

The Autonomic Nervous System and Intermediary Carbohydrate and Fat Metabolism

Richard J. Havel, M.D.*

METABOLISM and the substrates subserving it are subject to neural and humoral regulation, central to successful adaptation to environmental stresses. These stresses include those associated with ingestion and storage of food-stuffs and those requiring augmented expenditure of energy. The importance of neural and humoral regulation in the absence of such stresses (the "basal" state) is less well defined, although it is clear that some sort of control is required to account for shifts in utilization of available substrates during the transition from the fed to the fasting state. The autonomic nervous system and, more specifically, its sympathetic division, may participate in the integrated responses to these changing requirements. In only a few instances, however, are the relative importance of neural and various humoral factors reasonably well established. Recent studies suggest that the sympathetic nervous system can influence metabolism not only by affecting the flow of major metabolic fuels (fatty acids and glucose directly), but also by effects on secretion of hormones which regulate metabolic processes. Therefore, although this brief review will emphasize neural regulation of carbohydrate and fat metabolism, it will be necessary also to discuss the current state of knowledge of regulation by various hormones.

Most aspects of work on this subject have been summarized recently.¹⁻⁵ Therefore, reference will be made to appropriate reviews for each topic, and specific citations will be limited to recent studies and to certain controversial areas. To simplify the presentation, species differences in regulatory mechanisms

will not be considered in detail and, where possible, man will be the focus of discussion.

Metabolic Effects of Catecholamines

Although most of the metabolic effects of the sympathetic nervous system probably are mediated by norepinephrine released from nerve endings at specific sites, much of our knowledge of the actions of norepinephrine depends upon its effects when injected into the vascular system or added to tissues *in vitro*. Much useful information has been collected in this way, but it must be remembered that although injected norepinephrine should mimic the actions of norepinephrine secreted by the adrenal medulla, these may differ from the effects of sympathetic stimulation. Also, it is important to realize that adrenergic blocking agents usually inhibit actions of injected catecholamines more effectively than norepinephrine liberated from nerve endings in target tissues.

LIPID METABOLISM^{1, 2}

Both norepinephrine and epinephrine are potent stimulants to mobilization of fat (triglycerides) from adipose tissue in man. This action is reflected in rapid increase in the plasma levels of free fatty acids (FFA) and glycerol, products of hydrolysis of stored fat (triglycerides) in adipose tissue. The concentration in blood of these readily-measured metabolites is generally a good indication of the rate of mobilization of fat, because adipose tissue is the principal source of circulating FFA and glycerol, and their removal from the blood usually keeps pace with the rate of mobilization. However, removal of FFA is generally a function of their plasma levels and the rate of blood flow through the various sites of uptake (mainly splanchnic tis-

* Cardiovascular Research Institute and Department of Medicine, University of California, San Francisco Medical Center, San Francisco, California.

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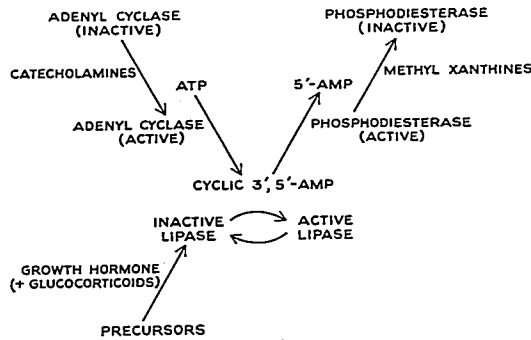
sues and muscle); therefore, under conditions of increased blood flow, increased mobilization may be masked by increased uptake. In contrast, glycerol leaves the blood mainly in liver so that increased flow to somatic structures (as in exercise) does not affect removal appreciably. For this reason, the level of glycerol more closely reflects the rate of mobilization of fat under certain conditions.⁵

The fat-mobilizing action of catecholamines results from the increased rate of formation of the "second messenger," adenosine cyclophosphate (cyclic 3'5'-AMP), which activates a hormone-sensitive lipase that catalyzes the hydrolysis of triglycerides to free fatty acids and glycerol (fig. 1). Abundant evidence indicates that the activity of this enzyme can control the rate of mobilization of fat and that it is influenced not only by catecholamines but also by other hormones, of which the most important probably is insulin. Insulin inhibits the lipase and thus tends to counteract the fat-mobilizing action of catecholamines.^{5, 6} This interaction is complicated by the fact that both norepinephrine and epinephrine are able to prevent secretion of insulin by the pancreas in

response to various stimuli.⁷ It is possible that catecholamines promote mobilization of fat by inhibiting pancreatic secretion of insulin, but they mobilize fat equally well in depancreatized dogs and in juvenile (insulin-dependent) human diabetics.⁸ This suggests a direct action on the hormone-sensitive lipase in adipose tissue. Recent evidence in dogs suggests that free fatty acids themselves stimulate secretion of insulin.^{9, 10} Thus, it may be that the ability of injected catecholamines to inhibit insulin secretion tends to prevent modulation by the action of FFA.

Mobilization of fat by catecholamines has easily-recognizable effects on tissues which normally take up FFA in substantial quantities.^{4, 11, 12} Increased uptake in tissues which normally utilize FFA as a major fuel (liver, kidney, lung, heart, and skeletal muscle) is accompanied by increased formation of triglycerides, which accumulate as fat droplets. In most tissues, fatty acids in such triglycerides can be metabolized only by oxidation, within mitochondria, to CO₂ and water. In liver, they also can be oxidized partially to ketones, and increased production of ketones by liver

FIG. 1. Regulation of hormone-sensitive lipase in adipose tissue. The enzyme reverts rapidly to the inactive form unless activated by cyclic 3'5'-AMP, which itself is destroyed rapidly by a phosphodiesterase. Thus, active lipolysis depends upon continuous synthesis of 3'5'-AMP which is under control of the adenyl cyclase system. Catecholamines entering adipose tissue from the blood or norepinephrine liberated at sympathetic nerve endings within the tissue can activate the adenyl cyclase system, thus increasing the rate of formation of 3'5'-AMP. The rapid turnover of all components of this system provides for rapid changes in rate of lipolysis and, consequently, mobilization of fat from adipose tissue. The sensitivity of the adenyl cyclase system to catecholamines and other lipolytic stimuli is thought to be increased by thyroid hormone. In contrast, growth hormone together with glucocorticoids increases synthesis of lipase, producing a more sustained increase in lipolysis which, however, is delayed in onset. Methyl xanthines promote lipolysis by inhibiting the phosphodiesterase which destroys 3'5'-AMP. Mobilization of fat is inhibited rapidly by insulin in two ways. First, in the presence of glucose, insulin promotes esterification of fatty acids released by lipase action, chiefly through increased formation of alpha-glycerophosphate, the precursor of the glyceryl moiety of triglycerides. Second, and probably more important, insulin inhibits the formation of active lipase, possibly by an action on the adenyl cyclase system. This action is independent of any effect on glucose metabolism.



rapidly follows increased hepatic uptake of FFA following injection of catecholamines. Also in the liver, some of the FFA can be re-transported, after esterification to triglycerides, back into the blood in the form of very-low-density lipoprotein molecules that carry hepatic lipid to extrahepatic tissues for storage or oxidation. In animals, such increased secretion and, eventually, increased plasma levels of triglyceride-rich lipoproteins, have been observed.

Recent studies suggest that hormone-sensitive lipases which are activated by catecholamines also exist in other tissues, including liver, heart and skeletal muscle. In the perfused rat heart, increased release of glycerol into the perfusate follows addition of catecholamines even when heart action has been arrested with potassium.¹³ The importance of a lipolytic effect of catecholamines in tissues other than adipose tissue needs further study.

CARBOHYDRATE METABOLISM⁵

Unlike the situation for mobilization of fat, epinephrine influences carbohydrate metabolism much more than norepinephrine. The major changes observed in intact animals are hyperglycemia and hyperlactatemia. The complex mechanisms underlying these changes are incompletely understood. The hyperglycemia usually is considered to reflect chiefly activation of hepatic glycogenolysis, but a direct effect of epinephrine on this reaction sequence is difficult to demonstrate in intact animals, and in dogs the hyperglycemic effects persist for many hours. There is evidence that glucagon released from the pancreas can mediate the glycogenolysis by activating adenylyl cyclase in liver.¹⁴ It is recognized that epinephrine activates adenylyl cyclase in many other tissues, and it is likely that its hyperglycemic action is related to metabolic effects at several sites. In muscle, 3',5'-AMP activates phosphorylase and accelerates conversion of glycogen synthetase to a less active (b) form. The result is accelerated glycogenolysis. As discussed below, this, together with other effects in muscle, results in greatly increased release of lactate into the blood. Some of this lactate is converted to glucose in the liver (Cori cycle) and the process of this conversion (gluconeogenesis) is

also accelerated by epinephrine. Thus, increased release of glucose from liver could result from increased rate of new glucose synthesis (partly from lactate). This effect may be related to increased levels of 3',5'-AMP also, since increased rates of oxidation of FFA (entering liver from adipose tissue or arising from hydrolysis of triglycerides stored in liver) are accompanied by changes in enzymatic activities. The latter divert pyruvate from oxidation in the citric acid cycle to the pathway leading to phosphoenolpyruvate (dicarboxylic acid shunt), thence to glucose.¹⁵ The fat-mobilizing effect of epinephrine gives rise to increased oxidation of FFA in muscle. This is accompanied by a reciprocal reduction in glucose uptake which could contribute to the hyperglycemia. However, the hyperglycemic effect of catecholamines is not inhibited by agents which selectively prevent fat mobilization. The hyperglycemia undoubtedly is augmented by inability of the pancreas to respond by secreting more insulin, when epinephrine is present. This action is less likely to initiate the event, however, since insulin levels do not fall below those prevailing before epinephrine was injected.⁷ Finally, augmented secretion of ACTH produced by epinephrine may contribute to persistence of the hyperglycemia. The lesser hyperglycemic effect of norepinephrine in all species, including man, reflects its lesser ability to activate the adenylyl cyclase system in tissues other than adipose tissue. This dissociation of action also demonstrates that the more potent hyperglycemic action of epinephrine depends to a major extent on effects other than mobilization of fat.

Although epinephrine clearly activates glycogenolysis and increases lactate release from muscle, it is not established that this is the only, or even the chief, cause of hyperlactatemia. The rate-limiting step in conversion of glucose-1-phosphate (derived from glycogen) to pyruvate is phosphorylation of fructose-6-phosphate to fructose-1,6-diphosphate. The enzyme catalyzing this reaction, phosphofructokinase, is activated by cyclic 3',5'-AMP. Recently, evidence that this reaction is facilitated by epinephrine has been obtained.¹⁶ Release of lactate from muscle could also be increased if entry of pyruvate into the citric acid cycle were impaired. Such an effect does result

from increased oxidation of FFA in muscle, and it has been shown that infusion of FFA or norepinephrine together with glucose increases blood levels of lactate.¹⁷ Finally, increased utilization of glucose in muscle accompanying the hyperglycemia could accelerate the Cori cycle and intensify the hyperlactatemia.

Epinephrine also activates phosphorylase in cardiac muscle, an action which has been considered to underlie the inotropic response. However, recent studies clearly show that activation of phosphorylase follows, rather than precedes, increased contractility of hearts perfused with epinephrine, and an inotropic effect can be observed with concentrations of epinephrine that do not activate phosphorylase. This does not exclude the possibility that the inotropic effect is mediated by cyclic 3'5'-AMP, the concentration of which increases together with the inotropic action of epinephrine. As indicated earlier, epinephrine and norepinephrine activate hydrolysis of stored lipid in heart as well as breakdown of glycogen; these metabolic events seem appropriate to the increased energy needs of inotropy.

METABOLIC RATE ^{2, 4, 5, 13}

Both epinephrine and norepinephrine increase respiratory gas exchange and heat production at rest. Except under special circumstances (to be discussed below), the effect of epinephrine is greater. The mechanism of the calorigenesis has been studied repeatedly, and it seems clear that multiple actions are involved. Those which are understood best are related to increased requirement for ATP. For example, infusion of norepinephrine into fasting humans at a rate which increases oxygen consumption about 25 per cent is accompanied by increased cardiac contractility and respiratory minute volume. These processes involve increased muscular work which drives oxidative metabolism by increasing availability of ADP for oxidative phosphorylation. In addition, increased uptake of blood-transported substrates, such as FFA and lactate, requires ATP-consuming reactions of fatty acid esterification and gluconeogenesis. Calculations indicate that these processes cannot nearly account for the extra oxygen consumed. Possibly, increased turnover of substrates within

specific tissues, unaccompanied by their transport via the circulation could require ATP. An example of this would be augmentation of the fatty acid hydrolysis-esterification cycle observed in adipose tissue *in vitro*.

Evidence has been adduced that the calorigenic action of epinephrine is coupled to increased transport and utilization of lactate by comparing the increase in oxygen consumption following epinephrine with that observed after infusing sufficient lactate to produce a comparable blood level. Similarly, the calorigenic action of norepinephrine has been related to increased mobilization and utilization of FFA by showing that specific inhibition of its fat-mobilizing action by nicotinic acid (which does not alter its cardiorespiratory or hyperglycemic action) approximately halves the calorigenic effect, and by correlating the increments of calorigenesis and fat mobilization. However, as already indicated, energy requirements for storage of these metabolites cannot account for the magnitude of calorigenesis.

Less-well-understood mechanisms for the calorigenic action depend upon electron transport, unaccompanied by phosphorylation of ADP. This could occur: (1) by uncoupling or bypassing phosphorylating steps; (2) by increased utilization of high-energy intermediates for purposes which do not require ATP. Evidence for the latter type of process comes from experiments in which residual oxidative metabolism was measured after inhibition of synthesis of high-energy phosphate with oligomycin. In heart, this can account for a large part of respiration not coupled to the contractile process.¹³ It is possible, therefore, that substrates such as lactate and FFA, which are mobilized by catecholamines, drive nonphosphorylating oxidations. Alternatively, the correlations which have been observed may be fortuitous, and such increased oxidations may be a more direct effect of catecholamines on one or more processes utilizing high-energy intermediates of the electron transport chain.

RECEPTORS FOR METABOLIC EFFECTS ^{2, 5}

Characterizations of the metabolic effects of catecholamines according to the dual receptor theory of Ahlquist have met with varying success. Where various mimetic and lytic agents have produced conflicting results, a partial ex-

planation may be the complex nature of the effect measured. This applies particularly to the hyperglycemia produced by epinephrine. As discussed earlier, this may be related to inhibition of insulin secretion, activation of hepatic phosphorylase, increased availability of lactate, and increased oxidation of FFA, both hepatic and extrahepatic. These various effects may be mediated by different receptors. Characterization of inhibitors also requires that the nature of the interaction (i.e., competitive or otherwise) be defined. This is difficult to achieve in intact animals and such studies are not always available for simplified systems. Available evidence suggests that the inhibitory effect on insulin secretion is an alpha effect¹⁹ (beta-mimetics stimulate secretion of insulin), the hepatic glycogenolytic effect is indeterminate, and the release of lactate from muscle is a beta effect. Both alpha and beta lytics can inhibit activation of lipolysis in adipose tissue. The former is noncompetitive and requires high concentrations, while the latter is competitive, so that this effect resembles that expected for a beta receptor. However, the dose-response relationships for activation of lipolysis in adipose tissue by beta-mimetic drugs indicate that a bimolecular reaction between receptor and drug is untenable and a trimolecular reaction is required.²⁰ Chemical characterization of the various receptors appears necessary for more meaningful classification.

Role of the Sympathetic Nervous System in Regulation of Metabolism in Physiologic and Pathologic States

The sympathetic innervation of adipose tissue is well documented by the high content of norepinephrine with respect to the actively-metabolizing mass and by demonstration of norepinephrine in nerve endings around arterioles. Nerve endings also have been demonstrated in close apposition to adipocytes, but it has been reported that in several species these endings do not contain norepinephrine.²¹ Very recently, catecholamine granules, and more specifically norepinephrine, have been identified histochemically along the plasma membranes of adipocytes from obese human subjects.²²

Stimulation of nerves to adipose tissue is

accompanied by vasoconstriction and decreased blood flow; when an alpha-lytic drug is injected first, stimulation then results in vasodilation which is not influenced by atropine.²³ This suggests, but by no means proves, that the vasodilation is not mediated by cholinergic fibers. The vasoconstriction accompanying nerve stimulation tends to inhibit release of FFA and glycerol, but such release can be demonstrated under appropriate circumstances in adipose tissue with an intact arterial blood supply.²³ Stimulation of nerves to isolated fat pads also leads to release of FFA, which can be prevented by prior sympathectomy.

Perhaps a more meaningful demonstration of effects of sympathetic discharge has been obtained by electrical stimulation of areas in the mesencephalon and diencephalon of the dog.²⁴ This usually increases plasma levels of FFA and glycerol together with heart rate and blood pressure. However, in both areas it has been possible to observe the presumptive effects of lipolysis in adipose tissue in the absence of cardiovascular effects. The lipolytic effects were blocked by prior injection of ganglionic blocking drugs and were not prevented by adrenalectomy. This suggests that "centers" representing the sympathetic innervation of adipose tissue are present. These are located close to the midline and extend from just above the pituitary and mammillary body into the thalamus in the diencephalon and in a limited area of the superior collicular gray matter in the mesencephalon. Evidence for a separate "center" influencing mobilization of fat has been obtained in experiments with 2-deoxy-d-glucose, an inhibitor of glucose metabolism which, like glucose, is phosphorylated through the action of hexokinase, but is not further metabolized. In dogs, its injection causes mobilization of fat which is unaffected by adrenalectomy and is blocked by ganglionic blocking drugs.²⁵ This action has been shown to depend upon an area in the lower cervical and upper thoracic spinal cord; sectioning the cord above or below this area does not prevent the response, which presumably depends upon disruption of metabolism in cells controlling sympathetic impulses to adipose tissue. Thus, it is reasonable to postulate that areas or "centers" in the hypothalamus, mesencephalon and lower cervical

spinal cord can influence rather selectively the rate of firing of sympathetic nerves innervating adipose tissue. The specificity is further supported by the observations that sympathetic discharge produced by occlusion of the carotid artery is not accompanied by evidences of lipolysis in adipose tissue²⁶ and that such lipolysis can occur during orthostasis in some subjects with absent postural reflexes²⁷ (see below).

ADAPTATIONS RELATED TO FEEDING
AND FASTING^{1, 2, 3, 5, 6}

Considerations of this topic often have been confused by failure to distinguish between the question of the importance of tonic stimulation of mobilization of fat by sympathetic nervous activity and the related but separate question whether alterations in this activity have a role in caloric homeostasis. Evidence for tonic stimulation derives chiefly from effects of autonomic blocking drugs. In dogs, ganglionic blockade with hexamethonium uniformly decreases the rate of mobilization of FFA. A point worth emphasis is that reduction of plasma levels of FFA is usually less pronounced than the reduction in their rate of entry into the blood. Presumably, this reflects reduction of cardiac output or redistribution of blood flow in such a way that rate of exit (fractional turnover rate) is reduced also. Whether the reduction of rate of entry also is related partially or entirely to redistribution of blood flow away from adipose tissue is not known.

Equally profound reductions of mobilization of fat can be produced by deep anesthesia with pentobarbital (Nembutal), and the rate of fat mobilization can be seen to vary with depth of anesthesia. In man, effects of ganglionic blockade on plasma levels of FFA have been considerably less striking, but it is unlikely that complete blockade has been produced, and measurements of entry rate of FFA into the blood have not been made. Recently, several investigators have reported that the beta lytic drug, propranolol, produces little reduction in plasma level or entry rate of FFA into the blood in man. In one such report,²⁸ it was concluded that beta-adrenergic blockade depressed mobilization of fat at rest only slightly. However, the rate of entry of FFA

into plasma was depressed about 20 per cent during the first ten minutes following completion of a 15-minute infusion of propranolol. In another study,²⁹ in which propranolol was infused for 130 minutes into subjects fasted overnight, the rate of entry of FFA was depressed about 50 per cent (the plasma level of FFA fell only 20 per cent as result of concomitant decrease in fractional turnover rate). These results are compatible with a substantial contribution of sympathetic tone to mobilization of fat in resting humans, particularly when it is recalled that blockade of transmitted impulses is more difficult to achieve with adrenergic blocking drugs than are effects of injected catecholamines.

In view of their widespread effects, studies with drugs blocking sympathetic nervous activity do not provide crucial tests of the importance of sympathetic tone in mobilization of fat. However, in man, other evidence can be brought to bear on this question. First, slight increases in sympathetic tone, such as are produced by upright posture, are accompanied by increased plasma levels of FFA and glycerol. This effect is absent in some, but not all, patients with orthostatic hypotension.²⁷ Similarly, spinal anesthesia to the level of high thoracic segments, of 60 to 90 minutes' duration, was accompanied by a fall in plasma levels of FFA and glycerol.³⁰ In another study, the sight of food usually was followed by a fall in plasma level of FFA in healthy men fasted for five hours.³¹ Finally, both in humans³² and in baboons,³³ intracarotid arterial infusions of glucose in amounts insufficient to affect measurably arterial plasma levels of glucose or insulin are accompanied by reduced plasma levels of FFA and glycerol. This effect is abolished by ganglionic blockade. Equivalent infusions into a peripheral vein are without such effect. These observations are compatible with the presence of areas in the brain which influence mobilization of fat via sympathetic pathways and are sensitive to small changes in carotid arterial glucose concentration. These could be the diencephalic or mesencephalic areas discussed earlier.

It can be concluded fairly that sympathetic nervous activity probably does influence the basal rate of mobilization of fat in some species, including man. This does not exclude an

equal or greater importance of humoral effects, particularly that related to the plasma level of insulin, an extremely potent inhibitor of the hormone-sensitive lipase in adipose tissue.

If the above conclusion is accepted, it is reasonable to consider that the prevailing level of sympathetic tone conditions the magnitude of fat mobilization occurring during more prolonged fasting. Thus, as the secretion of insulin gradually falls, the magnitude of the increase in mobilization of fat should be determined by the level of sympathetic nervous activity and other fat-mobilizing stimuli. Whether sympathetic nerves to adipose tissue increase their activity with starvation is a separate, and still unresolved, question. The early observation that denervation of certain fat organs in the rat inhibits to some extent loss of fat during fasting does not bear on this question, unless it is assumed that the innervation is without influence until some arbitrary time after fasting is initiated.⁶ Likewise, the observed reduction of plasma levels of FFA by ganglionic blockade in diabetic dogs withdrawn from insulin (considered to be "superfasted")²⁵ and evidence of reduced fat mobilization in sympathectomized diabetic dogs²⁶ may reflect only loss of a normal complement rather than increase in the level of sympathetic tone. Some points in favor of increased sympathetic activity during fasting can be adduced, however. First, the evidence that a small increase in concentration of glucose perfusing the brain can influence fat mobilization^{22,23} suggests that the gradually-falling level during the first two days of starvation may be accompanied by increased activity of certain central areas regulating fat mobilization. Second, increased number and size of fluorescent catecholamine granules in adipose tissue of obese subjects starved for 72-96 hours have been reported.²² Third, it has been observed that blood flow to certain white adipose tissue depots (expressed per unit fat-free wet weight) is increased during fasting in rats.³⁴ It appears that a contribution of increased sympathetic tone in adipose tissue to mobilization of fat during fasting is a reasonable possi-

bility, although it is by no means established by the limited information available.

ADAPTATIONS ACCOMPANIED BY HYPERTROPHY OF BROWN FAT

Under certain conditions in which the size of the interscapular (brown) fat pad is increased, the calorogenic effect of norepinephrine is magnified greatly. This tissue differs from ordinary (white) adipose tissue in that the cells contain many small droplets of fat rather than one central droplet, and in the tremendously increased number of highly-developed mitochondria per cell. Norepinephrine increases blood flow and oxygen consumption in this tissue and the hydrolysis, re-esterification and oxidation of triglyceride fatty acids. Animals in these situations tend to increase heat production in response to exposure to cold by a process that does not involve shivering (nonshivering thermogenesis).

Adaptation to Extrauterine Life.^{2,5} Mobilization of fat accompanies the general arousal of the nervous system that immediately follows birth. The rapidity of the response, its inhibition by hexamethonium and its correlation with other evidences of arousal all tend to implicate an adrenergic mechanism. When such animals are exposed to cold, nonshivering thermogenesis occurs. Numerous experiments indicate that most of the increased metabolism responsible for this heat production occurs in brown adipose tissue, and that increased sympathetic activity liberating norepinephrine, locally, mediates the thermogenic response. Brown adipose tissue may have an important role in maintenance of body temperature in newborn infants, since considerable brown fat is normally present in the thorax and dorsal scapular areas at birth and this tissue is depleted of fat in premature infants that die in hypothermia.

*Arousal from Hibernation.*⁵ Temperature measurements indicate that brown adipose tissue is the first site to warm when certain hibernators are aroused. Again, evidence suggests that this response is mediated by norepinephrine released locally, and that much of the increased oxygen consumption during arousal occurs within the tissue. Further, the arrangement of veins draining brown fat is such as to provide for direct warming of the blood flow-

* The effect of denervation could be related to reduced blood flow rather than to inhibited lipolysis in the denervated organ, but recent studies have failed to confirm this possibility.²⁴

ing through the great vessels and the nervous system. This is considered to activate the circulatory system and brain and, eventually, the entire animal.

Exposure to Cold.⁵ Heat production during short-term exposure to cold is produced mainly by shivering. When rats are exposed to cold for several weeks, the brown adipose tissue undergoes hypertrophy and hyperplasia, and nonshivering thermogenesis replaces shivering. In contrast to the situation in the newborn and in hibernators, it is unlikely that the small mass of brown fat can account for the extra oxygen consumed in this process. However, the calorogenic effect of norepinephrine is increased, and studies with blocking drugs and other procedures implicate the extra-adrenal part of the sympathetic nervous system in the response. Mobilization and oxidation of FFA and glucose are increased in proportion to the increased metabolic rate. The mechanism of the nonshivering thermogenesis is unknown. Possibly, by analogy with the calorogenic action of catecholamines in unadapted animals, augmentation of some nonphosphorylating pathway of oxidative metabolism is involved.

MUSCULAR EXERCISE^{2, 3, 5, 37}

When men perform leg exercises in the postabsorptive state, mobilization of fat increases within five to ten minutes, and can increase severalfold with prolonged activity. Several observations indicate that increased activity of the sympathetic nervous system chiefly mediates this response. First, plasma levels of norepinephrine increase rapidly during such exercise, while levels of insulin change little.^{38, 39} Second, the response is blunted by injection of beta lytic drugs. Secretion of growth hormone also increases during such exercise, but this cannot initiate the mobilization because it does not occur until 20 minutes or more after exercise begins. It seems likely that secretion of growth hormone serves to maintain fat mobilization during prolonged exercise, or to continue it during the period of recovery from exercise, since its action is delayed in onset and prolonged (fig. 1). Quantitative studies of substrate use during prolonged exercise indicate that local stores of fat are used to a considerable extent also. It is unknown whether a hormone-sensitive lipase in muscle

is activated during exercise and whether such activation is mediated by the nervous system.

When mobilization of fat is prevented with nicotinic acid during exercise, utilization of stored fuels (probably both fat and glycogen) increases. In McArdle's syndrome, where stored glycogen cannot be used effectively because of absence of muscle phosphorylase, ability to exercise is impeded further by nicotinic acid.⁴⁰ This suggests that sources other than muscle glycogen and FFA transported in the blood cannot be mobilized sufficiently rapidly or extensively to furnish the energy required for muscular work. Even during aerobic exercise in the postabsorptive state, use of glycogen stored in muscle and blood glucose increases.^{41, 42} The role of sympathetic innervation of muscle in activating phosphorylase under these conditions is not established, but not essential since other mechanisms activate phosphorylase in contracting muscle. Production of glucose from liver also increases, maintaining blood levels in the face of increased muscular uptake. Here again, whether increased sympathetic activity underlies this response is unknown.

PSYCHOLOGICAL STRESS^{1, 2, 12}

Various short-term situational stresses in man cause rapid mobilization of fat which can be prevented by ganglionic blockade. Presumably, this response has biological meaning because of the increased need for readily-oxidized substrates and the importance of conserving limited stores of carbohydrate for the nervous system when the organism needs to increase muscular activity rapidly ("fight or flight"). The effect of more prolonged situational stresses where mobilization of fat could be inappropriate for energy needs is not established. One potentially deleterious effect that might be expected is hypertriglyceridemia. Secretion of triglyceride-rich very-low-density lipoproteins from the liver is a direct function of hepatic uptake of FFA in man.⁴³ When mobilization of fat is increased during muscular exercise, triglyceride levels actually tend to fall, in part, at least because the mobilized FFA are diverted to the working muscles and away from the liver. When mobilization increases in the absence of muscular exercise, the resulting increased entry of FFA into the

liver should increase hepatic production of lipoprotein-bound triglycerides and the level should rise. Increased levels of plasma lipoproteins have been observed in relation to psychological stress in man. A related, but different, mechanism through which the sympathetic nervous system might influence plasma levels of lipoproteins is suggested by the observation that plasma levels of triglycerides are correlated directly with the extent of rise in FFA levels produced by a standard intravenous infusion of norepinephrine.⁴⁴

TRAUMA AND SURGICAL STRESS¹²

Plasma levels of FFA increase after major surgical procedures. In extensive burns, this evidence of increased mobilization of fat is related to the extent of the injury.⁴⁵ Increased urinary excretion of catecholamines implicates the sympathetic nervous system but, as in the case of muscular exercise, it is likely that "stress" hormones of the pituitary (growth hormone and ACTH) also participate. Possible adverse effects of excessive mobilization of fat in such conditions include fatty infiltration of the heart and other organs, increased body temperature related to the calorogenic action of catecholamines, and a tendency to thrombosis. The last possibility derives from the ability of fatty acids, particularly saturated ones, to activate the clotting process, both *in vitro* and *in vivo*. The relevance of these observations to human disease is an important but unanswered question, but the excessive mobilization of fat produced by ACTH in rabbits⁴⁶ and by norepinephrine in dogs¹¹ frequently is followed by death.

In the presence of metabolic acidosis, the fat-mobilizing and calorogenic actions of catecholamines are impaired.⁴⁷ This could be an important metabolic concomitant of various types of shock, possibly contributing to decreased availability of oxidizable substrates.

SPECIFIC DISEASE STATES

Diabetes Mellitus. Partial inhibition of mobilization of fat by ganglionic blockade in ketotic diabetic dogs has been mentioned. Since mobilization of fat can increase hepatic ketogenesis, promote gluconeogenesis and inhibit uptake of glucose in muscle, a mechanism by which various stresses can impair con-

trol of diabetes, particularly in insulin-dependent subjects, is clearly provided.

Lipoatrophy. An intense chromaffin reaction in subcutaneous fat has been described in Russell's syndrome, a disorder resulting from hypothalamic tumor, in which loss of adipose tissue is prominent.⁴⁸ It is unknown whether the loss of fat results from intense stimulation of sympathetic nerves to adipose tissue. In patients with generalized lipodystrophy, mobilization of fat as FFA and glycerol is extraordinarily large in relation to the very limited fat stores.⁴⁹ Again, it is not known whether the function of the sympathetic nervous system is abnormal.

Pheochromocytoma. Increased plasma levels of FFA frequently are observed.⁵⁰ The hypermetabolism characteristic of this state can be explained by the mechanisms discussed earlier.

Hyperthyroidism.^{5, 51} Increased mobilization of fat is a regular accompaniment of this abnormality and is reflected in moderate increases in plasma levels of FFA (modulated by the increased cardiac output) and more striking increases in glycerol. This does not seem to be related to increased sympathetic nervous activity. Catecholamines injected *in vivo* or added to surviving adipose tissue *in vitro* cause a greater increase in lipolysis in the presence of hyperthyroidism. This appears to reflect increased sensitivity of the adenylyl cyclase system, to this as well as other lipolytic stimuli.⁵² While the increased availability of substrate produced by the increased lipolytic rate is appropriate to the energy needs of the hyperthyroid state, the hypermetabolism is essentially independent of rate of fat mobilization. Inhibition of lipolysis (with nicotinic acid) does not decrease oxygen consumption appreciably in either euthyroid or hyperthyroid humans. However, some sympathicolytic drugs can reduce oxygen consumption in hyperthyroidism.

Coronary Heart Disease. There is evidence that individuals at high risk for this disorder have increased sympathetic nervous activity during the waking hours. Hypertriglyceridemia is considerably more prevalent in such subjects. FFA levels rise to a greater extent during a standardized series of psychological tests in hypertriglyceridemic men who have

recovered from myocardial infarction.⁵³ It is reasonable to postulate that hyperactivity of the sympathetic nervous system is one of the causes of the hypertriglyceridemia, but this is not established.

PHARMACOLOGIC AGENTS^{2, 5}

Methyl Xanthines. These compounds increase the concentration of 3'5'-AMP by inhibiting the phosphodiesterase that hydrolyzes it (fig. 1). Beverages containing caffeine and related substances can, therefore, promote lipolysis.

Nicotine. Nicotine increases sympathetic nervous activity in several ways, and smoking cigarettes can cause mobilization of fat, even in regular users.

Sympathomimetic Agents. Beta-mimetic agents, such as isoproterenol, are potent lipolytic stimulants. Certain commonly-used central nervous system stimulants increase mobilization of fat in the rat. Amphetamine and related compounds may increase mobilization of fat by direct action on adipose tissue as well as by a central effect.⁵⁴ Theoretically, these appetite depressants could also contribute to weight loss by a calorogenic action related to their ability to cause fat mobilization. Considering the large amounts of catecholamines required to increase oxygen consumption in man, such an effect is unlikely to be sufficient to contribute to weight loss.

Conclusions

The sympathetic nervous system participates in an integrated neurohumoral response to stress which increases the supply of substrate for demands of oxidative metabolism. It appears to constitute the rapidly acting part of this response, later supported by similar effects of growth hormone and ACTH secreted by the pituitary. The mobilization of fat and inhibition of insulin secretion that result from increased sympathetic nervous activity serve to decrease use of carbohydrate in non-nervous tissues and to inhibit many anabolic processes. Potentially, excessive sympathetic activity may have deleterious effects, which include hyperlipoproteinemia, increased tendency to thrombosis, inhibition of reparative processes, and unnecessary increase in certain oxidative reactions. Conversely, undue inhibition of sympa-

thetic activity could impair metabolic processes by limiting the supply of substrate. The importance of counteracting effects of sympathetic nervous activity in pathologic states is not established, but attempts to increase the supply of glucose and insulin appear to be the most rational approach to treating certain acute illnesses.

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Anesthesia

CESAREAN SECTION For cesarean section 12 patients were anesthetized with spinal anesthesia. Blood pressure, pulse, cardiac output, stroke volume, blood volume, and acid-base studies were performed before anesthesia, after anesthesia, and after delivery. Anesthetic levels varied between T2 and T8. Every patient developed a fall in systolic and diastolic blood pressure after anesthesia. In eight of the 12 patients heart rate declined. There was a mean drop in cardiac output from 5,400 ml./min. to 3,560 ml./min. Turning the patients on their sides increased cardiac output, heart rate and stroke volume. Delivery resulted in a mean increase in cardiac output of 2,880 ml. to 8,410 ml., compared with a mean output of 5,530 ml. just before delivery. Heart rate declined by an average of 11 beats per minute, systolic pressure increased 21.8 torr and central venous pressure rose from 4.9 to 9.75 cm. H₂O. Blood volume decreased 16.2 per cent or 1,004 ml. after delivery, and then continued to decline until the fifth postpartum day. Cesarean section under spinal anesthesia seems contraindicated in the pregnant patient with heart disease because of the extensive cardiovascular changes encountered. (*Ueland, K., Gills, R., and Hansen, J.: Maternal Cardiovascular Dynamics, Amer. J. Obstet. Gynec.* 100: 42 (Jan.) 1968.)