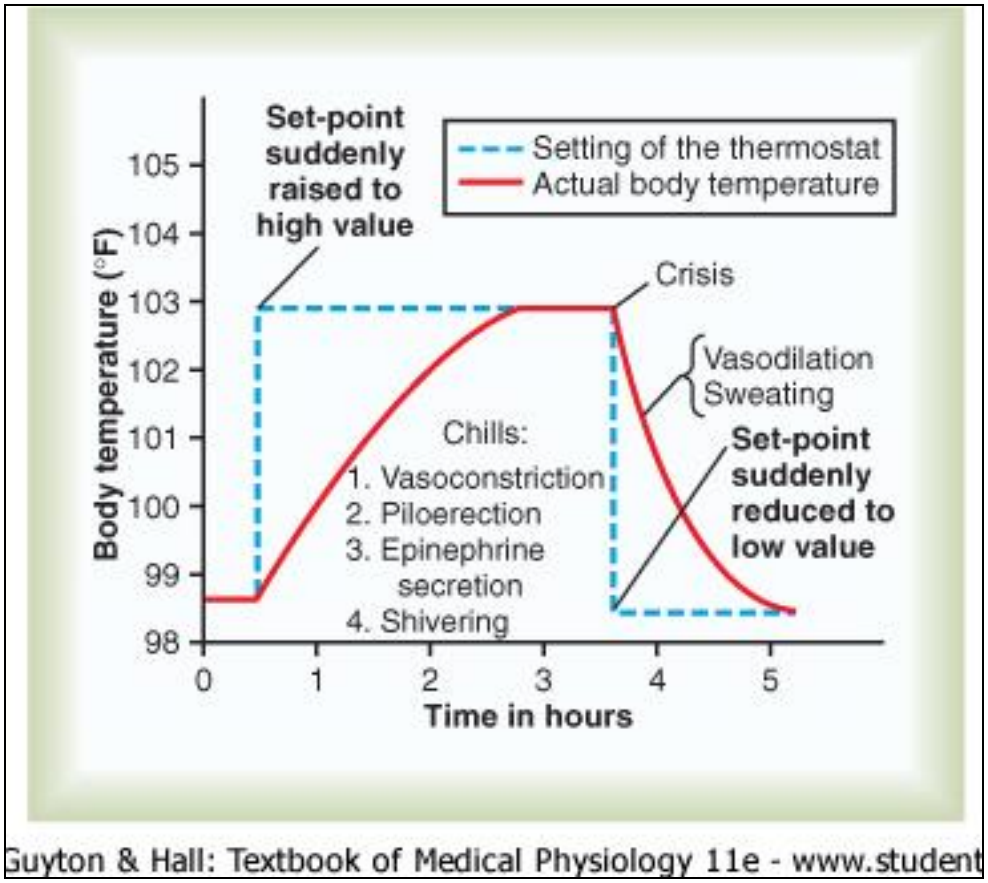

Figure 73-11 Effects of changing the set-point of the hypothalamic temperature controller.

Resetting the hypothalamic temperature regulating center in febrile disease- effect of pyrogens:

Many proteins, breakdown products of proteins, and certain other substances, especially lipopolysaccharide (LPS) toxins released from bacterial cell membranes, can cause the set-point of the hypothalamic thermostat to rise.

Substances that cause this are called ***pyrogens***.

Pyrogens can thus cause fever during disease.

Within a few hours after the set-point has been increased for the body, the body temperature also approaches this level, as shown in figure 73-11.

Mechanism of action of pyrogens in causing fever- role of interleukin-1

- When bacteria or breakdown products of bacteria are present in the tissues or in the blood, they are phagocytized for example by the blood leukocytes, and by tissue macrophages.
- These cells digest the bacterial products and then release a substance called interleukin-1 (IL-1).
- IL-1, upon reaching the hypothalamus, immediately activates the process to produce fever.
- As little as one ten-millionth of a gram of LPS from bacteria, acting in concert with the blood leukocytes and tissue macrophages can cause fever.
- Several experiments have indicated that IL-1 causes fever by first inducing the formation of prostaglandins, which act on the hypothalamus to elicit the fever reaction.
- This mechanism may be where aspirin acts to diminish fever because aspirin impedes the formation of prostaglandins from arachidonic acid. Drugs such aspirin that reduces fever are called ***antipyretics***.
- Fever caused by brain lesions.
- When a brain surgeon operates in the region of the hypothalamus, severe fever almost always occurs.
- Another condition that frequently causes prolonged high temperature is compression of the hypothalamus by a brain tumor

End!