THE METABOLIC EFFECTS OF EPINEPHRINE AND RELATED AMINES[1]

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INTRODUCTION

This review is an attempt to survey the vast literature, which has accumulated since the beginning of the century, on the many metabolic effects of epinephrine and related sympathomimetic amines. The effect of epinephrine on carbohydrate metabolism was the first of these metabolic responses to be discovered. Effects on carbohydrate metabolism continue to be the most widely studied of the biochemical actions of this group of drugs. In recent years great progress has been made in disclosing the fundamental mechanism by which epinephrine influences carbohydrate metabolism. It has been necessary, therefore, to devote a large segment of the review to this subject. There has been less interest in the actions of the sympathomimetic amines on the metabolism of protein, amino acids, and certain other nitrogenous organic substances. More attention has been directed toward the effects of epinephrine on the metabolism of lipide, which appears to be the major fuel in the calorigenic action of epinephrine. A large amount of investigative work has been done to delineate the effects of epinephrine on lipide metabolism in the intact organism, and recent reports indicate that epinephrine catalyzes fatty acid catabolism in isolated tissues and in tissue homogenates. The observed changes in the concentrations of citric acid cycle intermediates have introduced yet another metabolic response to epinephrine. This subject is treated separately in view of its role in the final steps in the metabolism of most organic substances.

The mechanism of the calorigenic action of epinephrine continues to be a controversial subject. Although this subject has been reviewed in recent years, there is sufficient new or neglected material to warrant further discussion of the evidence bearing on the mechanism by which epinephrine increases oxygen consumption. Since there has been no extensive survey of the effects of sympathomimetic amines on inorganic metabolism, this subject is discussed in detail.

This survey of metabolic effects of the sympathomimetic amines would be incomplete without a section on the interactions of epinephrine and various hormones. Therefore, two essentially distinct facets of these interactions are considered; namely, the influences of the hormones on the metabolic effects of epinephrine, and the effects of epinephrine on the secretion and utilization of the hormones. There are metabolic effects of epinephrine which appear to be partially or completely dependent upon the presence of certain of the hormones. In addition, epinephrine appears to influence the production or utilization of

certain hormones and, consequently, a metabolic effect of epinephrine may be *secondary* to an epinephrine-induced change in hormonal activity. The final section of the review includes a miscellaneous group of topics.

The actions of sympathomimetic amines other than epinephrine and their relative potencies for a specific effect are discussed under the specific topic. These data have been used in several places to assist in analyzing or in supporting a proposed mechanism of action of epinephrine. For this purpose it is assumed that the sympathomimetic amines under discussion have the same mechanism of action. For structures closely akin to epinephrine this appears justifiable. The hyperglycemic activities of sympathomimetic amines have been investigated extensively and it is from these results that generalizations concerning structure-activity-relationships have been drawn.

No attempt has been made to relate the actions of the injected amines to the actions of the sympathetic nervous system or to discuss the nature of the adrenergic nerve mediators. These matters have been reviewed in detail by von Euler (193, 194, 195). The effects of the body on the sympathomimetic amines in so far as it concerns their metabolism have been reviewed by Bacq (18), Bernheim (32a), Beyer (34), and Blaschko (38). For detailed summaries of the pharmacology of the sympathomimetic amines the reader is referred to the book by Bovet and Bovet-Nitti (52), the reviews by Lands (333, 334), and the recent book, "Noradrenaline," by von Euler (195).

Most of the early literature on the pharmacology of epinephrine and related sympathomimetic amines was included in Trendelenburg's reviews (547, 547a). A more recent, though less detailed, survey is to be found in the book on the adrenal gland by Hartman and Brownell (252). More selective reviews of particular metabolic effects of these drugs are referred to in discussions of the individual topics.

I. CARBOHYDRATE METABOLISM

A. Blood glucose

1. Epinephrine hyperglycemia; glucose liberation and assimilation. During the half-century since Blum's (42) discovery of "Nebennierendiabetes" the mechanisms involved in epinephrine hyperglycemia have been analyzed in minute detail (99, 113, 547). As a result of the activation of hepatic glycogenolysis epinephrine causes an increased amount of glucose to enter the circulation from the liver (566). Since the amount of hepatic carbohydrate present in the liver at the start of the epinephrine action would account for only a small fraction of the carbohydrate output of the liver during the period of the hyperglycemia, it was evident that other substrates for gluconeogenesis must supply a substantial amount of this glucose. Protein was not the main source of this new carbohydrate, and the fat-carbohydrate interconversion was not yet established. Simultaneously with hepatic glycogenolysis, increased muscle glycogenolysis (216) contributes large amounts of lactic acid (97, 107). Lactic acid from muscle was shown to be largely responsible for hepatic gluconeogenesis through the lactic acid cycle (99, 101).

Interesting indirect support for the importance of the lactic acid cycle in the action of epinephrine comes from recent comparative studies with glucagon, an agent which mimics the action of epinephrine on the liver but has no glycogenolytic action on muscle. Whereas epinephrine produced a transient loss of liver glycogen and a rapid recovery to, or above, the control level, hepatic glycogen remained low for several hours after the administration of glucagon (118). In addition, glucagon infusions, unlike epinephrine infusions, did not produce a sustained hyperglycemic level (183, 525). The limitations of hepatic gluconeogenesis during epinephrine action may be indicated in the "adaptation" to the glycosuric effect of continuous administration of epinephrine in partially pancreatectomized rats (286).

Further details have been suggested to complete this picture, but most of these suggestions remain controversial. Decreased glucose utilization by peripheral tissues would place a lesser burden on the liver. This was first suggested by Wiechmann's experiments in man (586). Much earlier, Underhill and Closson (552) suggested that maintained epinephrine hyperglycemia would require a reduced uptake of glucose by the liver. The possibility that part of the hepatic glucose might be derived from fat has been adequately supported by subsequent work (512, 515). Blood glucose supplied by the kidney (91, 457; but see 46) or decreased glucose utilization in tissues other than muscle could be of some importance, but the role of these factors in epinephrine hyperglycemia has received little attention. A small number of tests of epinephrine on veno-arterial glucose differences in eviscerated dogs gave no evidence that epinephrine increased the output of glucose from the kidney (457). Glycogenolysis in adipose tissue was activated by epinephrine (499), but glucose was not formed as an end-product of glycogenolysis in this tissue (396). The many problems which arose in the course of the development of the present knowledge of epinephrine hyperglycemia have been discussed extensively (69, 99, 105, 244).

Wiechmann (586) suggested that epinephrine depressed glucose assimilation by peripheral tissues when he found that the arteriovenous (A-V) glucose difference was less during epinephrine hyperglycemia than during a comparable hyperglycemia induced by glucose administration. Since the time of Wiechmann's report a considerable amount of experimental data and discussion have accumulated in the literature concerning effects of epinephrine on peripheral utilization of glucose. The validity of Wiechmann's observation has been confirmed repeatedly in man and in animals (10, 108, 112, 509, 510, 556). It has been stressed that the liver is unable to supply sufficient glucose to account for the magnitude and duration of epinephrine hyperglycemia. Evidence in favor of, and in opposition to, a diminished peripheral utilization of glucose has been reviewed (99, 244). In spite of the many claims of reduced peripheral utilization of glucose during epinephrine hyperglycemia, it should be understood that this claim does not imply a glucose utilization below normal resting utilization at normal glycemic levels. There is a utilization below the expected utilization accompanying simple glucose plethora. Cori and Cori (106) stated it thus, "after epinephrine . . . carbohydrate oxidation may be increased in spite of diminished blood sugar utilization."

The fact that epinephrine produced a potentiated hyperglycemia with glucose (510) or glucagon (556), together with a reduced A-V glucose difference, has been interpreted as evidence that epinephrine reduces peripheral assimilation of glucose. In their rapid, intravenous glucose tolerance tests Amatuzio and his associates (10) found that epinephrine greatly decreased the rate of blood glucose removal. When rabbits under chloralose were infused with maximally effective amounts of insulin, the glucose infusion rate necessary to maintain a normal blood level was reduced by epinephrine (132). All of these results can do no more than *suggest* decreased peripheral utilization; they *do not prove* decreased peripheral utilization. Effects of epinephrine on hepatic glucose production and assimilation complicate the interpretation of the data.

More direct evidence that sympathomimetic drugs cause a decreased peripheral utilization of glucose comes from the work of Ingle and Nezamis (288, 289). In eviscerated rats infused with glucose and insulin they found that both epinephrine and isoproterenol (isopropylarterenol, *dl*-N-isopropyl-norepinephrine, Isuprel®, Aleudrine), a substance without hyperglycemic activity in rats (175), reduced glucose assimilation.

There is, however, a large body of information which has been interpreted as indicating that epinephrine either does not influence, or actually increases, the assimilation of glucose by peripheral tissues (244). Some workers (71) compared the A-V glucose difference before and after epinephrine. Samson and Jacobs (478) found little increase in A-V glucose difference in prolonged infusions of epinephrine which maintained hyperglycemia. Griffith *et al.* (247) found only increased glucose use by a cat limb during hyperglycemia at the end of a 5-minute intravenous infusion of epinephrine. In a further investigation (245) similar hyperglycemias induced by infusing glucose (50 mg/kg and min for five minutes) or epinephrine (4 μg/kg and min for 5 min) resulted in less glucose utilization, and more blood flow and oxygen use in the case of glucose infusions. An explanation of this effect may be found in the suggestion of Cori *et al.* (112) that during the first minutes of a rapid rise in blood glucose the A-V difference measures mainly the loss of blood glucose to the interstitial spaces. Another difficulty in experiments in which epinephrine is administered intravenously either as an injection or as a continuous infusion over a period of several minutes is that the effects of epinephrine may be dissipated within five to ten minutes after the end of the injection. During this interval A-V differences measure mainly the exchange between intravascular and interstitial fluids. By the time measurements related to assimilation can be made, the effect of epinephrine has been dissipated.

There are two crucial facts to be reconciled in the question of whether or not epinephrine depresses glucose utilization: 1) The influence of epinephrine on glucose assimilation at normal blood glucose levels, in the absence of insulin, has not been demonstrated conclusively. At relatively normal blood glucose levels epinephrine did not appear to depress glucose utilization in intact animals (247, 509), in perfused limbs (373a), or in eviscerated rats (289). Nonetheless, Griffith *et al.* (246) infused epinephrine into the femoral arteries in cats and observed an increased lactic acid output at rates of infusion that did not change

flow, and a suggestion of decreased glucose uptake at rates of infusion which reduced flow. The experiments of Ingle *et al.* (289), in which glucose was infused into eviscerated rats, showed that these preparations maintained similar glucose levels whether or not epinephrine was administered. Epinephrine did depress glucose assimilation when a large amount of glucose was administered along with insulin which markedly elevated glucose utilization.

2) The depression of glucose assimilation by epinephrine in isolated muscle has been demonstrated conclusively (68, 176, 533a, 573). The magnitude of the depression of glucose assimilation by epinephrine in the isolated rat diaphragm deserves attention. In either low or high concentrations of glucose epinephrine depressed assimilation about 30% (569). Similarly, with large variations in insulin concentration the effect of epinephrine was about 40% depression (68). Obviously, the action of epinephrine is independent of the glucose or insulin concentration. An application of these figures to the problem in the intact animal is instructive. If the maximal depression of glucose utilization is only about 30%, under normal conditions, with a glucose arteriovenous difference of about 2 mg %, the change would be about 0.6 mg %. This difference would be well within experimental error and, thus, not determinable. However, when the glucose A-V difference is magnified to 10 mg % by hyperglycemia or insulin, a decrease in uptake of 3 mg % would be detectable.

The explanation for the varied results reported for the action of epinephrine on glucose assimilation can be that the result will depend necessarily upon whether the experimental conditions will allow the action to be demonstrated. A large amount of the controversial data on whether or not epinephrine hinders glucose uptake may be brought into accord by the evidence discussed in the preceding paragraph.

There is agreement that when blood sugar is increased there is increased tissue utilization of glucose. The authors who contend that peripheral utilization is diminished by epinephrine, maintain that, during epinephrine hyperglycemia, tissue utilization of glucose is less than during glucose administration to an equal glycemic level. Those who disclaim this epinephrine effect state that apparent reductions in glucose utilization are due to measurements of A-V glucose differences without accurate, simultaneous measurement of blood flow.

There are several papers which can be interpreted more readily if we accept the results of *in vitro* investigations which show that with a larger control rate of glucose uptake, the absolute depression of glucose assimilation by epinephrine is greater and, thus, more readily measurable. In this light several studies, which showed epinephrine to have no effect on glucose utilization by perfused limbs, may be attributed to low glucose levels and, thus, low control assimilation rates. Lundsgaard and his co-workers (373a) presented excellent experimental evidence to support this interpretation. They found little effect of epinephrine at low sugar levels, but with high glucose levels, and thus with elevated control assimilation rates, epinephrine depressed glucose utilization. This evidence would explain the apparent ineffectiveness of epinephrine on the glucose-infused, eviscerated rat, and the marked effect of epinephrine on the glucose assimilation of

the glucose-insulin-infused, eviscerated rat (289). This interpretation would account as well for the fact that low dosages of epinephrine, which have little effect on blood sugar, do not appear to decrease the arteriovenous glucose difference, while doses which raise blood sugar prevent the rise in arteriovenous glucose difference.

Another factor has been overlooked in experiments on glucose absorption by animal preparations devoid of a liver. Drury *et al.* (154) reported that the liverless preparation developed a high blood lactate, and that glucose assimilation was reduced by the elevated lactate utilization. These changes may prejudice studies in liverless preparations in that glucose uptake may be so limited that epinephrine effects may be masked.

Observations which require explanation are those of Himsworth and Scott (265) in which epinephrine increased the rate of fall of blood glucose in rabbits with livers excluded from the circulation, and those of Ingle and Nezamis (289) in whieh epinephrine increased glucose utilization in eviscerated rats. Under these circumstances the calorigenic effect of epinephrine may be sufficient to increase the overall utilization of glucose.

During exercise (148) epinephrine increased glucose consumption. This observation must be investigated more extensively. Just as the effect of insulin on glucose utilization is magnified by muscular exercise, the effect of epinephrine in reducing glucose utilization may be overcome by exercise. If this is the case, epinephrine hyperglycemia and muscle exercise would be acting synergistically to increase carbohydrate metabolism.

a. Species sensitivities to epinephrine hyperglycemia. These data are available

TABLE 1

Minimal doses for epinephrine hyperglycemia in various species by various routes of administration

Species	Infusion	Injection				
	Intravenous	Intravenous	Intraperitoneal	Intramuscular	Intracisternal	Subcutaneous
	μg/kg min	*μg/kg*	*μg/kg*	*μg/kg*	*μg/kg*	*μg/kg*
Man	0.025 (103)			3 (208a)	30 (347)	10 (241) 3 (509)
Rabbit	0.05 (109)	1 (171) (323)			100 (82)	50 (82) 10 (171)
Cat	0.05 (112) 0.009 (353)	1 (175a)			50 (353) 5 (347)	
Rat	0.2 (109)	20 (467)	<100 (175)	20 (467)		50 (81)
Dog	0.25 (112)	50 (346)				
Horse						31 (37)

References are given in parentheses.

for several species and for several routes of administration. This information is of value in making comparisons with other species differences in the action of epinephrine. Table 1 summarizes the available information. The basis for the differences appears to be species differences in receptor affinity for epinephrine in the liver. Experiments with liver slices indicate that the rabbit liver is about eight times as sensitive as rat liver to epinephrine (179). The ratio for minimal hyperglycemia indicated a ratio of about 1:4 in favor of the rabbit.

In crocodiles a large, intracardiac dose of epinephrine produced a prolonged hyperglycemia which started after a latent period of two hours, reached its peak in about twenty hours, and declined slowly so that the control level was approached in three days (118a).

b. Effect of route of administration on epinephrine hyperglycemia. Leimdorfer and his co-workers (347) presented evidence that the injection of epinephrine and related amines into the cisterna magna increased blood sugar. They suggested that the blood brain barrier was impermeable to these drugs and that the effect was not due to a direct action of the blood-borne drugs on the liver. This interpretation has been adequately refuted by his own investigation (347) of the effects of cutting various nerve pathways and by other investigators (353). Cori has stressed the relative sensitivities of blood pressure and of blood glucose to epinephrine and has shown that hyperglycemia occurs before any effect on blood pressure (111a). Portal infusion increased the difference between the hyperglycemic and the pressor doses (330). Liljedahl (353) has extended these studies to the cat in order to show that the effects of intrathecal injections of either epinephrine or levarterenol (*l*-norepinephrine, *l*-arterenol) on blood sugar may occur without any significant blood pressure rise. It is pertinent that only those amines which were hyperglycemic by intravenous administration did increase blood sugar by the intracisternal route (346). These data seem to explain Leimdorfer's results as a slow absorption of the sympathomimetic amines from the cerebrospinal fluid spaces.

Sherlock's (500) conclusion that the hepatic arteries are essential for the hepatic glycogenolytic action of epinephrine in the rat was based on the intraportal administration of epinephrine at a rate somewhat below that rate at which other investigators obtained hepatic glycogenolysis (406a). Furthermore, in a group of rats in which surgical removal of the total hepatic arterial supply had been accomplished, intraperitoneal epinephrine produced hyperglycemia identical with that observed in intact rats (175a).

With rapid intravenous epinephrine injection the effects of epinephrine on the denervated heart and on the rising phase of the hyperglycemic response were over in less than ten minutes, but the hyperglycemia continued for a considerably longer time (170, 171). The prolonged hyperglycemia depends on slow utilization of glucose. The rising portion of the hyperglycemic curve ends in about ten minutes and its steepest portion is during the first minute. In rested, anesthetized rats and cats intravenous epinephrine activated hepatic phosphorylase to its highest level within one minute, and within ten minutes the phosphorylase activity had returned approximately to its control level (175a).

c. Effects of season, sex, and disease on epinephrine hyperglycemia. Significant seasonal and dietary variations in epinephrine hyperglycemia in man have been observed (9). Epinephrine hyperglycemia was more pronounced in women than in men (189).

Patients with certain mental diseases (8, 259) or with epilepsy (163) exhibit poor hyperglycemic responses to epinephrine. Very small hyperglycemic and hyperlacticacidemic responses were obtained in patients with chronic psychoses, and the responses were restored to the normal range by frontal lobotomy whether or not the psychosis persisted (259). The investigators had no explanation for this interesting observation. The insensitivity of patients with mongolism to epinephrine hyperglycemia was attributed to an associated pituitary insufficiency (36).

The average hyperglycemic response to epinephrine was subnormal in patients with liver disease (263, 264, 357, 576) and with diabetes (263, 357). Since the individual responses within each group vary considerably, the test has little diagnostic value (9). In the liver disease the hyperglycemic response to glucagon also did not differ sufficiently from the normal response for diagnostic purposes (556). Van Itallie and Bentley (556) have proposed a test of liver function based upon the hyperglycemia which follows the combined actions of subcutaneous epinephrine and intravenous glucagon. In this test the rise in venous blood sugar in patients with liver disease was only one-quarter of the rise observed in normal subjects. The test with glucagon alone did not elicit a markedly different response in hepatic disease. It was concluded that the test with glucagon and epinephrine combines effects on glucose production with effects on glucose assimilation and thus exaggerates the response to only one hyperglycemic agent. The test does not appear to measure the ability of the diseased liver to convert glycogen to glucose since large doses of glucagon increased the blood sugar more in patients with liver disease than in normal subjects (389a). In addition, it is doubtful that the results of this test reflect the hepatic glycogen content. Hepatic glycogen may be normal in diabetes and in liver disease (263, 576). It is possible that another metabolic cycle accounts for the ability of epinephrine to potentiate glucagon hyperglycemia in normal subjects, but not in patients with liver disease. In normal subjects the increased blood lactate may be rapidly converted by the liver into blood glucose. The damaged liver assimilates lactate at a very low rate (408a). Therefore, the epinephrine-glucagon hyperglycemia test may be measuring the hepatic function involved in the conversion of lactate to glucose.

The hyperglycemic responses of stable, insulin-insensitive diabetics to glucagon (315a) and to epinephrine (263, 315a) were of normal magnitude but were of longer duration. In unstable, insulin-sensitive diabetics glucagon (315a) produced only a slight elevation of blood sugar and a fall in blood pyruvate and lactate, whereas epinephrine caused in one study (315a) an abnormally large elevation in blood glucose, lactate, and pyruvate, and in another study (263) a subnormal hyperglycemia. The decrease in blood phosphate which followed the administration of either glucagon or epinephrine indicated a greater utilization

of glucose (or insulin secretion) in the unstable than in the stable diabetic. There is need for additional studies of epinephrine hyperglycemia in unstable diabetics to determine the usual response and the basis for the modified response in the diabetic patient.

2. Hyperglycemic activities of sympathomimetic amines; structure-activity-relationships. Interest in the effects of epinephrine-like compounds on carbohydrate metabolism began early (358). Nonetheless, data on the relative hyperglycemic potencies of sympathomimetic amines are mainly crude estimates, rather than quantitative comparisons. Most workers have used subcutaneous administration in rabbits, employing doses which raise blood sugar less than 100 mg %. In this range the slope of the log dose-response curve is small and large variations in estimates of potencies are inevitable. On the log dose-response curve, the slope is steepest between 100 and 200 mg % and comparisons here should be more accurate.

Subcutaneous administration involves many factors which enter into the final potency results: absorption from the site of administration; glycogen content of the liver; relative potency of the amine with regard to liver glucose production and to peripheral utilization of glucose; etc. The relative contribution of each of these factors to the hyperglycemic response to one amine may differ greatly from that to another amine.

Continuous intravenous infusion circumvents certain of the difficulties of subcutaneous tests, but effects on glucose production and utilization are both estimated. For various drugs these two factors may differ independently.

Procedures involving rapid intravenous injection and estimation of the maximal rise in blood sugar during the following ten minutes produce ratios of activity which differ greatly (236, 346) from the ratios obtained by subcutaneous administration and from those obtained with liver slices.

In estimating hyperglycemic potencies some workers have given entirely misleading figures by determining the ratio of the effects on blood sugar of the same dose of each compound, rather than the ratio of the doses which produced equal hyperglycemic effects. The fact that increases in blood sugar are more nearly proportional to the logarithm of the dose makes a comparison on the basis of proportionate effects quite inaccurate.

Some examples of the difficulties of making comparisons may be drawn from the data of Chen *et al.* (82) and of McChesney *et al.* (376). These authors found that isoproterenol was much less than $1/100$ as potent as epinephrine. This figure is derived from responses to subcutaneously administered doses which produced blood sugar rises above 70 mg %. When the drugs were administered subcutaneously or intravenously in doses which produced about a 40 mg % rise in blood sugar, the ratio of activities was about 1:10. The question arises as to which value is closer to the true effect on the liver cell. From comparative studies on glucose production by rabbit liver slices, we find that isoproterenol approaches the potency of epinephrine and its potency is certainly greater than $1/10$ that of epinephrine. Thus, isoproterenol is a potent hepatic glycogenolytic agent in the rabbit. Some of the data obtained in dogs (346) and in rabbits (82) agree with

this conclusion. In rats, the picture is far different: isoproterenol is without action on the blood sugar (175) and it is essentially ineffective on rat liver slices (175a). These are, we believe, extreme examples; nevertheless, the potential error is so great that, for our purposes, only broad comparisons may be drawn.

The hyperglycemic potencies of the sympathomimetic amines are influenced mainly by the configuration at certain sites in the basic β-phenylethylamine structure: 1) the groups combined with the nitrogen atom, 2) the presence of phenolic hydroxyl groups in the *meta* and *para* positions, 3) the alcoholic hydroxyl group on the alpha-carbon and its spatial orientation, and 4) the length of the carbon chain beyond the carbon to which the nitrogen is attached.

1) Modifications of the groups attached to the nitrogen have a pronounced effect on potency. Removal of the N-methyl group of epinephrine results in norepinephrine[2] which has a potency variously estimated at $\frac{1}{4}$ to $\frac{1}{20}$ that of epinephrine (25, 33, 41, 82, 102, 120, 121, 175, 228, 241, 271, 274, 376, 467, 492, 493). Hydroxytyramine (270) is about $\frac{1}{5}$ as hyperglycemic as epinine (492). Kephrine (adrenalone) is far more potent than its demethylated derivative (400). Phenylephrine (*l-meta*-sympatol, Neo-synephrine®) is about $\frac{1}{20}$ as hyperglycemic as epinephrine, whereas norphenylephrine is less than $\frac{1}{200}$ as effective as epinephrine (27, 121). Also norsympatol (121) is much less effective than sympatol (*dl-p*-sympatol, Synephrine®) (12, 23, 339, 436). However, butylsympatol was more potent than sympatol (60). 1-(3,4-Dihydroxyphenyl)-isopropylamine with a primary amine group was far less hyperglycemic than N-methyl-1-(3,4-dihydroxyphenyl)-isopropylamine, which possesses an N-methyl substituent (175).

Increasing the number of carbons attached to the nitrogen also depresses hyperglycemic potency. When a second N-methyl group is added to epinephrine, converting the compound to methadren (N-methyl-epinephrine), the hyperglycemic potency is reduced to $\frac{1}{30}$ to $\frac{1}{40}$ that of epinephrine (215, 526). A somewhat higher potency for methadren was obtained from studies on rabbit liver slices (102). Methadren was $\frac{1}{15}$ as potent as epinephrine, and methadren and norepinephrine were about equal in potency. Morita (400) found that the dimethylamino-, diethylamino-, and piperidino-compounds related to kephrine retained only a very small amount of the hyperglycemic activity of kephrine. A similar reduction in potency is observed when epinephrine containing an N-methyl substituent is compared with its N-ethyl (324, 376) or with its N-isopropyl homologues (376). The hyperglycemic activity of isoproterenol has been studied in several species and considerable differences in potency have been recorded. In man the tolerated subcutaneous dose (0.06 mg) did not produce hyperglycemia (214), but this dose of epinephrine would produce little or no hyperglycemia (189). In rabbits potency ratios varied from $\frac{1}{10}$ to less than $\frac{1}{100}$ of the potency of epinephrine (82, 324, 376) depending on route of administration and other factors which were discussed above. Isoproterenol produced no hyperglycemia in rats even at high dose levels (175). This difference in re-

[2] The designation *norepinephrine* is used in this review as an inclusive term in contrast to *levarterenol* which refers specifically to *l*-norepinephrine.

sponse of intact rabbits and rats has been traced to differences in the response of liver slices; rabbit liver slices respond to very low concentrations of isoproterenol, but rat liver slices do not respond even to high concentrations. With the less effective compound kephrine, a change from N-methyl to either the N-ethyl or the N-β-hydroxyethyl derivatives had little effect on potency (400).

2) The importance of the phenolic hydroxyl groups is evident from the fact that those compounds which have been found to produce hyperglycemias comparable with epinephrine have either a catechol or a phenol nucleus. The hyperglycemias obtained with sympathomimetics containing a phenyl substituent without phenolic hydroxyl groups may be related to nervous stimulation. It has been found that drugs which depress nervous activity prevent hyperglycemia due to this type of agent, but do not interfere with epinephrine hyperglycemia. Furthermore, these compounds do not have epinephrine-like action on liver slices *in vitro*.

Examples in this category are insufficient. When the *para*-hydroxyl group of epinephrine is eliminated, the resulting phenylephrine, containing only the *meta*-hydroxyl group, has about $\frac{1}{20}$ the potency of the parent compound. On the other hand sympatol, which has the same configuration as phenylephrine except that the phenolic hydroxyl is in the *para*-position, has about $\frac{1}{200}$ to $\frac{1}{400}$ the potency of epinephrine (23, 339). Whereas *nor*-epinephrine has at least $\frac{1}{20}$ the activity of epinephrine, the related compound nor-phenylephrine with only the *m*-OH group has less than $\frac{1}{200}$ the activity of epinephrine, and the compound with only the *p*-OH group is inactive at a dose 400 times that of epinephrine (121). Similarly, hydroxytyramine (270) is about $\frac{1}{100}$ the potency of epinephrine, whereas tyramine is less than $\frac{1}{1000}$ as active as epinephrine (84, 303, 400). A loss of activity occurs when the effective N-methyl-2-(3,4-dihydroxyphenyl)-ethylenediamine is converted to its *meta*-hydroxy homologue, or when isoproterenol is converted to its *meta*-hydroxy homologue (175). Paredrine (hydroxyamphetamine) has slight hyperglycemic activity in dogs (346), but not in rats (175).

From these few examples it appears that for hyperglycemic effectiveness the *m*-OH group is more important than the *p*-OH group, just as the *m*-OH group is the more important for other pharmacological responses.

Ephedrine is a good example in point for the weak activity, or inactivity, of compounds without phenolic groups. Nagel (407) had found this compound to possess less than $\frac{1}{500}$ the activity of epinephrine in rabbits. Wilson (590) confirmed this potency in the rabbit and found the dog slightly more sensitive to ephedrine. Chen and Schmidt (83) reviewed the literature and concluded that ephedrine has a very weak hyperglycemic activity in animals, including man. This effect of ephedrine appeared to be an indirect effect on the liver through the nervous system, since pentobarbital prevented the hyperglycemic action of ephedrine, but not that of epinephrine (67). More recent tests of ephedrine on liver slices indicate a small, but inconstant effect (535). We have confirmed this finding. Cornblath (117) has been able to produce a small, but regular, effect of ephedrine on the phosphorylase activity of rabbit hepatic slices, and raising the concentration did not increase the effect to the maximum obtainable with

epinephrine. From the available data it is not possible to determine whether or not ephedrine does act directly upon the hepatic cell. We have been unable to demonstrate any influence of ephedrine on glucose output in rat hepatic slices. This failure has strengthened our suspicion that ephedrine may produce its effect by releasing neurohumors from the surviving sympathetic nerve endings. According to Hökfelt (268), the concentration of epinephrine in rat liver is 1:500,000,000. If the concentration in rabbit liver is similar, a release of this amount of epinephrine is more likely to stimulate the rabbit liver than the rat liver, since the former is approximately ten times more sensitive than the latter.

Several hydroxyphenyl and phenylethylamine derivatives and aliphatic amines have been found to be essentially without effect on blood sugar. The ineffective hydroxylphenyl compounds include *p*-hydroxyephedrine, *p*-hydroxymethamphetamine (Paredrinol®) (459), tyramine, hordenine, paredrine, N-isopropyl-*p*-hydroxyphenylethanolamine, and N_1-methyl-2-(*m*-hydroxyphenyl) ethylenediamine (175). The ineffective phenylethylamine derivatives include ephedrine (175, 459), norephedrine (propadrine) (346), amphetamine, methamphetamine (175, 249, 459), and mephentermine (Wyamine®) (172). The aliphatic amines, 2-aminoheptane (346), 2-methylaminoheptane, 4-methyl-2-aminohexane, and 2-methyl-6-methylamino-2-heptene (175), elicit no change in blood sugar.

Certain sympathomimetic amines only distantly related to phenylethylamine have hyperglycemic activity despite the absence of any structural component similar to catechol. The dose of tetrahydro-*beta*-naphthylamine which caused hyperglycemia (400) also produced central nervous system stimulating effects. However, naphazoline (Privine®) and tetrahydrozoline (Tyzine®) were about one-fifth as potent as epinephrine in producing hyperglycemia, and these agents were central nervous system depressants (283). An analysis of the mechanism of action of the latter agents is needed since they appear to be exceptions in the biochemorphology of amines which produce hyperglycemia. For agents which produce hyperglycemia by affecting hepatic glucose production the mechanisms appear limited to (a) direct or reflex discharge of the sympathetic nerves, (b) effective combination with the hepatic receptors for epinephrine, and (c) actions which mimic the action of, or which release, glucagon. Other effects such as anoxia or dinitrophenol poisoning may cause glycogenolysis by a direct action on liver metabolism, but this will not lead to increased glucose production unless sympathetic stimulation occurs.

3) For the hyperglycemic effect the structure of *l*-epinephrine appears to be optimal. The configuration at the carbon adjacent to the aromatic ring is important. Thus, a change from the *l*- to the *d*-form in epinephrine reduces the potency of *d*-epinephrine to about $\frac{1}{20}$ that of epinephrine[3] (155). A similar ratio of potency is observed in a comparison of *l*- and *d*-forms of norepinephrine (376).

Unless the β-carbinol group is in the *l*-form the change in potency is the same whether the alcohol group is in the *d*-form (*vide supra*), is oxidized to the ketonic form as in kephrine (175), is reduced as in epinine (492), is converted into a methyl or ethyl ether (155), or is replaced by a primary amine group (175).

[3] The expression *epinephrine* refers to *l*-epinephrine.

Another example of the importance of the β-carbinol group is the reduction in potency that occurs when norepinephrine loses its alcoholic group in becoming hydroxytyramine (270). However, in the absence of the N-methyl and *m*-OH groups, as in tyramine, addition of the alcoholic group to form 2-(*p*-hydroxyphenyl)-ethanolamine appears to have little influence on the hyperglycemic potency (529).

A methyl group at position-6 in the ring appears to interfere with molecular combination which may involve the alcoholic hydroxyl group. Thus, 6-methylepinephrine was found to have about $\frac{1}{16}$ the hyperglycemic potency of epinephrine (242).

4) Lengthening the aliphatic chain beyond the carbon to which the nitrogen is attached has a deleterious effect on hyperglycemic activity. This change adds a second asymmetric carbon atom and it may constitute severe steric hindrance about the critical amine group.

The addition of a single carbon atom at this point converts epinephrine to 3,4-dihydroxyephedrine which reduces the potency to about $\frac{1}{20}$ (12, 487). The related 3,4-dihydroxynorepinephrine (cobefrine, corbasil) has a slightly greater potency which is about $\frac{1}{10}$ that of epinephrine (12, 459, 487). In this case the N-methyl group tends to reduce hyperglycemic activity.

The addition of a two carbon chain, as in butanefrine (ethylnorepinephrine), eliminated hyperglycemic activity in the rat (175), and markedly reduced activity in the rabbit (376, 487). Isoproterenol was apparently less effective than its homologue containing two additional carbons in its sidechain (376).

The slight hyperglycemic activity (less than $\frac{1}{1000}$ of epinephrine) of dihydroxyphenylalanine (DOPA) *in vivo* (85, 267) was produced by the metabolic conversion of DOPA into hydroxytyramine, an effective hyperglycemic agent (270). Consistent with the selectivity of DOPA-decarboxylase for *l*-DOPA, *dl*-DOPA was required in twice the dose of *l*-DOPA to produce a similar hyperglycemia (270). With recently improved analytical techniques it is possible that DOPA could be proven to be converted in part into epinephrine or norepinephrine. This conversion is made quite probable since Abelin and Goldstein (4) found an increased excretion of the neurohumors when protein was administered. Compounds with 2,4- or 2,5-dihydroxyphenyl rather than the catechol nucleus were inactive (267).

The extensive literature over the past half-century on the structure-activity relationship amongst sympathomimetic amines is notably deficient in attempts to relate changes in potency to anything more than empirical measurements and gross appearance of the structures on paper or, recently, in three-dimensional models (123a). Lewis (351) determined the ionization constants of the amino and phenolic groups in a large series of sympathomimetic amines in the hope of finding some basis for the changes in potency. No correlation between ionization constant and potency was found.

B. Carbohydrate metabolism in various tissues

1. Liver. The liver was established early as the *sine qua non* for epinephrine hyperglycemia (382, 557, 566). Recently, experiments on human subjects have

supplemented the numerous animal data on the markedly increased hepatic glucose output in response to epinephrine (25). Epinephrine multiplied glucose output in these experiments.

It is common to find liver glycogen at or above the control level after the first hour of action of subcutaneously administered epinephrine. Before this fact was established (197), there was a difference of opinion on whether epinephrine decreased or increased liver glycogen. Only with high rates of intravenous infusions of epinephrine was it possible to demonstrate a maintained depletion of liver glycogen (477).

It has been reported that the infusion of epinephrine into the portal vein of rats did not reduce their hepatic glycogen below the average found with saline infusions. On this basis it was suggested that epinephrine does not have a direct glycogenolytic effect on the liver (500). This conclusion was shown to be incorrect by a more recent investigation which confirmed the aforementioned results, but did demonstrate hepatic glycogenolysis with epinephrine when it was infused intraportally at a slightly higher rate (406a).

An increased glucose output occurs in response to epinephrine with perfused livers of frogs (350, 400), cats (373) and dogs (11, 48), and with liver slices from rats, rabbits, cats, dogs, and pigs (535, 589). However, Kepinov (309, 310) did not observe the glycogenolytic effect of epinephrine with perfused livers of frogs, rats or guinea pigs unless the "glycogenotropic hormone" of the anterior pituitary was added to the perfusing solution. He concluded that an anterior pituitary hormone was involved in the removal of epinephrine from the perfusate since epinephrine passed through the liver without fixation unless the pituitary preparation was administered (308). It is difficult to reconcile the negative findings of Kepinov with the many positive findings with isolated liver listed above. The requirement for a pituitary hormone for the action of epinephrine is of interest in view of the reduced epinephrine hyperglycemia in hypophysectomized animals (335, 364). However, in hypophysectomized animals epinephrine hyperglycemia is reduced because of a deficiency of adrenocortical hormones (131). Glucose formation in mouse liver homogenates was reported to be increased by epinephrine (253), but we have been unable to confirm these results with the reported methods or several modifications thereof (175a).

Underhill and Closson (552) made the suggestion that a more satisfactory explanation for the magnitude and duration of epinephrine hyperglycemia would be possible if, in addition to increasing hepatic glucose production, epinephrine also diminished glucose uptake by the liver. Recently, this viewpoint has been put forth with renewed vigor by Somogyi (509, 510). A diminished assimilation of glucose by the epinephrine activated liver would supplement the hyperglycemia. This effect is feasible since separate enzyme systems are involved in the transfer of glucose in the liver cell into the form of glucose-6-phosphate and in the liberation of glucose into the blood stream from the hepatic pool of glucose-6-phosphate. Glucose-6-phosphate appears to control the rate of glucose liberation from hepatic cells and it may inhibit glucose uptake by inhibiting hexokinase (119, 579). The availability of C^{14}-glucose should make possible a test of the hypothesis that epinephrine can interfere with hepatic glucose assimilation.

Determinations of glucose assimilation and production have been accomplished with liver slices (458a); more elaborate experiments might solve this epinephrine problem in perfused livers or possibly in intact animals. For quantitative studies, in addition to the specific activities of glucose going to and coming from the liver, it will be necessary to determine the specific activity of the glucose-6-phosphate. The latter, being the source of the secreted glucose, may approach the specific activity of the glucose supplied to the liver when glucose uptake is increased (as by insulin) or may be modified in the direction of the specific activity of the liver glycogen when glycogenolysis is increased (as by epinephrine).

In a paper by Teng and his associates (539) it was reported that, in a medium which allowed glycogen deposition from glucose, rat liver slices showed less glycogen deposition in the presence of epinephrine. Since the concentration of epinephrine at which this effect occurred is a concentration which induced glycogenolysis in the absence of glucose (175a), these data cannot be interpreted as necessarily representing decreased glucose uptake by liver cells in the presence of epinephrine. A similar criticism must be leveled at the conclusion of Cross and Holmes (123) that in liver slices epinephrine reduced glycogen synthesis from either glucose or lactate.

Synthesis of glycogen from sources other than glucose has been demonstrated by treating animals with epinephrine and determining the incorporation of D_2O (520) or $C^{14}O_2$ (519) into hepatic glycogen. These data do not supply the answer to the direct effect of epinephrine on glycogen synthesis. Epinephrine in these cases may serve merely to deplete liver glycogen and to raise blood lactate, thus setting the stage for more rapid glycogen deposition. A similarly complex set of data is available in the studies on liver slices from starved rabbits (28). During the first hour in glucose-containing medium, epinephrine-treated liver slices synthesized less glycogen than did control slices, but during the second hour, synthesis in the epinephrine-treated slices surpassed the controls. Glycogen formation from injected lactate was not reduced by epinephrine (73).

Conjugation of borneol with glucuronic acid by liver slices was depressed by low concentrations of epinephrine (356a).

Cellular mechanism of action of epinephrine. In recent years many fundamental details have been added to explain the mechanism by which epinephrine causes an increased hepatic glucose output. With characteristic foresight Cori (100) suggested "that epinephrine exerts its effect by increasing the concentration of active enzyme (phosphorylase) in the cell." In experiments in which the effects of epinephrine on phosphorylase were explored, only negative results were obtained (100, 344) prior to the work of Sutherland and Cori (535). This extremely important paper demonstrated that epinephrine increased liver phosphorylase activity *in vitro* in slices and also *in vivo*. Sutherland and Cori (535) first established that in the chain of reactions glycogen → glucose-1-phosphate → glucose-6-phosphate → glucose, the first reaction is the slowest and, thus, the rate-limiting step. They further demonstrated that epinephrine increased the concentration of glucose-1-phosphate and glucose-6-phosphate. These facts further implicated phosphorylase as the most likely site of action for epinephrine in

activating glycogenolysis. As a final *tour de force*, phosphorylase activity was shown to be increased when liver slices were in contact with epinephrine for only a few minutes. Subsequently it was found that epinephrine increased phosphorylase activity in the diaphragm (533) and in the heart (450a). Phosphorylase activity in liver and muscle cells was postulated to be in a dynamic state, active phosphorylase $\rightleftharpoons$ inactive phosphorylase, which is controlled by the competing actions of an inactivating enzyme and an epinephrine-catalyzed system which reactivates the inactive phosphorylase. Details of the mechanism by which epinephrine influences phosphorylase activity have been accumulating rapidly.

Sutherland (533) showed that epinephrine increased the phosphorylase activity of intact liver cells *in vitro* or *in vivo*, and that similar treatment did not influence glucose-6-phosphatase activity. However, when liver cells were damaged by homogenization or by freezing and thawing, epinephrine did not affect phosphorylase activity. The following treatments also interfered with the action of epinephrine on liver cells: prolonged anoxia, cyanide, azide, alcohols, 0.1 M fluoride, arsenate replacing phosphate, or a very low concentration of phosphate (532). These treatments affected similarly the actions of epinephrine and glucagon. The two agents appeared to act in the same manner. Only a few differences in their actions have been reported. Sutherland found that octodecyldimethylammonium chloride abolished the action of glucagon without influencing the response of the liver to epinephrine. *In vitro* and *in vivo* dihydroergotamine selectively antagonized the action of epinephrine without affecting the response to glucagon (177). Thus, it would appear that glucagon, which mimics epinephrine only in its action on liver, must in part act by a different series of reactions since it is possible to blockade selectively the effect of glucagon without limiting the action of epinephrine, and *vice versa*. From studies on synergisms and antagonisms amongst glucagon, epinephrine, and ephedrine, Cornblath (117) came to a similar conclusion.

Sutherland and Cori concluded that the cell structure was essential for the action of epinephrine on the liver since homogenization or freezing eliminated the response. In the latter case the manner of freezing or the species must be of importance. Although we have confirmed the findings of Sutherland and Cori in what we considered a quick-freeze process for rabbit liver slices, Eser and Tüzünkam (190) used a freezing microtome to prepare guinea pig liver slices, and these slices responded satisfactorily to glucagon. These results indicate either a better protection of the structure or the preservation of essential reactants by freezing and thawing the tissue under appropriate conditions.

There has been some investigation of the energy requirements for the activation of phosphorylase by epinephrine and glucagon. Sutherland and Cori (534) observed that anoxia for a few minutes did not interfere with the action of glucagon, but that twenty minutes of anoxia prevented the reactivation of phosphorylase. Further study of the effect of oxygen lack on the response of rabbit liver slices to epinephrine showed that the anoxic blockade of epinephrine action on the liver slices was reversible by reoxygenation of the slice (179). This suggested a need for energy in some phase of the action of epinephrine. Fifteen

minutes of anoxia is known to reduce severely the adenosinetriphosphate of liver slices. An energy requirement for the reaction of liver phosphorylase is suggested also by the observations that epinephrine had no influence on liver phosphorylase at 0°C. or when the liver slice was incubated in 2,4-dinitrophenol in concentrations which reduced the high energy phosphate content of the cell (178).

The energy requirement for the action of epinephrine on the phosphorylase activity of the intact cell might be at one or more sites. Some of the obvious steps are: 1) the combination of epinephrine with the cell (this is rather unlikely, since this is probably a physical adsorption); 2) a process by which epinephrine is taken into and concentrated within the cell; and 3) the conversion of inactive into active phosphorylase. More detailed information is needed on 1) and 2). Although it is generally accepted that 1) must be the first step in the combination of epinephrine with the cell "receptor," available information does not allow a decision regarding the functioning of 2) (211). There are some very recent discoveries which appear to make 3) the point at which energy is required for reactivating phosphorylase. Sutherland and his associates (450, 536, 598) found that inorganic phosphate was released in the course of the enzymic inactivation of purified phosphorylase. It was found that in liver slices epinephrine stimulated the incorporation of P^{32} orthophosphate into phosphorylase and that the P^{32} which was bound to phosphorylase was released by a selective, phosphorylase-inactivating enzyme. In keeping with Sutherland's concept that fluoride controls phorphorylase activity by inhibiting the inactivating enzyme, only a small amount of P^{32} was incorporated into phosphorylase in the presence of fluoride (449). The conversion of inactive into active phosphorylase in cell-free systems has been accomplished with muscle phosphorylase by Fischer and Krebs (204) and with liver phosphorylase by Rall *et al.* (450). For the conversion of inactive phosphorylase to active phosphorylase the requirements were an enzyme (dephosphophosphorylase kinase), a divalent cation (magnesium, liver; manganese, muscle), and adenosinetriphosphate. The requirement for adenosinetriphosphate is most interesting.

Sutherland's group has made the very important announcement that phosphorylase activation was stimulated by epinephrine or glucagon in liver homogenates fortified with magnesium and ATP (449).

The cellular mechanism of action of epinephrine in muscle and heart appears to resemble the mechanism proposed for the liver. In muscle the conversion of phosphorylase *b* (inactive) to phosphorylase *a* (active) is a dimerization requiring ATP (204, 306). It is of interest that actin appears to go from its globular to its fibrous form also by dimerizing and that ATP is required. For this dimerization of actin, epinephrine, in relatively high concentration, acted as a catalyst (524).

2. Muscle. Although the effects of epinephrine on muscle glycogenolysis and on lactic acid formation have been demonstrated *in vivo* (107, 543) and *in vitro* (257, 405, 406, 573), opinion is divided on the effect of epinephrine on glucose assimilation by muscle. Some of this literature has been examined previously in section I, A, 1. The several reports (10, 108, 510, 556, 586) that epinephrine decreases the arterio-venous glucose difference present data which have been minimized

only by the argument that this change was caused by an increased flow of blood (244, 512). There can be no similar argument leveled at *in vitro* data such as those obtained by Walaas and Walaas (573) with the rat diaphragm. In this study glycogenolysis and lactic acid production were increased, and glucose assimilation was reduced. The inhibition by epinephrine of glucose uptake in the rat diaphragm has been confirmed (176, 533a, 569). Inhibition by epinephrine of mannose and fructose uptake by rat diaphragm is consistent with the fact that these sugars also are assimilated through hexokinase (569).

Inhibition of glucose use, as measured by anaerobic glycolysis in rat diaphragm, was found when epinephrine was injected into the animal, but not when it was applied to the isolated diaphragm. The latter observation needs some explanation. The fact that anaerobic glycolysis was not inhibited by epinephrine applied to the rat diaphragm *in vitro* was taken as evidence that there is no direct effect of epinephrine on glucose utilization (88). This interpretation of the result was unjustified, since no measurements of glucose utilization were made, and since epinephrine was added after the tissue was anaerobic for 30 minutes at 38°C. When comparable experiments on diaphragms from epinephrine-treated rats were done under aerobic conditions, increased glucose assimilation and reduced lactate production were found (573).

Muscle extracts from epinephrine-treated rats used less glucose than extracts from control animals. The hexosemonophosphate contents of muscle extracts from control and from epinephrine-treated animals were not different. Since sodium fluoride diminished glucose use in control extracts and eliminated the difference between epinephrine-treated and control muscle extracts, it was concluded that ATP synthesis might be the controlling mechanism influenced by epinephrine (90).

Hexokinase was partially inhibited by glucose-6-phosphate concentrations which occur in normal muscle (119, 579). Crane and Sols (119) suggested that the increased glucose-6-phosphate content of muscle treated with epinephrine was sufficient cause for a reduced glucose assimilation. Results of experiments on cyanide-poisoned rat diaphragms led Walaas (569) to suggest that the explanation for the inhibition of glucose uptake by epinephrine cannot be the increased glucose-6-phosphate. In the presence of cyanide epinephrine caused some reduction in glucose uptake, but did not cause an increase in glucose-6-phosphate or in glycogenolysis. Since severe metabolic (571a) and functional (180) effects of anoxia occur in rat diaphragms at 37°C. (180) in much less than the 60 minute incubation period used by Walaas, the above results do not justify the exclusion of glucose-6-phosphate from a role in the inhibition of glucose uptake caused by epinephrine.

During a period of exercise epinephrine either did not influence (206), or actually increased (148), glucose use. Exercise alone is known to increase glucose use much above the resting level. An interference with the action of insulin occurred in stimulated muscle (206). The effects of exercise on glucose uptake may be explained by permeability changes, but more attention should be given to the variations in phosphorylase activity and glucose-6-phosphate concentrations as

possible causes of the apparently complex modifications of carbohydrate metabolism in active muscle.

Epinephrine did not change the oxygen consumption or the respiratory quotient of rat diaphragm (573). The adenosinetriphosphate and phosphocreatine contents of frog muscle (257) and of rat diaphragm (568) were not influenced by epinephrine.

An interesting paper appeared on the combination of epinephrine with muscle. Stadie and co-workers (516) exposed rat diaphragms to epinephrine for one minute at 25°C.; the diaphragms were tested subsequently in epinephrine-free solution for their ability to synthesize glycogen from glucose. When it was found that the epinephrine-treated muscles synthesized less glycogen than control muscles, the result was interpreted as a demonstration of firm fixation of epinephrine by the diaphragm. This interpretation is open to criticism on the basis of two facts: 1) Sutherland (533) found that the action of epinephrine on muscle at 37°C. occurred within three minutes or less; 2) the diaphragm is quite active metabolically at 25°C. Stadie's results were confirmed, but when the treatment with epinephrine and washing were performed at 0°C., there was no activation of glycogenolysis (178). The latter result suggests that there is a temperature-regulated metabolic process involved in the epinephrine activation of diaphragm phosphorylase. A reversible combination of epinephrine with its receptor should take place at 0°C. if this combination is a physical adsorption. Apparently, the subsequent processes, which activate phosphorylase are inactive or are so slow at 0°C. that epinephrine has no effect before it is washed from the tissue. From this evidence it was concluded that a rapid *effect* of epinephrine occurred at 25°C., rather than that epinephrine combined firmly with the diaphragm.

The concentration of free intracellular muscle glucose is increased during rapid glycogenolysis induced by epinephrine (or tetanic stimulation) (115). The free glucose is now known to come from the nonphosphorylytic cleavage of some glucose from glycogen by the debranching enzyme (amylo-1,6-glucosidase) (114).

Atypical results were obtained with intra-arterial infusions of epinephrine. No significant fall in gastrocnemius muscle glycogen and no increase in femoral vein lactate were observed when epinephrine was infused into the femoral artery (262). A similar rate of infusion of epinephrine into a forearm vein produced the expected decrease in muscle glycogen and increase in venous lactate (263). The arterial route, however, would cause a higher concentration of epinephrine in the leg. Related observations (246) indicated that lactate production was increased by epinephrine when the rate of intra-arterial infusion did not diminish blood flow, but lactate production was not increased when a higher concentration of epinephrine severely hindered blood flow.

McArdle (374) described a hitherto unknown muscle disease in which there was muscle pain, weakness, stiffness, and severe shortening during ischemic exercise. In this disease there is a deficiency in the glycogenolytic system of the muscle such that epinephrine does not elevate the blood lactate nor reduce the blood phosphate (374). Hepatic glycogenolysis is normal. It is conceivable that this condition is a result of a deficiency in the phosphorylase activating system of muscle which has been described by Fischer and Krebs (204).

When epinephrine is injected into an animal, muscle glycogen decreases progressively during the time that blood sugar is elevated. The rat diaphragm in glucose-containing medium responded differently to epinephrine (570). During the first five minutes glycogenolysis occurred, but, as a probable result of a balance between glycogen formation from glucose and glycogenolysis activated by epinephrine, there was no further decrease in glycogen at the end of one hour. Nevertheless, the difference in glycogen content between the control and epinephrine-treated diaphragms increased with time as a consequence of the progressive increase in glycogen content of the control tissue (570).

3. Heart. Increased cardiac glycogenolysis from the effect of epinephrine has been demonstrated *in vivo* (80, 482) and *in vitro* (124, 125, 431). Cardiac glycogenolysis was greater when epinephrine was administered to anaerobic or cyanide-treated hearts (44). Many investigators have failed to find an effect of epinephrine on cardiac glycogen in intact animals (41, and references given therein). The factors which determined whether or not the cardiac glycogen was reduced were the dose of epinephrine and the time the cardiac muscle was taken for analysis. A moderate dose of epinephrine was required for this action. In rats, the subcutaneous administration of epinephrine, 0.5 mg/kg, produced a half-maximal rise in blood sugar (81). This dose also caused a marked fall in cardiac glycogen in 20 to 30 minutes (175a). A dose of 0.2 mg/kg was not effective (41). The reduction of cardiac glycogen which followed the administration of epinephrine was relatively transient. After one hour cardiac glycogen had returned to the control level, whereas liver glycogen had reached its minimum value, and muscle glycogen was still diminishing (80). It is of interest that an earlier controversy concerning the effect of epinephrine on liver glycogen was resolved when it was shown that the interval of time between the administration of epinephrine and the sampling of the liver determined whether a decrease or an increase of glycogen would be observed (475). An exceptional result was the decreased glycogen found in pigeon heart four hours after the administration of epinephrine (483).

Decreased glucose uptake by the isolated heart of an epinephrine-treated rabbit was reported quite early (359, 587). This effect was observed when the heart was removed from an epinephrine-treated animal, but not when epinephrine was administered to the isolated heart (196). Cohen (87) obtained analogous results on rat diaphragm. This effect was observed when epinephrine was administered to the rat prior to the removal of the diaphragm; application of epinephrine to the diaphragm *in vitro* was ineffective.

Increased glucose assimilation has been reported for epinephrine-stimulated hearts (431, 587). It is conceivable that the increased rate of the heart may influence glucose uptake just as activity changes the glucose utilization in skeletal muscle. In this case any depressant effect of epinephrine on glucose assimilation may be counteracted by the greater effect of work.

Although epinephrine did not change pyruvate utilization by the dog heart, prolonged stimulation by epinephrine reduced subsequent glycogen formation from pyruvate (55).

The mechanism of the glycogenolytic effect of epinephrine on the heart, like that on the liver and muscle, involves the activation of phosphorylase. In rabbit

ventricle slices epinephrine reduced the glycogen, increased the phosphorylase activity, and increased the concentration of glucose-6-phosphate (175a).

4. Smooth muscle organs. In strips of bovine carotid arteries epinephrine increased the lactate concentration and caused contraction (527). In spayed female rats treated with estrogens, which increased uterine glycogen, epinephrine by the intraperitoneal route decreased uterine glycogen (325). Subcutaneously administered epinephrine was not effective (325, 572). Epinephrine increased glycogenolysis, phosphorylase activity, and glucose-6-phosphate in strips of rabbit uterus *in vitro* (175a). Since the major portion of the uterine glycogen is in the endometrium, the effect of epinephrine on the myometrium requires investigation. In intact rats, epinephrine reduced the glycogen content of seminal vesicles (175a).

Epinephrine increased the rate of glucose absorption from the intestine. This action was not shared by ephedrine (592). It is interesting that both kidney tubular reabsorption (150, 273) and intestinal absorption of glucose (592) are accelerated by epinephrine. Epinephrine reduced the glycogen content of rat small intestine *in vivo* and of segments of smooth muscle from dog small intestine *in vitro*. The glycogen content of segments of rabbit small intestine was not affected by epinephrine (175a).

Increased glycogenolysis occurred in segments of rabbit bladder exposed to epinephrine (175a).

5. Other tissues. a. Glandular organs. Interest in epinephrine effects on carbohydrate metabolism was first aroused by Blum's observation of epinephrine glucosuria (42). Paradoxically, the renal glucose Tm was elevated by epinephrine (150, 273). Adrenal gland glycogen was reduced by epinephrine and also by trauma, by adrenocorticotropin, and by insulin (412). Epinephrine reduced the glycogen contents of spleen, lymph node, and thymus gland in the rat (523).

b. Blood. The glycogen content of leukocytes was unchanged by the administration of epinephrine (443, 531). The blood glycogen of rats was reduced at one and thirteen hours after the subcutaneous administration of epinephrine, but was normal four hours ofter epinephrine (523).

c. Adipose tissue. Shapiro and Wertheimer (499) reported a marked decrease in the glycogen content of the adipose tissue of rats which had received an injec tion of epinephrine.

d. Brain. The administration of epinephrine to cats did not change the glycogen content of the brain (312). In mice a transient increase in brain glycogen was observed following the intravenous administration of epinephrine (79).

e. Fetus. Since the injection of epinephrine into pregnant rats reduced fetal glycogen, it appears that epinephrine crosses the placental barrier (229).

6. Relative potencies of sympathomimetic amines. a. Tissue glycogenolysis in vivo: With regard to liver glycogenolysis in mice norepinephrine was less than $\frac{1}{5}$ and nor-*m*-sympatol (Novadral) was less than $\frac{1}{25}$ as potent as epinephrine. At the same dosage ratios only epinephrine caused muscle glycogenolysis (120).

For reducing muscle glycogen in rabbits *dl*-norepinephrine was much less than $\frac{1}{4}$ as active as epinephrine, and phenylephrine was ineffective at ten times the effective dose of epinephrine (476).

b. Liver carbohydrate metabolism in vitro: Sutherland and Cori (535) found that half-maximal stimulation of glucose production by rabbit liver slices was achieved at a concentration of epinephrine of 1:15,000,000. Half-maximal stimulation of rat liver slices required eight times the concentration of epinephrine required by rabbit liver slices (179). A similar difference in sensitivity to epinephrine hyperglycemia was found between intact rats and rabbits (109).

Other sympathomimetic amines have been tested on liver slices. Sutherland and Cori (535) found the following potencies relative to epinephrine: levarterenol and *d*-epinephrine, 1/6; *d*-norepinephrine, less than 1/60; ephedrine, weak and irregular; amphetamine, inactive. Cori (102) reported that, on rabbit liver slices, N-methyl-epinephrine (methadren) had about $\frac{1}{15}$ the potency of epinephrine. With a larger series of sympathomimetic amines we have found a good correlation of relative potencies on liver slices and on blood sugar. Catechol and *m*-hydroxyphenyl derivatives were potent agents. Tyramine, methedrine, and aliphatic sympathomimetic amines were inactive. Isoproterenol and butanefrine were from $\frac{1}{5}$ to $\frac{1}{10}$ as potent as epinephrine on rabbit liver slices, but these compounds were ineffective on rat liver slices (175a). The actions of isoproterenol on rat and rabbit liver slices correspond to the potent effect of isoproterenol on rabbit blood sugar and the ineffectiveness of this compound in the rat (175, 175a).

Cornblath (117) tested some amines on the phosphorylase activity of liver slices after first incubating the slices to reduce the phosphorylase activity. He found a small but consistent effect of ephedrine and little or no effect with amphetamine. Ephedrine, when combined with epinephrine, either showed little addition or blockade; under similar conditions amphetamine prevented the effect of epinephrine. In the intact animal blockade of epinephrine hyperglycemia by ephedrine has been observed in rats (175) and in rabbits (323).

c. Muscle carbohydrate metabolism in vitro. In rat diaphragms epinephrine increased glycogenolysis at a dilution of 1:30,000,000 (w/v) and ephedrine at 1:300,000. Tyramine was ineffective (550). For effects on glycogen synthesis and on glucose utilization the potency of levarterenol was $\frac{1}{5}$ and the potency of *dl*-norepinephrine was $\frac{1}{15}$ that of epinephrine (571). Another report indicated that levarterenol and phenylephrine were less than $\frac{1}{10}$ as potent as epinephrine, and isoproterenol was ten times as potent as epinephrine in reducing the glycogen of the rat diaphragm (181). Amphetamine (561) and ephedrine (181) had little effect on the glycogen of the rat diaphragm.

d. Lactic acid production. Several compounds have been investigated for their ability to produce hyperlacticacidemia. With the exception of norepinephrine there has been no quantitative investigation of other amines on blood lactate. Information on the effect of several sympathomimetic amines on blood lactic acid concentration and on oxygen consumption would be useful for testing Lundholm's (370, 371) hypothesis that the calorigenic effect of epinephrine is caused by the hyperlacticacidemia.

Levarterenol by continuous infusion in man was estimated to be about $\frac{1}{6}$ as potent as epinephrine in raising blood lactate (25). For producing hyperlacticacidemia in rabbits (371) and rats (41) levarterenol is about $\frac{1}{10}$ as potent as epinephrine. In dogs the intravenous infusion of epinephrine at a rate of 1 μg/kg

and min increased blood lactate, but at this rate of administration levarterenol was ineffective (58).

The following amines caused hyperlacticacidemia in rats at doses which caused hyperglycemia: epinephrine, levarterenol, kephrine, and 1-(3,4-dihydroxyphenyl)-N^2-methylethylenediamine. Other phenolic amines such as isoproterenol, butanefrine, tyramine, 1-(3-hydroxyphenyl)-N^2-methylethylenediamine, and 2-(4-hydroxyphenyl)-N-isopropylethanolamine, and aliphatic amines such as 2-methylaminoheptane, and 2-aminoheptane in relatively high doses produced hyperlacticacidemia even though hyperglycemia did not occur (174, 175a).

Large doses of epinephrine increased lactate liberation and decreased glucose assimilation by the brain (408).

In early investigations it was thought that the effects of epinephrine on carbon dioxide production could be studied by observing the change in color of the pH indicator phenolsulfonphthalein. This method determined the total acid liberated. Since, in the presence of epinephrine, most of the acid produced by tissues is lactic acid, these early studies showed that epinephrine increased lactic acid production in several tissues. Garrey (213) found an increased production in the cardiac ganglion of Limulus. Martin and Armitstead (385, 386) found an increase in frog muscle, brain, mesonephron, liver, stomach, and intestine. In more direct studies by chemical analysis lactic acid formation was found to be increased by epinephrine in rabbit intestine, bovine tracheal muscle, and guinea pig uterus. Other amines which were effective on rabbit jejunum were levarterenol, isoproterenol, *dl*-3,4-dihydroxyephedrine, *dl*-3,4-dihydroxy-norephedrine, and phenylephrine. Ephedrine did not stimulate lactate production. Either ephedrine or ergotamine was able to block the effect of epinephrine on lactate production (397). In frog unstriated muscle, which was relaxed by epinephrine, lactic acid production was insignificantly reduced (453).

II. METABOLISM OF NITROGENOUS ORGANIC SUBSTANCES

1. Protein metabolism. It was first noted by Blum (42) that "Nebennierendiabetes" was not associated with an elevated urinary excretion of nitrogen. Similarly negative results were obtained upon prolonged infusion of epinephrine (478). In the intact animal, however, epinephrine-induced changes in urine flow, which regulate the rate of urea excretion, might lead to an underestimation of the total change in protein catabolism (545).

Urinary nitrogen excretion was increased by epinephrine in subjects fed an inadequate diet or fasted (6, 430, 456, 552). Conversely, glucose or glucose and insulin administration reduced the action of epinephrine on protein catabolism (186, 456). These results are in accord with the concept that fasting magnifies the negative nitrogen balance caused by stress (581). With large "stressing" doses of epinephrine in rats protein catabolism was stimulated (186, 413). The protein catabolic effect was very marked when epinephrine was superimposed on trauma (413). Engel (186) suggested a "permissive" role for the adrenocortical hormones in this "stress" effect of epinephrine, since the protein catabolic effect of epinephrine was absent in adrenalectomized-nephrectomized rats, but was present

in adrenalectomized-nephrectomized rats which were pretreated with cortisone. Rose and Nelson (467a) found that intravenous epinephrine and intraportal epinephrine or glucagon increased urea production in nephrectomized rats when the rate of administration was sufficient to deplete liver glycogen. These results suggest that the stress required for the protein catabolic effect may be the depletion of hepatic glycogen, but in the absence of the cortical hormones the liver is unable to respond to this stress by increasing protein catabolism. Albeit, only a small portion of the calorigenic effect and of the gluconeogenesis can be attributed to the action of epinephrine on protein metabolism (99).

The hypoalbuminemia which followed large repeated doses of epinephrine cannot be interpreted as an increase in protein catabolism (222) without taking into account the amount of albumin excreted by the kidneys. Proteinuria associated with the administration of epinephrine has been reported repeatedly (315, 517, 545, 599).

Another indication of increased protein metabolism is the decreased amino acid nitrogen content of the blood which follows the administration of epinephrine (61, 209, 470, 474). This action of epinephrine is not mediated by the pituitary or the adrenal glands (243, 366, 470). In fact, levarterenol caused significant lowering of blood amino nitrogen only in hypophysectomized rats, not in intact rats (243).

The mechanism of the action of epinephrine on blood amino acids is not completely defined. Since hypoaminoacidemia followed the administration of either insulin or epinephrine (122, 128, 367, 474), the epinephrine response may be an indirect effect mediated by the pancreas. Consistent with this interpretation it has been found that epinephrine must be given in an amount sufficient to produce hyperglycemia in order to produce hypoaminoacidemia (128, 470). Further support is gained from the observation that insulin reduced the blood amino acid level in eviscerated or in eviscerated-adrenalectomized rats, whereas epinephrine has no tendency to reduce the blood amino acids in the eviscerated rats (287). Several interpretations of the latter result are possible; 1) an absence of the pancreas eliminates insulin release; 2) the liver, or other viscera, may be required for the effect of epinephrine; 3) other less obvious factors may modify the results in the eviscerated preparation. If insulin is required for this effect of epinephrine, blockade of epinephrine hypoaminoacidemia by pentobarbital anesthesia may be attributable to a reduced hyperglycemic response under anesthesia (279) and, consequently, a diminished secretion of insulin.

Luck and his co-workers concluded that insulin influenced blood amino acids through the release of epinephrine because it had been observed that insulin did not produce hypoaminoacidemia in adrenodemedullated rabbits (129) or in adrenalectomized rats (243). This interpretation cannot encompass the result that insulin decreased the blood amino acid level when insulin hypoglycemia was prevented by glucose administration (368). Another fact at odds with an indirect mechanism for insulin is Ingle's observation that insulin, but not epinephrine, reduced the blood amino acids in eviscerated or eviscerated-adrenalectomized rats (287).

After reviewing the evidence, Russell (470) concluded that epinephrine and insulin have independent effects on blood amino nitrogen. The present reviewer finds that much of the evidence favors an indirect effect of epinephrine which, through its hyperglycemic action, causes the secretion of insulin.

Luck and Morse (367) had reported that two hours after the administration of epinephrine the amino acid content of rat liver and muscle was reduced. Friedberg and Greenberg (209) found that one hour after the administration of epinephrine to rats the amino nitrogen of the kidney was reduced and the amino nitrogen of the liver and skeletal muscle was slightly increased. The apparent discrepancy between the two reports on the changes in amino acids of muscle and liver may indicate merely that the fall in amino acid content of these tissues occurs during the second hour when the blood amino acids are also lower. Castro and Monaco (76) analyzed tissues from control and epinephrine-treated rats for glycine, alanine, threonine, glutamic acid, and aspartic acid. They found that epinephrine produced the following significant changes from the amounts found in control rats: aspartic acid was increased in the liver; glycine was increased, and alanine and glutamic acid were diminished in skeletal muscle; glutamic acid and glycine were increased in the heart.

Epinephrine reduced the non-protein sulfhydryl compounds (mainly glutathione) of liver and kidney, but not those of blood or muscle. There was no change in blood or hepatic ergothioneine, another sulfhydryl compound, so that there is a certain selectivity in the effect (455).

The relative potencies of epinephrine-like substances in lowering blood amino acids were similar to their relative potencies for causing hyperglycemia: *i.e.*, epinephrine $\gg$ norepinephrine $>$ phenylephrine $\geqq$ *m*-hydroxypropanolamine = epinine (474). However, a later report indicated that only epinephrine produced this effect; other amines, namely, norepinephrine, phenylephrine, ephedrine, methamphetamine, propadrine, phenylethylamine, and tuamine, were ineffective (61). A dose of levarterenol which was ineffective in intact rats caused hypoaminoacidemia in hypophysectomized rats (243). Several points might be clarified by concurrent data on blood sugar and blood amino acid changes in response to the sympathomimetic amines.

2. Creatine metabolism. Rose (468) reviewed the early literature which suggested a relationship between muscle glycogenolysis and increased creatine excretion. Epinephrine caused creatinuria when muscle glycogen was severely depleted, as indicated by an insignificant increase in blood lactate, but not when there was adequate muscle glycogen. Comsa (94) has summarized the more recent literature.

Increased excretion of creatine occurred in animals after the administration of epinephrine (94, 436). The thyroid hormone plays an essential role in this action of epinephrine (94, 95). Increased creatine excretion was induced by epinephrine in patients with pathologically elevated creatine excretion caused by progressive muscular dystrophy or diabetes mellitus, but creatinuria was not induced by epinephrine in normal subjects (445). The significance of the increased creatine excretion is not clear. Some of the excreted creatine may come from muscle

stores, but much of creatine lost may be due to a decreased assimilation by muscle of the creatine which normally is formed in the liver and is transferred to muscle (29, 479).

Some doubt is cast upon the reports of epinephrine creatinuria by the fact that glucose and other substances in the urine interfere in the usual colorimetric determination of creatine. When additional tests were done to prove that the color reaction was measuring only creatine, it was found that epinephrine did not produce true creatinuria (327).

Tissue creatine was reported to be increased (428), unchanged (327), or slightly reduced in muscle, greatly reduced in heart, and unchanged in testicle and brain (422) after the administration of epinephrine.

Epinephrine accelerated the synthesis of creatine from arginine in rat muscle pulp (428). This is an interesting *in vitro* effect of epinephrine, but it cannot be determined from the data whether the reaction occurred in a cell-free preparation. The fact that dihydroergotamine and dihydroergocornine did not prevent this *in vitro* effect of epinephrine does not supply significant information, because these adrenergic blocking agents have a relatively weak antagonism against epinephrine actions on skeletal muscle.

In man, large repeated doses of epinephrine increased the daily creatinine excretion (39), but on a somewhat reduced dose schedule the changes in creatinine were not consistent (156). The observed effects on creatinine excretion are more likely a measure of the effects of epinephrine on glomerular filtration rate than a measure of changes in creatine-creatinine metabolism.

Pflug (436) observed that sympatol, unlike epinephrine, did not increase urinary creatine. In this investigation the dose of sympatol, which did not produce creatinuria, did not produce hyperglycemia comparable to that produced by epinephrine. Reports indicating that epinephrine congeners do not produce the effects elicited by epinephrine may not mean that the response is selective for epinephrine, but may indicate that the administered dose of the congener was insufficient. For example, in experiments in which the subcutaneous doses were based upon the relative pressor potencies of the compounds by the intravenous route (61), norepinephrine, phenylephrine, and ephedrine did not reduce blood amino acids. However, Sahyun (474) did observe hypoaminoacidemia with several congeners. It might be of interest to investigate activities of congeners in doses which produce hyperglycemic effects as great as epinephrine. Thus, Mosonyi and Hermann (401) found that sympatol did not increase the urinary glucose:nitrogen ratio in dogs treated with phloridzin, but the dose of sympatol was probably insufficient to produce other metabolic effects characteristic of the action of epinephrine.

3. Uric acid metabolism. Some of the work on the effects of epinephrine on uric acid metabolism was reviewed recently by Bishop and Talbot (35). The early literature was summarized by Chaikoff *et al.* (78).

Excretion of uric acid and allantoin was increased in animals by epinephrine or by activating the adrenal medulla through insulin hypoglycemia (78, 337, 395). Ordinary therapeutic doses in man and small doses in rabbits did not pro-

duce this effect (395), but large repeated doses in man did increase uric acid excretion (39, 156). Epinephrine also increased the blood uric acid in dogs (78, 337). The "uricosuric" effect of epinephrine may be a consequence of an elevated blood uric acid concentration. With the available experimental evidence it is impossible to determine whether or not there is a direct effect of epinephrine on the tubular mechanisms controlling uric acid excretion.

It has been suggested that the uricosuric effect of epinephrine may come about by the activation of the pituitary-adrenal axis. The facts in favor of this mechanism are: 1) the large dose of epinephrine needed for the action; 2) adrenocorticotropin and cortisone have uricosuric activity (35); 3) epinephrine uricosuria was not observed in an Addisonian patient with a dosage regimen effective in normal individuals (39); 4) in adrenalectomized dogs with a small residuum of adrenal cortex epinephrine was effective (337).

4. Hexosamine. Large doses of epinephrine in man did not modify the serum hexosamine level (43).

III. FAT METABOLISM

The effects of epinephrine on fat metabolism may be subdivided for convenience of discussion into its effects on fat catabolism and on fat transport. References to the literature before 1930 are contained in the papers of Cori and Cori (105) and Page, Pasternak and Burt (425). Wertheimer and Shapiro (583) and Deuel (144) have reviewed the more recent contributions.

1. Fat catabolism. Cori and Cori (105) reviewed the work on the effects of epinephrine on metabolism. From the published evidence and their own results they concluded that fat was the major fuel for the increased metabolism induced by epinephrine.

It is all the more striking, then, that one of the first differences to be noted between the glycosurias of diabetes mellitus and of "adrenalin diabetes" was the absence of ketonuria in the latter (42, 599). Many subsequent investigators found that epinephrine caused no changes in blood and in urinary ketones in well-nourished subjects (14, 149, 424, 576), or even a fall in blood ketones as blood glucose and lactate increased (332).

Ketone body production was increased by epinephrine, however, when hepatic glycogen was low (173, 280, 459, 576), or when glycogen utilization was impaired as in glycogen storage disease (424). It is of interest in this connection that demedullation of the adrenals reduced the ketonuria which normally accompanied phloridzin treatment (198). Epinephrine increased ketone formation in perfused cat liver (40), in rat liver slices (254, 411), and in liver homogenates (251).

Epinephrine reduced the amount of radioactive acetate incorporated into the fatty acids of rat liver slices (255). This effect was similar with glucagon (HGF) and with the latter the depression of acetate incorporation was similar whether acetate, fructose, or glucose was in the medium (254). Increased production of acetoacetate and diminished fatty acid synthesis by the liver was postulated to result from an increased oxidation of fat (254). Support for this conclusion is found in the increased oxidation of octanoate observed by Harel-Ceddaha (250)

when epinephrine was added to a rat liver homogenate fortified with cytochrome *c* and ATP. In further studies Harel-Ceddaha (251) found that epinephrine increased the conversion of octanoate into acetoacetate, a result which was interpreted as an interference with the condensation of acetate with oxaloacetate. Addition of malate, an oxaloacetate generator, prevented the augmentation of acetoacetate formation during the increased octanoate oxidation. Thus, an alternative explanation would be that there was insufficient oxaloacetate to condense with acetyl-coenzyme-A which was being formed at a higher rate.

The investigations in intact animals suggest that epinephrine elevated ketone production only when hepatic carbohydrate metabolism was inadequate. Experiments on hepatic tissue *in vitro* indicate a consistent activating effect of epinephrine on ketone production. There is rapid depletion of glycogen from the liver *in vitro*, especially in rat liver slices, and epinephrine and glucagon increase the rate at which glycogen is depleted. This evidence raises the question of whether epinephrine has a direct catalytic effect on fat metabolism or whether the glycogenolytic effect is the only primary action which, under certain experimental conditions, secondarily increases fat catabolism.

2. Fat transport. Under this heading the changes in the concentrations of blood and tissue lipides will be considered. Catabolism of lipides, undoubtedly, influenced the results, but the relative importance of this factor has not been determined.

In the early investigations various groups reported that epinephrine increased, decreased, or did not change the amount of fat in the blood (425). Some unusually high epinephrine hyperlipemias (266) were found to be based on faulty analytical methods (221, 363). The more recent investigations with sound analytical procedures continue to show diverse changes in blood fat. The factors which appear to determine the type of response obtained are the dose of epinephrine, the duration of its action, the nutritional state of the subject with special reference to the liver glycogen, and the existing level of blood fat. Similar factors determine whether liver fat will be modified by epinephrine. With these factors at hand, it is possible to account for many apparently discrepant results on the basis of variations in experimental conditions without assuming an extremely variable action of epinephrine.

Some investigators reported that epinephrine produced little or no change in total blood fat (221, 363), but others found that chronic administration of epinephrine increased blood phospholipide, total cholesterol, and fatty acids (305). In chickens, which have an especially high blood phospholipide level, epinephrine decreased the concentration of this lipide (379). Other reports showed a decrease in blood fat fractions following epinephrine administration (425, 486). Under certain conditions, individual lipide fractions were modified by epinephrine when the total lipide concentration remained unchanged (167, 168). Epinephrine increased the concentration of unesterified fatty acids in the blood (152a, 233).

Cholesterol changes following epinephrine administration have been as diverse as the changes in total blood fat. Bruger and Mosenthal (59) reviewed the early literature which included reports of increased, of decreased, and of unchanged

cholesterol levels after the administration of epinephrine. Their own studies indicated no changes in blood cholesterol. Others have reported small increases (95, 381, 434, 477) or decreases (486).

In keeping with an action on fat transport, epinephrine increased liver lipides (86, 378, 425, 441, 537, 560, 582, 594, 595) and reduced adipose tissue lipide (86). The action of epinephrine on fat depots in rats was selective in that perirenal fat was reduced, but interscapula fat remained unchanged (86). After small doses of epinephrine, the carcass fat of mice was slightly reduced, but the change was of doubtful significance (126). A color reaction with thiobarbituric acid, which appears to measure unsaturated fatty acid peroxides, has been used to show that epinephrine increased the reactive substance in brain, kidney, and liver (153). An increase in hepatic neutral fat without a change in total fat was found in the rat one hour after the administration of epinephrine (167). Six hours after a large dose of epinephrine in oil and some radioactive phosphate were administered to rabbits the total lipides, neutral fats, and esterified cholesterol were increased in the liver, only phospholipides were elevated in plasma, and none of the lipides was changed significantly in the aorta. The rate of phospholipide formation in liver and in aorta was significantly increased. Daily intravenous administration of epinephrine to rabbits increased the plasma neutral fat and decreased plasma cholesterol esters. This treatment did not change the liver lipide fractions or liver phosphorus turnover, but did increase the specific activity of aortic phospholipide phosphorus without affecting the concentrations of the various lipide fractions of the aorta (162). In another paper from the same laboratory (166) increased plasma total lipides, phospholipide, and neutral fats, and reduced hepatic neutral fat were reported for rabbits on a similar treatment schedule. On the day following the last series of daily or twice daily injections of epinephrine there was an increase in the blood neutral fat:phospholipide ratio and a visible lipemia (166). These effects on plasma fat may be an aggravating factor in the pathogenesis of the vascular lesions caused by epinephrine.

The limited studies of the effects of norepinephrine on fat metabolism indicate that this agent does not elevate blood cholesterol under the same experimental conditions and at the same rate of administration as were used for epinephrine, which did increase blood cholesterol (433). Norepinephrine increased the neutral fat of the liver but did not change the cholesterol or phospholipide content (17).

The development of fatty livers, which normally follows the administration of hepatotoxic agents or pancreatectomy, requires the adrenal gland (86, 378, 560). In more recent studies Wool *et al.* (594, 595) found that ethionine did not increase liver fat in adrenalectomized, adrenodemedullated, or ergotamine-treated rats. Further support for an important role for epinephrine in fat mobilization comes from their observations that adrenalectomized rats required "permissive" doses of cortisone to allow epinephrine to restore the ability of the rat to mobilize fat to the liver, and that epinephrine restored the response to adrenodemedullated rats. Since epinephrine elicited little effect in the absence of the cortical hormones, an interaction of hormones of the adrenal cortex and the adrenal medulla is again demonstrated. An explanation for these results may be that the adrenalec-

tomized animal cannot maintain a normal amount of fat in adipose tissues and the "permissive" dose of cortisone presents the ethionine-epinephrine treated animals with fat for transport to the liver. More extensive discussions of the relation of adrenal gland to adipose tissue and fat transfer were presented by Wertheimer and Shapiro (583) and Deuel (144). The several effects of epinephrine on fat transport would be fundamentally in agreement with the opinion of Wertheimer and Shapiro (583) that the sympathetic innervation of adipose tissue is important for normal fat storage and transport.

The mechanism of the epinephrine effect on fat transport is not clear. One possibility is that there is a direct relationship to the glycogenolytic effect in the liver. Some studies of the actions of glucagon may be relevant. This agent appears to affect only liver glycogenolysis. Glucagon did not reduce the glycogen content of adipose tissue (188), whereas epinephrine did reduce this glycogen (499). Glucagon, however, was as effective as epinephrine in stimulating the transport of fat into the liver (432a). The fact that epinephrine (432) did not increase fat transport under similar experimental conditions may be related to the observation that epinephrine caused only a transient reduction in liver glycogen, whereas glucagon caused a diminished liver glycogen during the entire period of the experiment on fat transport to the liver (118). Another possible mechanism for the action of epinephrine on fat transport is an effect mediated by the pituitary and adrenal glands. The recent observation (118) that glucagon depleted the adrenal ascorbic acid makes this mechanism deserving of experimental investigation. In addition to adrenocorticotropin there may be a release of pituitary hormones more directly concerned with fat mobilization.

IV. BLOOD CITRIC ACID CYCLE INTERMEDIATES

To the well-established hyperlacticacidemia and the less frequently studied rise in blood pyruvic acid (426, 490), which are regular responses to epinephrine, there now must be added a parallel rise in some of the citric acid cycle intermediates. Pincus and his associates (439) observed that epinephrine administration in man caused an increased blood level of citric acid. The elevation of blood citrate was confirmed by this group and others in man and was demonstrated also in other animals (259, 440, 564). Villano and Tritto (564) reported a rise in the α-keto acids, which include pyruvic, α-ketoglutaric, and oxaloacetic acids. With a specific method for α-ketoglutaric acid Henneman and her coworkers (259) confirmed the observation that epinephrine raised the blood level of this acid. Other investigators concluded that epinephrine lowered the α-ketoglutaric acid level of rabbit blood (285). Their data, however, did not demonstrate a significant change, so that this report only failed to confirm the rise in α-ketoglutaric acid.

Some attempts have been made to determine whether the increased blood concentrations of these organic acids are secondary to epinephrine hyperglycemia. Villano (563) reported that glucose administration produced a temporary rise in acids of the citric acid cycle and a subsequent fall below resting level, but Pincus *et al.* (439) recorded only a fall in blood citrate following glucose. From

these results it appears that glucose plethora does not produce the same changes as epinephrine, and thus it seems unlikely that epinephrine hyperglycemia mediates the rise in citric acid cycle intermediates.

Epinephrine may raise the blood levels of the citric acid cycle intermediates as a consequence of the primary elevation of blood lactate and pyruvate. Experimental evidence for this mechanism is the recent observation that the intravenous infusion of sodium *d*-lactate in man raised the α-ketoglutaric acid concentration of the blood (7a). It is also possible that the activation of glycogenolysis or other metabolic processes in the cell may increase the formation and liberation of the citric acid cycle intermediates. Whatever the mechanism of the increased formation of these acids, it would be of interest to learn which tissue(s) is (are) responsible for the increased formation of the citric acid cycle intermediates.

V. OXYGEN METABOLISM

1. The calorigenic effect. The discovery of the increased oxygen consumption of the body in response to epinephrine has been attributed to Belawenez, who, according to Juschtschenko (302), observed this effect in 1903. Boothby and Sandiford (47) reviewed the early work on this effect, which they called the calorigenic action of epinephrine. Exhaustive bibliographies on this subject are included in the reviews by Lundholm (370), by Griffith (244), and by Sarzana *et al.* (484). Even the earlier work indicated that a major portion of the extra oxygen consumption was attributable to fat catabolism (98, 106).

It has been well-established that epinephrine increases oxygen consumption in most species (244, 370). Nonetheless, there have been some studies in which epinephrine either did not change, or actually diminished, oxygen consumption. For a possible explanation of these divergent results we may refer to the original findings of Belawenez (302) who first observed the calorigenic effect of epinephrine, but more to the point, he also observed that large amounts of epinephrine reduced both oxygen use and body temperature. Many later investigators confirmed the observation that larger doses of epinephrine lead to a fall rather than to a rise in body temperature (547, for early references see 192). With larger doses of epinephrine there was a preliminary decrease in oxygen use due to respiratory depression followed by a more prolonged effect on oxygen use due to interference with pulmonary circulation (192) and, no doubt, interference with gaseous exchange as a result of pulmonary edema. Jones and Griffith (300) called attention to the respiratory changes which occurred with large doses of epinephrine. The respiratory effects may account for the early decrease followed by an increase in oxygen and carbon dioxide exchanges which Delaunois *et al.* (134) observed in dogs to which epinephrine was given in relatively large, intravenous doses. That respiratory depression by epinephrine was involved in the reduced oxygen metabolism was demonstrated by overcoming some of the depression of oxygen metabolism with artificial respiration (134, 370). Effects of epinephrine on pulmonary blood flow obviously could not be modified by artificial respiration.

In certain species, such as fishes (505) and pigeons (423, 481), epinephrine did

not cause a calorigenic effect. The doses of epinephrine used in these studies were very large. There is some evidence of interference with tissue oxygenation under these experimental conditions. Thus, Feinschmidt and Ferdmann (200a) found that a similar dose of epinephrine decreased the phosphocreatine and increased the inorganic phosphate of pigeon muscle.

The excess metabolism evoked by the administration of epinephrine is not limited to an effect on a single organ. Newer techniques have been employed to demonstrate that epinephrine and levarterenol increase the oxygen use of the liver *in vivo* (25, 506). A transient increase in apparent heat production of the liver was recorded in the first few minutes after the administration of epinephrine (299). Stimulation of hepatic oxygen consumption by epinephrine must come about through an indirect action. Epinephrine did not increase the oxygen consumption of liver slices (136). Additional evidence against a direct stimulation of hepatic oxygen consumption is the fact that intraportal administration of epinephrine produced a smaller effect on metabolism than did intravenous administration (133).

Experiments in hepatectomized frogs, however, indicated that the liver was not essential for the calorigenic effect (104). Previous to this report Soskin (511) had found that the calorigenic effect was absent in eviscerated or hepatectomized dogs. Similarly contradictory results were obtained when the importance of the liver was evaluated for the increased temperature of muscle which regularly followed the administration of epinephrine (74). A recent investigation of the effects of evisceration on blood lactate may explain the conflicting results. Drury and his co-workers (154) noted a marked hyperlacticacidemia in eviscerated animals. Since Lundholm (370) found a relation between epinephrine hyperlacticacidemia and the calorigenic effect, it is possible that the high bood lactate of hepatectomized animals might mask the effect of epinephrine on oxygen metabolism. Soskin (511) found no increase in blood lactate, as well as no increase in metabolism, in his eviscerated animals.

Intravenous infusion of epinephrine increased cerebral oxygen use, whereas levarterenol did not produce an increased cerebral metabolism (314). When epinephrine or levarterenol was administered intramuscularly, there was no increase in cerebral oxygen consumption (498). Other investigators (402) recorded no increase in cerebral oxygen use with levarterenol or *l*-1-(*meta*-hydroxyphenyl)-2-amino-propanol (metaraminol, Aramine®) at continuous infusion rates which produced pressor effects. Many sympathomimetics depressed oxygen use of brain slices *in vitro* (446, 447). Minced brain tissue of rats used less oxygen if the animal had been injected previously with epinephrine (184, 596).

A controversy revolved about the relation of epinephrine to cardiac efficiency. Under some conditions it has been found that the oxygen use increased far more than work. From the discussion of the problem by Green, Euler, and Moe (239) it is evident that the controversy has not been resolved. An excessive oxygen use out of proportion to the increased work has been shown in hearts of mammals (240, and others) and of frogs and turtles (212, 352). A reduced efficiency of the heart in the heart-lung preparation was found with N-phenyl-N-isobutyl-nor-*p*-

sympatol and N-phenyl-N-butyl-norepinephrine, as well as with epinephrine (230). The effect of epinephrine on cardiac oxygen use is controlled to some extent by reflex activity for, when nervous reflexes were intact, there was less oxygen use and less chronotropic and inotropic action (231). The increase in cardiac metabolism was less in the innervated heart-lung preparation, and still less in the heart *in situ*, than in the denervated heart-lung preparation. In the dog heart-lung preparation veratramine, which antagonized the cardioaccelerator action of epinephrine, did not interfere with the positive inotropic effect of epinephrine nor with the effect of epinephrine which increased the oxygen consumption per beat (327a).

Epinephrine or sympathetic stimulation increased the oxygen use of rhythmically contracting cardiac muscle (231a, 240, 343), but epinephrine did not increase the oxygen use of resting cardiac tissue (77, 260, 297). A fine demonstration of the differences in the improvement of contraction by a cardiac glycoside and by epinephrine was presented by Lee. He found that ouabain improved the force of contraction of the rhythmically stimulated cat papillary muscle without modifying the oxygen consumption (342). With epinephrine, however, increased oxygen consumption accompanied the increased force of contraction (343). These results showed that the cardiac glycoside improved the "efficiency" of the failing heart, whereas epinephrine improved contraction without increasing the "efficiency."

There is little evidence that a persistent increase in oxygen metabolism occurs in skeletal muscle in parallel with the general calorigenic effect of epinephrine. Several authors (62, 316) have recorded transiently increased metabolism in the leg following an intra-arterial injection of epinephrine. This apparent increase in oxygen use during the first few minutes is reminiscent of the "Initialzacke" reported by Mertens and Rein (393a) in the intact animal. In intact animals the transient large increase in oxygen use which follows the administration of epinephrine has been attributed to the reoxygenation of "pooled" blood. However, Bücherl and Schwab (62) measured venous return from the leg which changed very little during the other recorded changes. Issekutz *et al.* (294) found that epinephrine increased the oxygen consumption of perfused dog limbs when constriction was prevented by dihydroergotamine. Griffith *et al.* (247) observed no significant change after five minutes of intravenous infusion of epinephrine at rates which increased lactic acid production and blood sugar. Since Lundholm's (370) results suggest that the calorigenic effect is related to blood lactate, more prolonged infusions of epinephrine, until the calorigenic effect is at its peak (and the hyperlacticacidemia is pronounced), should produce a more critical answer to the role of muscle metabolism in the calorigenic response.

The oxygen uptake of rat diaphragms *in vitro* was not changed by epinephrine, whether the epinephrine was injected into the animal prior to the removal of the diaphragms, or applied *in vitro* (136, 573).

Few data are available on the effect of epinephrine on oxygen use of smooth muscle. DeMeio (136) found that epinephrine increased oxygen consumption of dog retractor penis and rabbit uterus, but not that of rabbit liver and rat diaphragm. These observations may include the metabolic effects of epinephrine-

induced contraction of the smooth muscles during the respiratory measurements. Bülbring (63) observed an increased oxygen use in epinephrine-treated taenia coli muscle of the guinea pig when the muscle tension was increased, but when conditions were such that epinephrine reduced tension, there was, concomitantly, a decreased oxygen consumption. The latter observation agrees with an earlier report (453) that frog smooth muscle, when depressed by epinephrine, used less oxygen.

The reduction of 2,3,5-triphenyltetrazolium chloride has been used as an indirect measurement of tissue respiration. One hour after the administration of epinephrine to intact, adrenalectomized, or hypophysectomized rats, the dye-reduction method indicated a depressed respiration in lymph node, thymus, spleen, liver and muscle (523). The authors made no attempt to interpret these findings.

Oxygen utilization by the dog kidney was increased by epinephrine an average of 60%, even though in four out of eleven tests epinephrine reduced the kidney oxygen consumption (273).

2. Mechanism of the calorigenic effect. Considerable effort has been expended in attempts to establish the mechanism of the calorigenic effect. In recent reviews of the calorigenic action of epinephrine Lundholm (370) concluded that the mechanism of the increased oxygen metabolism involved the hyperlacticacidemia which increased tissue metabolism, but Griffith (244) attributed the calorigenic action of epinephrine to a multiplicity of changes which include increased body temperature, increased activity of cardiac and skeletal muscle, plethora of blood glucose and lactic acid, and increased cellular metabolism.

Direct stimulation of tissue oxygen use *in vitro* has not been found regularly except in a few specialized tissues (136, 145, 575). The early evidence for stimulation or inhibition of oxidations by epinephrine in various tissue preparations was reviewed by Griffith (244). A recent analysis of the inhibitions and stimulations of isolated oxidative enzyme systems agreed with the early work of Green and Richter (238), in that many of the observed effects were attributable to the epinephrine decomposition product, adrenochrome, which may act as an inhibitor of certain enzyme systems, and as an activator of other enzyme systems (448).

Restriction of skin blood flow by epinephrine causes a diminished heat loss and an increase in body temperature which may account in part for the delayed increase in oxygen use. This effect is prominent at moderate doses, but at higher doses hypothermia results (192, 547) despite more intense vasoconstriction in the skin. Whitcher and Griffith (585) found that, in intact cats, the temperature increased in response to epinephrine, and that, in skinned cats, the temperature decreased and the calorigenic effect of epinephrine was smaller. Since body temperature fell in skinned cats in contrast to the rise in intact cats, it must be concluded that constriction of skin vessels by epinephrine may raise the body temperature by conserving heat and thereby may increase the calorigenic effect, but that the skin itself must play only a secondary role in the calorigenic effect. Isoproterenol increased oxygen consumption and body temperature in the rat (577). This agent produces many of the effects of epinephrine, but it produced

reddening, rather than blanching, of the skin. Since isoproterenol in these experiments may have lowered blood pressure sufficiently to reduce blood flow in the skin, this does not necessarily eliminate the factor of diminished heat loss in the calorigenic effect.

Increased muscular activity as a result of the action of epinephrine on the nervous system may be quite important in the calorigenic action. The absence of the calorigenic effect, occasionally observed in anesthetized or curarized animals, may thus be explained. A more specific action of certain general anesthetics on the action of epinephrine on metabolism was discovered by Lundholm (370). He found that the anesthetics which reduced the calorigenic action also reduced the rise in blood lactate in response to epinephrine. In common with other pharmacological effects of epinephrine, extirpation of the sympathetic nervous system did not reduce the calorigenic effect of epinephrine (345).

Epinephrine hyperglycemia does not coincide with the calorigenic effect either in magnitude or in duration (47). Additional evidence against an important role of hyperglycemia in the calorigenic effect is the fact that certain adrenergic blocking drugs which prevent hyperglycemia did not prevent epinephrine hypermetabolism (360). Likewise, isoproterenol increased the metabolism of the rat (577), but did not increase its blood sugar (175).

Lundholm (370) found a good correlation of the effects of epinephrine on oxygen metabolism and on blood lactate. He also found that oxygen consumption was increased in proportion to the elevation of blood lactate whether the hyperlacticacidemia was produced by epinephrine administration or by the intravenous infusion of lactate. Numerous data on tissues *in vitro* indicate that lactate increases the oxygen use of many different types of resting tissues. Elevation of blood lactate in epinephrine-treated animals may explain the report of Issekutz *et al.* (293) that plasma obtained from epinephrine-injected ducks increased the oxygen use of duck erythrocytes obtained either from control or from epinephrine-injected ducks. A significant contribution to the mechanism of the calorigenic effect of epinephrine might be made by a comparison of the oxygen use of various tissues of an animal in control serum and in serum from epinephrine-injected animals.

Whelan and Young (584) compared ten minute infusions of epinephrine and norepinephrine and found that both amines stimulated respiration, but only epinephrine increased oxygen metabolism. Elevated oxygen use persisted after the infusion of epinephrine was discontinued. Bearn *et al.* (25) did not find significant increases in lactate until about 10 minutes after the start of similar rates of epinephrine infusion. The combined data from the latter two groups of investigators would be consistent with a relation between the elevated blood lactate and the calorigenic effect. It must be recalled, nevertheless, that increased oxygen consumption during the first few minutes may be a measure of the reoxygenation of the poorly oxygenated, pooled blood swept into the general circulation by vasoconstrictor action (393a).

A recent argument against the lactic acid theory was the fact that, although pigeons exhibited the usual carbohydrate changes with hyperglycemia and

hyperlacticacidemia and rapid recovery of liver glycogen after a marked depletion, there was no effect of epinephrine on oxygen metabolism in the pigeon. Another exceptional finding, in the pigeon, is a severely depleted cardiac glycogen four hours after the administration of epinephrine (483). In rats, cardiac glycogen is found to be low only during the first thirty to forty-five minutes following epinephrine. However, it does not appear that the result in pigeons can be attributed to general anoxia because the liver glycogen after four hours had risen far above the control level.

Brewster *et al.* (58) have presented evidence which appears contrary to a relationship between the calorigenic effect and the elevation of blood lactate. They found that the infusion of 1 μg/kg and min of either epinephrine or levarterenol increased the oxygen consumption of anesthetized dogs, but that at this rate of administration only epinephrine increased blood lactate. The observations of Vleeschouwer *et al.* (564a) and Smythe *et al.* (506) also suggested that for the calorigenic action in the dog levarterenol is as potent as epinephrine. This is an important exception to the usual statement that epinephrine has a much more potent metabolic action than levarterenol.

Some reports (292, 488) indicate no inhibition of the calorigenic effect of epinephrine by dihydrogenated derivatives of ergot alkaloids when these alkaloids were injected shortly before rather large doses of epinephrine. Ergot alkaloids affix themselves to tissue receptors quite slowly even *in vitro* (393) so that they must be given about one-half hour before epinephrine in order to produce their maximum adrenergic blocking action. When Lundholm and Mohme (372) gave ergotamine to guinea pigs twenty minutes before epinephrine, the calorigenic effect was inhibited. Other investigators also reported that ergot derivatives antagonized the calorigenic action of epinephrine (354, 469). Antagonism between ergot alkaloids and epinephrine is of the competitive type (393). An analysis of the conflicting results indicates that ergot alkaloids did not antagonize the calorigenic action of large doses of epinephrine (292, 488), and that these alkaloids antagonized the action of small doses of epinephrine (354, 372, 469). The evidence that the ergot alkaloids (and also yohimbine (397a)) can prevent both the calorigenic effect and the hyperlacticacidemia adds further support to the hypothesis that the elevated blood lactate causes the calorigenic effect of epinephrine (226, 372).

3. Effect of related amines on oxygen metabolism of intact animals. The calorigenic potency in mice of *d*-epinephrine was only $\frac{1}{10}$ that of epinephrine (2). Estimations of the calorigenic potency of norepinephrine vary from a value approximately equal to the potency of epinephrine down to about $\frac{1}{11}$ the potency of epinephrine (22, 26, 58, 135, 329, 371, 540, 548, 584). Continuous intravenous infusion of levarterenol at a rate of 0.25 μg/kg and min did not increase oxygen consumption in man; epinephrine, when it was infused at a rate of 0.1 μg/kg and min, was effective (227, 454). Equivalent increases in oxygen consumption were observed in dogs when either epinephrine or levarterenol was infused intravenously at a rate of 1 μg/kg and min (58). Since the amount of epinephrine administered may be considerably above the amount required for the calorigenic

effect, these findings may not represent equal potencies. Levarterenol in doses which produced maximal cardiac effects in dogs caused only slight increases in oxygen consumption (135). This evidence supports the viewpoint that the cardiac effects of epinephrine contribute only a small amount to the total calorigenic action of epinephrine.

Isoproterenol increased the oxygen consumption of rats while their physical activity was actually reduced. Body temperature was increased by isoproterenol despite the pronounced skin dilatation (577). In man, nor-*m*-sympatol in a dose of 10 mg did not affect oxygen utilization, but nor-*p*-sympatol showed a slight effect at a dose of 60 mg (121). In comparable tests epinephrine in a dose of 0.3 mg increased oxygen consumption.

The effect of ephedrine on oxygen consumption in man was small and irregular (93, 518). In dogs ephedrine in doses up to 1 mg/kg only lowered respiratory exchange (137). Amphetamine in a dose of from 1 to 10 mg/kg increased the body temperatures of rats (414). The following amines increased oxygen consumption in rats in proportion to the increase in bodily activity: amphetamine, methamphetamine, and N-methylcyclohexylisopropylamine (577).

Issekutz and Murányi (295) found that morphine-scopolamine anesthesia prevented the usual increase in oxygen use which occurred after the administration of ephedrine or *p*-hydroxyphenylisopropylamine. Since the stimulation of respiratory metabolism by epinephrine was only slightly reduced by this anesthetic mixture, the authors concluded the central nervous system effects accounted for the stimulation of metabolism by ephedrine and *p*-hydroxyphenylisopropylamine.

4. Sympathomimetic amines and the specific dynamic action of protein. Abelin and Goldstein (3) obtained suggestive evidence that the specific dynamic action of protein may be mediated by an excess production of sympathomimetic amines which can be made metabolically from tyrosine. When they fed 200–300 g of meat to human subjects and analyzed the subjects' six-hour urine samples, they found a markedly increased urinary excretion of hydroxytyramine, a small increase in norepinephrine, and a very slight increase in epinephrine. Later evidence (4) indicated a large percentile increase in the excretion of free and conjugated epinephrine and a smaller percentile increase in the excretion of norepinephrine. These observations may lead to a better understanding of the elusive mechanism of the calorigenic action of protein. If there is, indeed, a common denominator for the increased metabolisms in response to protein and to epinephrine, the suggestion of Lusk, which induced Boothby and Sandiford (47) to change the name of the epinephrine action on oxygen consumption from "specific dynamic action" to "calorigenic action," may have caused a long delay in relating the two effects.

Tyrosine, in doses which did not influence blood sugar, potentiated epinephrine hyperglycemia (85). A diet containing 10% of tyrosine increased the rat's blood sugar (389). This effect on blood sugar was intensified by the addition of 5% methionine to the tyrosine diet (442). Some additional results are applicable to a consideration of the specificity of this effect. Phenylalanine (85) or *d*-alanine

(427) did not potentiate epinephrine hyperglycemia. These results are of particular interest in the light of the findings of Abelin and Goldstein referred to above.

VI. INORGANIC METABOLISM

1. Potassium. Potassium exchange in liver and muscle and epinephrine influences thereon have been reviewed by Fenn (202) and by Fleckenstein (205).

a. Blood potassium. A transient increase in plasma potassium occurs as a result of intravenously administered epinephrine in animals (139, 140, 383, 494, 522) and in man (57). Hyperkalemia occurred also after splanchnic nerve stimulation. The response to sympathetic nerve stimulation depended upon the presence of the liver. Since hepatic nerve stimulation produced hyperkalemia in adrenalectomized animals, the adrenal glands were not essential for this response (277). After the usual administration of epinephrine, however, hypokalemia has been the more common finding (140, 278, 466, 528), especially in man (7, 75, 163, 313). Until it was shown that, subsequent to the intravenous administration of epinephrine, there was a transient rise followed by a more prolonged fall in plasma potassium (57, 434), it was thought that potassium changes in man differed from the changes which occurred in animals.

It is now established that the route of administration of epinephrine and the elapsed time before a blood sample is obtained, rather than the species studied, will determine whether an increased or a decreased plasma potassium will be found. Immediately after an effective intravenous injection of epinephrine there is a marked increase in the plasma potassium. Peak hyperkalemia occurs about one minute after the injection of epinephrine and the potassium concentration returns to the control level in three to five minutes (140). The potassium level usually falls below the control level ("afterfall") before the final return to the resting level. Repetition of the hyperkalemic response was produced by epinephrine injections at three-minute intervals (142), but during a continuous infusion of epinephrine, which sustained the hyperglycemia, the plasma potassium returned to, or fell below, the control concentration (336, 464). Since there were no significant changes in the blood concentrations of sodium, calcium, or magnesium during epinephrine hyperkalemia, the potassium effect appeared selective (141, 384).

The liver has been established as the major source of the extra potassium in epinephrine hyperkalemia (141, 384, 415). When epinephrine was injected into a perfused cat liver, the same transient output of potassium occurred (141). It was reported recently that the potassium concentrations of the non-particulate fraction of the liver and of the hepatic mitochondria were reduced soon after the administration of epinephrine (16). Marenzi and Gershman (384) demonstrated that the following organs were not essential for epinephrine hyperkalemia: digestive tract, spleen, kidney, thyroid, pancreas, adrenals, and carotid sinus. They also showed that the hyperkalemic response was potentiated by cocaine and was blockaded by ergotamine or yohimbine. When the liver was out of the circulation, epinephrine caused a small increase in blood potassium (338, 415). In

vascularly perfused dog lungs epinephrine released potassium, and this epinephrine effect also was inhibited by ergot alkaloids (256). It has not been demonstrated that potassium release from the lungs contributes to epinephrine hyperkalemia in the intact animal.

Although the site of action for epinephrine hyperkalemia has been adequately established, the mechanism by which potassium is released from the liver has not been ascertained. Epinephrine is not the only substance which elicits this unusual type of transient hyperkalemia. It has been produced by other sympathomimetic amines closely related to epinephrine (143, 278, 416, 504). Anoxia, ether, barium chloride, and posterior pituitary extract also caused hyperkalemia (140, 276). The latter treatments can induce sympathetic discharge. Indeed, Houssay *et al.* (276, 278) reported that hepatectomy, adrenalectomy, or merely adrenodemedullation prevented the hyperkalemic responses to posterior pituitary and to tyramine, and reduced the response to ephedrine. Houssay and his associates (276) emphasized three mechanisms in regard to increased hepatic loss of potassium. These were: 1) epinephrine acts directly on the sympathectomized liver, 2) several drugs act partially or completely through the sympathetic innervation to the liver and to the adrenal medulla, and 3) hepatic hypoxia as a result of decreased blood flow or of inadequate blood oxygenation allows a loss of potassium from the directly impaired liver cells.

D'Silva considered the possibility that, since the laying down of tissue glycogen is accompanied by potassium storage (202), epinephrine glycogenolysis must result in hepatic loss of potassium. D'Silva's investigation disclosed that epinephrine hyperkalemia occurred in animals with high or with very low hepatic glycogen (142). Furthermore, his and other studies showed that the potassium and glycogen concentrations of the liver were not directly related (141). Also, there was no loss of potassium from muscles when epinephrine stimulated glycogenolysis, but, on the contrary, potassium uptake was increased (225, 355, 383, 522).

Certain observations suggest that epinephrine hyperkalemia may be more directly correlated with the vascular effects of epinephrine than with its glycogenolytic action. However, no clearcut interdependence of the hyperkalemic effect with either the vascular or the glycogenolytic effect of epinephrine has been established. Martin (387, 388) could not correlate the time characteristics or the magnitude of epinephrine hyperkalemia with either its hyperglycemic or pressor effects. In addition, the relative potencies of related sympathomimetic amines for hyperkalemic action are quantitatively different from the relative potencies for hyperglycemic action (143). After larger doses of epinephrine potassium rises then falls at a time when blood glucose continues to rise (464). Continuous intravenous administration of epinephrine allowed potassium to fall toward normal during the infusion, but a quick injection superimposed on the infusion caused a large rise in blood potassium (57). However, levarterenol infusions which maintained a high blood pressure also maintained a slightly elevated plasma potassium which decreased only after the end of the infusion (403). This difference in the duration of the hyperkalemic responses may be related to the fact that norepinephrine limits, and epinephrine increases, hepatic blood flow (25,

237). The continued hyperkalemia with norepinephrine could be caused by hepatic anoxia, since it has been shown that a maintained hyperkalemia is characteristic of any condition which severely depresses hepatic oxygenation (521).

Some facts concerning the potassium metabolism of the liver are pertinent to the present discussion of the possible mechanism of epinephrine hyperkalemia and especially the effects of agents which produce severe, prolonged hepatic vasoconstriction. Poor oxygenation of the liver, whether through hypoxia, blood loss, or vascular occlusion, leads to a greater increase of potassium in the hepatic vein than in other veins (521). The rise in hepatic vein potassium proceeds slowly and is prolonged. With epinephrine the rise in hepatic vein potassium is very rapid and transient so that anoxia cannot be the mechanism of this effect.

The ability of adrenergic blocking agents to prevent epinephrine hyperkalemia supplied evidence which appears to relate the hyperkalemia more to the vascular effect rather than the glycogenolytic effect. Thus, ergotoxine (140), ergotamine (494), dihydroergotamine (416), and also dibenamine (203, 416) prevented epinephrine hyperkalemia. Since all these blocking agents antagonize the constrictor action of epinephrine, and since, with the exception of some of the less commonly used chlorethylamine derivatives, only the ergot derivatives prevent epinephrine hyperglycemia (253, 323, 530), these data seem to lend no support to the concept that the potassium release from the liver is related to glycogenolysis. This interpretation of the evidence must be tempered by the fact that tests for the blockade of epinephrine hyperkalemia and hyperglycemia by dibenamine were done by different investigators and the techniques were different. Simultaneous determinations of the effects of dibenamine on the blood sugar and blood potassium changes induced by epinephrine indicate that blockade of the hepatic release of potassium is not accompanied by the blockade of glucose liberation (180a).

If it were true that hepatic glycogenolysis is not necessarily associated with hepatic loss of potassium, then glucagon, a substance with a selective action on hepatic glycogenolysis and without cardiovascular action, would not be expected to cause hyperkalemia. Glucagon, however, did produce a transient hyperkalemia indistinguishable from the hyperkalemic response to epinephrine (593). Glucagon also increased blood sugar, but it produced no effect on blood pressure. This evidence supports a relationship of glucose production to potassium loss in the liver. This relationship is not a simple one because of the very transient potassium change and the long continued outpouring of glucose. The blood potassium was above the control level during the time that blood glucose was rising. The peak blood sugar occurred in about ten minutes when either glucagon (593) or epinephrine (17) was given intravenously and, thus, the effect on the liver was mainly dissipated by this time. This was also the duration of epinephrine action on the denervated heart (170). Under comparable conditions it has been found that the hepatic phosphorylase activity reached its maximal activity in thirty to sixty seconds after the administration of epinephrine and returned toward the control level within five or ten minutes (175a). The temporal changes in plasma

potassium correlated more directly with the rapid increase in phosphorylase activity and its less rapid decrease to the resting activity than with the blood glucose changes or with the blood pressure effect.

It must be concluded that the mechanism of epinephrine hyperkalemia is still problematical. It is not possible to define unequivocally the relationship between the release of potassium from the liver and either hepatic glycogenolysis or hepatic vasoconstriction. Although the available evidence suggests that glycogenolysis may be the more important correlated event, the fact that dibenamine can prevent the hyperkalemic response to epinephrine (and to glucagon (180a)) without grossly changing the hyperglycemic response remains as a strong objection to this simple relationship.

Epinephrine hypokalemia has been attributed to an increased uptake of potassium by muscle (383, 522) and also by the liver, which begins to store potassium immediately after its primary release of potassium (56, 141, 383). Potassium retention by muscle *in vitro* has been observed as a direct response to epinephrine and related amines (225, 355, 419, 522). It has been suggested that the accumulation of hexosemonophosphate is responsible for the tissue retention of potassium which is drawn from the plasma (113, 355).

Since pancreatectomy almost eliminated the "afterfall," D'Silva (140) concluded that potassium uptake is activated by the reflex discharge of insulin. This observation could not be confirmed (336). Contrariwise, it has been claimed that insulin hypokalemia is a "reflex" response dependent upon the presence of adrenal medulla (169). Later studies, however, showed that either epinephrine or insulin produced hypokalemia in adrenalectomized-alloxanized rats (160). The epinephrine hypokalemic effect was not dependent on the presence of the adrenal or pituitary glands (169).

The hypokalemic effect of epinephrine may be used to lower the hyperkalemia which accompanies glucose administration to adrenalectomized or adrenomedullectomized rats (157), or benzene poisoning in rabbits (365). It is possible that a blockade of epinephrine action on potassium metabolism accounts for the observation (551) that ergotamine sensitized rats to potassium poisoning.

Glucose administration to adrenalectomized rats induced a crisis which was fatal to some of the experimental animals. The crisis was associated with hyperkalemia and cardiac failure. Pretreatment with epinephrine was lifesaving. Dury (157, 158) places considerable emphasis on the hyperkalemia as a possible cause of death. The lethal blood potassium levels were only 6–7 mEq./l, but adrenalectomized animals are notably less resistant to stress. Since the surviving animals had much higher blood sugar levels, but lower potassium levels, than those which were obviously dying, it is possible that the hyperkalemia of the fatally affected animals was a response to cardiovascular failure and subsequent hepatic anoxia and loss of potassium. In those animals which did not show the acute effect, sympathetic reflex activity was sufficient to support the circulation and to cause a rise in blood glucose and a fall in plasma potassium.

The following hyperkalemic potencies of some sympathomimetic amines relative to the hyperglycemic potency of epinephrine were derived from the reports

of D'Silva (143), O'Brien *et al.* (416), and Siebens *et al.* (504): epinephrine, 1; *d*-epinephrine, 1/6; *dl*-norepinephrine, 1/4 (143) or lower (504); *dl*-cobefrine, 1/25; *dl*-N-methylcobefrine, 1/14; epinine, 1/20; phenylephrine, much less than 1/10; ephedrine, less than 1/1000; methadren, sympatol, tyramine, ephedrine, phenylethanolamine (143) and aranthol (2-methyl-6-methylamino-2-heptanol) (416) were inactive.

b. Tissue potassium. Muscle. When epinephrine was administered intravenously, there occurred a temporary improvement of muscular contraction and an elevation and a subsequent fall in demarcation potential. These changes indicated that muscle potassium may increase temporarily and then may fall below the resting level. Experiments *in vitro* have shown that potassium loss from muscle is reduced for ten minutes or more after the administration of epinephrine, or of related amines, and then potassium loss is increased (225). Epinephrine also reduced the loss of potassium from frog muscle *in vitro* (355). Direct determinations of muscle potassium during the period of hyperkalemia have not been made. However, an increased uptake of potassium by muscle occurred during epinephrine hyperkalemia (383, 522). After the subcutaneous administration of epinephrine to intact animals the muscle potassium was reduced at thirty to sixty minutes (165, 528) and muscle potassium had increased above control levels in two to four hours (394, 528).

Liver. Shortly after the intravenous administration of either epinephrine or norepinephrine the hepatic concentration of potassium was diminished (16). These sympathomimetic agents caused a marked loss of potassium from the supernatant fraction of hepatic tissue and, in addition, epinephrine reduced the potassium concentration of hepatic mitochondria. One hour after the subcutaneous administration of epinephrine liver potassium tended to be above the control level (165).

On the basis of the available experimental evidence a tentative summary of the effects of epinephrine on body potassium may be given. The potassium shifts which occur after the intravenous administration of epinephrine are a rapid transfer of liver potassium into the blood plasma and thence to muscle. The potassium changes which occur somewhat later after subcutaneous administration of epinephrine are a transfer of some muscle potassium to the liver during the hypokalemic phase. During the period of hypokalemia, blood sugar is high, liver glycogen is at its minimal level, and muscle glycogen is diminishing progressively. After a few hours, when muscle glycogen is at its lowest level and liver glycogen is at, or above, the resting level, muscle potassium is restored to, or is above, the resting level.

Fenn (202) and Fleckenstein (205) have reviewed the evidence that potassium liberated from muscle during contraction may be taken up rapidly by the liver, and, conversely, potassium released from the liver may be absorbed rapidly by muscle. Marenzi and Gerschman (383) showed that in the anesthetized animal at rest there was a loss of potassium from muscle and a withdrawal of potassium into the liver. The process was reversed during epinephrine hyperkalemia which involved a rapid potassium output from the liver and an almost equally rapid

storage in muscle. Thus, the potassium cycle, like the lactic acid cycle, may be influenced by epinephrine.

Fenn (202) suggested that epinephrine effects on tissue potassium may play a physiological role during exercise when epinephrine may liberate hepatic potassium to replenish muscle losses. This might be an aid to physiological economy during a short, extreme burst of muscular activity. Another action of epinephrine is to reduce the loss of potassium from muscle and to increase the hepatic storage of potassium. The latter effects may be of importance for maintaining relatively normal potassium distribution during prolonged muscular exercise.

Heart. A single large dose of epinephrine decreased the potassium and increased the sodium concentrations in the heart, but when epinephrine was administered by continuous infusion, cardiac potassium was increased (464). Increased loss of potassium at the height of the stimulating effect of epinephrine or norepinephrine must be considered a non-specific effect of increased activity until it can be shown that a similar change is not induced by other kinds of stimulation (392).

Smooth muscles. Continuous infusion of norepinephrine, to sustain a 100 mm rise in blood pressure, caused a loss of potassium and some gain in sodium of the femoral artery (542). It is not known whether these electrolyte changes were the result of constriction, or selective effects of sympathomimetic activity. Contraction of rabbit uterine strips induced by norepinephrine, but not by acetylcholine or histamine, resulted in potassium loss from this tissue (127). When the *taenea coli* muscle of the guinea pig was treated with epinephrine, the radioactive potassium efflux was either unchanged or somewhat increased and the potassium influx was increased (47a).

Erythrocyte. Epinephrine did not affect potassium influx in human red cells (304).

2. Sodium. D'Silva (141) reported that epinephrine caused no significant change in plasma sodium at the time when the potassium level was doubled. This observation has been confirmed by others (384). During epinephrine hypokalemia, Dury and Moss (165) found no significant fall in plasma sodium but a moderate increase in muscle sodium. In patients, there were no changes in sodium during epinephrine-induced hypokalemia (163). Infusions of levarterenol, which maintained a high blood pressure and an elevated plasma potassium, caused a fall in serum sodium, which, after the infusion was terminated, recovered to the normal level more slowly than did the serum potassium (403). Dury and Treadwell (167) reported that epinephrine elevated plasma sodium in rats. However, Eversole *et al.* (199) found that serum sodium in the rat was elevated by norepinephrine and not by epinephrine.

Available evidence on the rate of passage of radioactive sodium out of the blood stream and on the rate of removal of sodium from tissues indicates that physical factors of pressure, filtration, etc., rather than metabolic effects, are involved. The rate of loss of Na^{24} from the plasma (261) either was unchanged, or was actually reduced, by epinephrine. After intra-arterial Na^{24}, which produced a local extravascular Na^{24} pool, epinephrine accelerated the rate of removal of the radioactivity from the region (152).

3. Calcium. During epinephrine hyperkalemia there was no significant change in plasma calcium (141, 384). However, Vollmer (565) found a slight increase in blood calcium concomitant with a decrease in blood potassium and phosphate. A slight elevation of serum calcium was also observed after the administration of epinephrine to patients with diabetes (421) or with glaucoma (444). During the prolonged hypokalemia and hypophosphatemia, which occurred with subcutaneous epinephrine, blood calcium and citrate were elevated (440). The rise in citric acid intermediates might explain the earlier observation that epinephrine did not change the total serum calcium, but did increase the ultrafiltrable calcium of the serum (341).

Epinephrine had no action on the calcium exchange of frog muscle *in vitro* (419).

4. Magnesium. Marenzi and Gerschman (384) found no early change in blood magnesium in response to epinephrine.

5. Iron. The literature on epinephrine hypoferremia in animals was reviewed by Laurell (340). In humans the response to a large dose of epinephrine consisted of a slight increase in serum iron for 15 to 30 minutes (21, 420), followed by a moderate fall in serum iron for one to three hours (21, 502). The spleen appears to play a role in epinephrine hypoferremia. In splenomegaly the reduction in serum iron by epinephrine was intensified; after splenectomy there occurred only a slight rise in serum iron (502).

Some doubt is cast upon the validity of the reported hypoferremia in humans by the finding of a diurnal variation in serum iron (429). Epinephrine caused no greater hypoferremia in daytime tests than the hypoferremia which occurred in the absence of specific treatment. During nocturnal hypoferremia epinephrine was without action on serum iron (429).

Studies with radioactive iron, Fe^{59}, indicated that epinephrine increased the disappearance from the blood of Fe^{59} whether this was injected as $Fe^{59}Cl_3$ or $Fe^{59}\beta_1$-globulin. Concomitantly, $Fe^{59}Cl_3$ was taken up more rapidly into liver, kidney, and lungs, and more slowly into spleen and muscle (261).

6. Chloride. Earlier work indicated that epinephrine reduced blood chloride (see 379). In rabbits given epinephrine subcutaneously, Lipschitz (356) observed a slight increase in blood chloride. This effect of epinephrine was blockaded by ergotamine. No significant variation in blood chloride was found in the more recent studies which have been summarized by MacVicar and Heller (379). These investigators and Jacobson *et al.* (298) presented further evidence that blood chloride is essentially unchanged by epinephrine. However, there have been additional observations that epinephrine reduced plasma chloride in rats (165) and in rabbits (151). When levarterenol was infused at a rate which maintained a high blood pressure, plasma chloride increased about 5 mEq./l (403). The effects of epinephrine on blood chloride are small, and the direction of the change is uncertain.

7. Phosphate. Since the early observations of Perlzweig *et al.* (435), of Tolstoi *et al.* (543), and of Vollmer (565), there has been rather general agreement that the administration of epinephrine leads to a lowering of serum phosphate in animals (20, 284, 379, 491, 580), and in man (20, 433, 435, 543, 565).

With the use of P^{32} it was found that the transfer of phosphate from plasma to liver and muscle was accelerated by epinephrine before the total plasma phosphate showed a significant fall (261). More rapid removal of P^{32} from the plasma under the influence of epinephrine has been confirmed (161), and in this study the specific activities of the phospholipides of plasma, liver, and aorta were increased. In an earlier investigation of the effect of epinephrine on the rate of elimination of radioactive phosphate from plasma, no difference from the control was observed (580). The time of sampling in the latter study may have been too late to observe a change.

In the search for the accumulator of the phosphate which leaves the plasma the kidneys were ruled out by the fact that the excretion of phosphate was diminished by epinephrine (6, 435). Epinephrine reduced the inorganic phosphate and did not change the total phosphate of the erythrocytes (379). The liver also has been ruled out (410). Cori and Cori (110) proposed that epinephrine, by reducing the inorganic phosphate content of muscle, caused the withdrawal of plasma phosphate into muscle. Small increases in muscle phosphate were found (394), but as Nelson *et al.* (410) pointed out, muscle contains one hundred times more phosphate than the blood and, with ordinary analytical techniques, it would be difficult to detect the transfer of this relatively small total amount of blood phosphate into the large mass of muscle phosphate. Although it has not been demonstrated that the epinephrine-treated muscle *in vitro* takes up more phosphate, epinephrine did reduce the normal loss of phosphate from frog muscle (355, 419).

A mechanism for withdrawal of phosphate from the plasma into muscle cells might involve the direct effect of epinephrine on muscle in which hexosemonophosphates are increased at the expense of inorganic phosphate (257). In support of epinephrine acting directly and not through the intermediation of insulin, it was observed that there was no effect of insulin on muscle hexosemonophosphate in adrenalectomized animals (110, 514). Another point in favor of a direct action of epinephrine on muscle as a cause of the hypophosphatemia was the observation that, in a muscle disease involving a defect in muscle glycogenolysis, epinephrine produced a normal hyperglycemia, a poor hyperlacticacidemia, and little change in serum phosphate (374).

A mechanism for epinephrine hypophosphatemia which would involve the reflex release of insulin is supported by the observation that epinephrine did not reduce plasma phosphate in depancreatized dogs (45, 514). Also compatible with an insulin release mechanism is the fact that hypophosphatemia occurred in adrenalectomized animals in response to either insulin or epinephrine (111, 182, 514). Nelson *et al.* (410) came to the conclusion that the hypophosphatemias in response to epinephrine and to insulin were independent effects, since they found a large increase in total phosphate of the liver in response to insulin, and only a slight increase in response to epinephrine. Some facts concerning phosphate and glucose assimilation in muscle and epinephrine effects on muscle would be more in accord with an indirect effect of epinephrine on phosphate metabolism. Phosphate is taken up by muscle in conjunction with glucose uptake. Since epineph-

rine depresses glucose assimilation in muscle, this effect may be more important in reducing phosphate assimilation than the effect of epinephrine which diminishes muscle inorganic phosphate and thus increases the diffusion gradient for inorganic phosphate.

Schrire (491) attributed some importance to the pituitary in epinephrine hypophosphatemia since he observed no change in phosphate in hypophysectomized *Xenopus laevis*. The significance of this observation is obscured by the low phosphate in the control hypophysectomized animals. In hypophysectomized dogs Soskin *et al.* (514) observed that epinephrine lowered blood phosphate, and Ichijo (284) found that epinephrine produced smaller changes in phosphate, glucose, and lactate in his hypophysectomized dogs than in his control dogs.

Levarterenol had less effect on blood phosphate and on carbohydrate metabolism than epinephrine (258). Large doses of nor-sympatol increased blood phosphate (529).

Tissue organic phosphates. After two hours of epinephrine infusion at a rate of 17.7 μg/kg and hr, canine hearts contained less than the normal amount of adenosinetriphosphate and a slighty increased amount of phosphocreatine (404). The excessive work of the heart and a relative oxygen deficiency, rather than a specific effect of epinephrine, may account for these findings. Previous studies on muscle phosphates indicated that the primary changes were a decreased inorganic phosphate, an increased hexosemonophosphate, and little change in phosphocreatine or in adenosinetriphosphate (99).

8. Water and electrolyte metabolism in tissues. Frog skin transfers water to within from a solution containing 6.5% sodium chloride. Epinephrine prevented and reversed the direction of active water transport (72). These observations explain in part the increased loss of body water by intact frogs which were treated with epinephrine (53). The imbibition of water by slices of various frog tissues was diminished by epinephrine (15).

Application of epinephrine to the inner surface of frog skin caused a greatly increased efflux of sodium and a slightly increased influx (321, 554). Epinephrine also increased the transfer of chloride from the inner to the outer surface of frog skin (301). The increased efflux of chloride (320) was later thought "to be performed by the skin glands which start secreting under the influence of adrenaline" (555).

The various effects of epinephrine on water and sodium changes summarized above suggest that epinephrine may have a general effect which causes the active transport of sodium and water out of the cell.

In adrenalectomized rabbits, epinephrine restored the ability of the ciliary processes to concentrate acid dyes in the stroma and basic dyes in the epithelium, and changed toward normal the rate of regeneration of intraocular fluid (210).

Inhibition of histamine-induced gastric secretion by epinephrine or norepinephrine may be due to the vascular effects rather than to a specific action on the secretory mechanisms (208).

The complex effects of epinephrine on water and electrolyte metabolism in

the kidney have been reviewed by Verney (558), Pickford (437), and Selkurt (496).

VII. INTERACTIONS OF EPINEPHRINE AND OTHER HORMONES

1. Interactions of epinephrine and insulin in carbohydrate metabolism. One report indicated that the calorigenic action of epinephrine was greater in diabetics than in normal subjects or in insulin-treated diabetics (272), but another group reported that the calorigenic effect was the same in diabetic as in normal subjects (263). Epinephrine hyperglycemia in diabetic patients was discussed in section I, A, 1, c.

Insulin antagonized the early fall in liver glycogen as well as the rise in blood sugar of rats treated with epinephrine (116). Lundsgaard *et al.* (373) found that in perfused rabbit livers insulin did not antagonize the epinephrine-induced increase in glucose output. This preparation also did not show an increased glucose uptake with insulin (except in one out of 10 experiments), so that insulin would not be expected to antagonize epinephrine. Similar results were obtained by Ambrus *et al.* (11) who studied perfused canine livers. The reason for the inability of recent investigators to reproduce some earlier demonstrations of insulin epinephrine antagonism in the liver is not evident (48, 290, 291).

Cori suggested (98) that epinephrine counteracts insulin hypoglycemia in large measure by antagonizing the effect of insulin on glucose utilization. The reduced peripheral utilization supplements the epinephrine-induced elevation of hepatic glucose production. Epinephrine, in this manner, elevates the blood glucose which is the main fuel for the central nervous system. Later, Cori and Buckwald (103a) demonstrated epinephrine-insulin antagonism on frog muscles under aerobic and under anaerobic conditions. The antagonism has been demonstrated also with mammalian striated muscle (54, 176, 461, 550,569). Antagonism between epinephrine and insulin on muscle glycogen changes in the absence of exogenous glucose would raise important questions concerning the sites of action of each of the hormones. It was reported (461) that insulin antagonized the glycogenolytic effect of epinephrine on the rat diaphragm suspended in a glucose-free medium, but other investigators (176, 550) could not confirm this finding.

Experiments on rat diaphragms, in which the insulin concentration was varied over a wide range and the epinephrine concentration was kept constant, indicated that the antagonism is not a simple one. The conjoint effect of the two agents is not the arithmetic sum of the individual effects, nor is it explained by a decreasing effectiveness of epinephrine with the increasing concentration of insulin. The percent inhibition of the insulin effect by epinephrine was about the same although the insulin effect on carbohydrate metabolism was increased four-fold (68). When the effect of epinephrine on glucose uptake was tested in low and in high concentrations of glucose, the percent inhibition also remained constant (569).

The glycogen content of adipose tissue in the rat responded to insulin and to epinephrine in the manner characteristic of the glycogen of the liver. The effects of epinephrine and insulin on adipose tissue glycogen appeared to be antagonistic when the two were administered conjointly (549).

Bouckaert and de Duve (51) reviewed epinephrine-insulin antagonism on carbohydrate metabolism. They call attention to the curious fact that each of these antagonists increases the cellular concentration of hexosemonophosphate which plays a central role in the absorption of glucose and the disposition of glycogen. Some of the more recent contributions on insulin-epinephrine antagonism were discussed by Weil-Malherbe (578).

2. Epinephrine and adrenocortical hormones. a. Carbohydrate metabolism. Adrenal cortical hormones are important for some of the common responses to epinephrine. Reference was made to some of these hormonal interactions in previous sections of this review.

An early indication of the importance of the adrenal gland for the action of epinephrine on carbohydrate metabolism was Eiselt's report (173) that epinephrine glycosuria did not occur in patients with Addison's disease. Several later investigators found that in adrenal cortical insufficiency there was a diminished hyperglycemic response to epinephrine (41, 92, 185, 473), but there occurred a greater fall in muscle glycogen (92, 591) associated with a normal epinephrine hyperlacticacidemia (41) and almost no rise in blood pyruvic acid (489).

In adrenalectomized rats, epinephrine frequently increased the metabolism and body temperature (462). This observation and the observation that epinephrine elevates blood lactic acid normally in adrenalectomized animals are interesting in view of the hypothesis that the calorigenic effect is a result of the hyperlacticacidemia (370). There is normally a rapid resynthesis of glycogen in the liver during the course of events which follow the administration of epinephrine. This resynthesis of glycogen in the liver was impaired in adrenalectomized rats (591). However, liver glycogen formation was increased by epinephrine in alloxanized-adrenalectomized rats which were given glucose (546). Cortical hormones administered to normal, adrenalectomized, or hypophysectomized rats antagonized epinephrine glycogenolysis in certain muscles (591, 597). In the above experiments cortisone, through two of its accepted actions, might appear to antagonize epinephrine glycogenolysis. Cortisone increases gluconeogenesis. Cortisone also potentiates epinephrine hyperglycemia and, thus, it may increase glucose uptake by muscle. Contrariwise, desoxycorticosterone potentiated epinephrine on muscle glycogenolysis in intact or adrenalectomized rats (538). Desoxycorticosterone possesses little of the glucocorticoid activity of cortisone and desoxycorticosterone was found to activate muscle glycogenolysis (54).

Adrenal steroids appear more important for maintaining a normal concentration of glycogen in the liver, whereas pituitary hormones appear to be the important factor for maintaining muscle glycogen (187, 361). With this evidence at hand, the effects of absence or plethora of adrenal glucocorticoids on muscle glycogen can be considered an indirect effect. The absence of the adrenals diminishes epinephrine hyperglycemia and does not appear to influence epinephrine hyperlacticacidemia. Therefore, the increased loss of muscle glycogen which follows epinephrine in adrenalectomized animals may be the result of a reduced blood glucose which, in the adrenalectomized animal, does not compensate for the epinephrine glycogenolytic effect in muscle. A similar interpretation would account for the antagonism of glucocorticoids toward epinephrine glycogenolysis

in muscle on the basis of the potentiated epinephrine hyperglycemia in corticoid-treated animals.

Kerpolla (311) has made the most interesting observation that daily doses of cortisone for 7 days increased liver and muscle glycogen and decreased the phosphorylase activities in these tissues. Since epinephrine reactivated the enzyme inhibited by cortisone, it would appear that cortisone did not change the total amount of phosphorylase. An earlier investigation (326) showed that the adrenal hormones depress liver glycogenolysis. If the depression of phosphorylase activity by cortisone (311) is involved in the above experiments, the increased percentile activity of phosphorylase, which occurs when epinephrine is given, would be expected to potentiate, rather than suppress, epinephrine glycogenolysis. This would be in accord with the potentiation of epinephrine hyperglycemia by cortisone. It has not been determined whether epinephrine hyperlacticacidemia is also potentiated. The absence of the adrenal gland, however, did not diminish the blood lactate rise in responses to epinephrine (41).

b. Potassium metabolism. Epinephrine hyperkalemia was depressed in adrenalectomized cats, but the magnitude of the hyperkalemic response appeared to be inversely related to the plasma potassium level (561). The resting level of plasma potassium is not always a controlling factor in epinephrine hyperkalemia. When cardiac glycosides elevated the plasma potassium, there was little effect on the magnitude of the epinephrine hyperkalemia (391). Furthermore, treatment of adrenalectomized cats with desoxycorticosterone partially restored the hyperglycemic and the hyperkalemic responses to epinephrine (561).

In adrenalectomized animals epinephrine reduced the elevated blood potassium to a normal level (169, 466).

c. Adrenal ascorbic acid depletion by sympathomimetic amines. It is now a well-established fact that epinephrine reduces the concentration of ascorbic acid and of cholesterol in the adrenal glands (362). The changes in the adrenals have been attributed to the release of adrenocorticotropin (ACTH) from the pituitary gland (218, 438). Recently, McCann and Brobeck (375) produced hypothalamic lesions which prevented the pituitary-adrenal stimulation by epinephrine. Thus, a direct action of epinephrine on the pituitary, or on the adrenal cortex, appears unlikely. With relatively large, intravenous doses of epinephrine, elevation of blood ACTH has now been demonstrated (200). Ordinary doses of epinephrine increased plasma 17-hydroxycorticosteroids in about one-third of the trials (282). However, methods for determining ACTH and cortical hormones in blood have been so inadequate that the present evidence based on these measurements is not considered to be reliable (390, 485).

There is little information on the mechanism of the ascorbic acid depletion which has been associated with activation of the adrenal cortex. Some miscellaneous observations on epinephrine effects may be related to the adrenal ascorbic acid change. A glycogen depletion of the adrenals follows the administration of epinephrine (412). The administration of epinephrine caused a depletion of blood ascorbic acid which ran a time course similar to that of the reported adrenal ascorbic acid depletion (224). Does the blood change cause, or is it a result of, the adrenal change? Ascorbic acid depletion is not a general effect of

epinephrine on tissues in view of the fact that hepatic ascorbic acid was not affected by epinephrine (480).

Some recent observations on the effects of glucagon, a substance which mimics the hepatic glycogenolytic effect of epinephrine, again raise the question as to whether the activation of the pituitary-adrenal system by epinephrine is a direct influence on the hypothalamo-pituitary system or an indirect action brought about through changes in blood composition (362). It has been reported that glucagon, like epinephrine, depleted the ascorbic acid content of the adrenal glands (118), and that intravenously administered glucagon produced a transient hyperkalemia followed by a more prolonged hypokalemia (593). The implications of these observations for the problem of the mechanism of activation of the pituitary-adrenal system are obvious.

Adrenergic blocking agents depress the ascorbic acid-depleting effect of epinephrine on the adrenals (248, 417, 467, 503). Whether this is a blockade of a direct action of epinephrine on the hypothalamo-pituitary system, or an indirect effect brought about by blocking the hyperglycemic, the hyperkalemic, or other effects of epinephrine, is still uncertain.

There is some disagreement concerning the potency of levarterenol relative to epinephrine in reducing adrenal ascorbic acid. Three groups of investigators found that levarterenol was much less potent in regard to this action than epinephrine (199, 409, 467). These results would agree with the lesser potency of levarterenol in reducing the eosinophiles in man (281). Chen *et al.* (82), however, reported that epinephrine and levarterenol were of equal potency in the adrenal ascorbic depletion test. The explanation for these conflicting data is not evident. The latter investigators also reported that isoproterenol is as potent in depleting adrenal ascorbic acid as the other two amines. Paredrine was effective in depleting adrenal ascorbic acid in intact rats (417), and hypophysectomy prevented this action of paredrine (418). Ephedrine was not effective (417), but amphetamine produced a prolonged depletion of adrenal ascorbic acid (409).

The relative doses of epinephrine, levarterenol, and sympatol which produced similar depletions of adrenal ascorbic acid are 1:4.5:1200 (409). (The ratios of 1:45:1200 which are in the discussion and also in the summary of the paper are in conflict with the data and are apparently misprints.) These ratios are unlike the relative pressor potencies which are 1:0.4:200 in the rat (409), but they are similar to the relative hyperglycemic potencies (175).

3. Interactions of epinephrine and pituitary hormones on metabolism. Epinephrine caused less hyperglycemia in hypophysectomized animals than in normal animals (92, 96, 130, 274, 284, 472, 473). Removal of the neurohypophysis alone did not affect epinephrine hyperglycemia (130). A reduced hyperglycemic response to epinephrine occurred in hypophysectomized animals when liver glycogen was normal (130, 471). Houssay and Gerschman (274) showed that the difference in blood sugar response was not due to a change in sensitivity of the liver to epinephrine. Since the administration of cortisone to hypophysectomized animals restored epinephrine hyperglycemia toward normal values, it appeared that the principle deficiency was in adrenal cortical function (131).

In fasting hypophysectomized rats, cortical hormones restored the levels of

blood sugar and of liver glycogen toward normal, but they failed to increase muscle glycogen (361). Although it has been reported that epinephrine has less action on muscle glycogen in hypophysectomized rats (92), Leonard (348) found that epinephrine produced similar percentage decreases of muscle glycogen in normal and in hypophysectomized rats. Growth hormone reduced the effect of epinephrine on the glycogen content of certain muscles in hypophysectomized (348), but not in intact, rats (349). In hypophysectomized rabbits, there was a normal increase in blood lactate in response to epinephrine (96). A normal hyperlacticacidemic response does not appear consistent with a smaller glycogenolytic effect of epinephrine on muscle in hypophysectomized animals. Some of the discrepancies in the reports on the effects of epinephrine on muscle glycogen and on blood lactate in hypophysectomized animals may be attributed to differences in muscle glycogen between fasted and fed animals. Muscle glycogen may be normal in well-nourished hypophysectomized animals, but a fast of only four hours depleted muscle glycogen in these animals (472).

Some of Cohen's (87, 89) results may be explained by these facts. He found that, when epinephrine was injected into fasted rats, there was a diminished glycolysis in the diaphragms subsequently tested *in vitro*. Adrenalectomy did not change the results, but hypophysectomy completely eliminated the inhibition of glycolysis by epinephrine. The elimination of the muscle response to epinephrine by hypophysectomy is in keeping with the reduced glycogenolysis and lesser increase in hexosemonophosphate found in the muscles of *fasted*, hypophysectomized rats (460, 472).

Kepinov (307, 309) has postulated that a pituitary hormone is required for epinephrine to be taken up by, and to cause glycogenolysis in, the hepatic cells. He was unable to demonstrate that epinephrine increased glucose production in perfused livers unless a pituitary extract was added to the fluid perfusing the liver.

Epinephrine produced a smaller increase in oxygen use in patients with Simmond's disease than it produced in normal subjects (272). Epinephrine stimulated the oxygen use and glucose consumption of anterior pituitary tissue of rats, but it did not affect posterior pituitary or hypothalamic tissues (463).

4. Interactions of epinephrine and sex hormones on metabolism. Epinephrine caused greater hyperglycemia in women than in men (189). In normal men and women the heterologous sex hormone slightly potentiated epinephrine hyperglycemia (317). Progesterone did not modify the effect of epinephrine on muscle glycogen (538), but testosterone antagonized this effect (597).

5. Interactions of epinephrine and thyroid hormone on metabolism. There is adequate justification in the literature for the generalization that the magnitude of most of the pharmacologic actions of epinephrine are regulated by the amount of thyroid hormone in the body. Thyroidal control of several metabolic effects of epinephrine has been observed by numerous investigators.

Thyroid administration to normal animals increased epinephrine hyperglycemia (64, 548). Thyroidectomy reduced epinephrine hyperglycemia, and the

response was restored to normal when thyroid hormone was administered (94, 95). In a few studies no effect of thyroidectomy on epinephrine hyperglycemia was detected (92, 217). It is not known whether the latter observations were due to differences in species, to incomplete removal of thyroid tissue, or to other experimental variables. Some explanation is also needed for the inability of thyroid hormone to increase the hyperglycemic response to levarterenol, especially since epinephrine hyperglycemia was potentiated (548). Chronic administration of thyroid to rabbits reduced epinephrine hyperglycemia by depleting liver glycogen (64). Rabbits were more sensitive to this hepatic effect of thyroid than were dogs and cats (1). This action of thyroid hormone would make the amount of thyroid administered and the duration of the treatment critical in some species for demonstrating a potentiation of epinephrine hyperglycemia.

The effect of epinephrine on muscle glycogenolysis was increased by the administration of thyroid (92, 348) and was reduced by thyroidectomy (92, 348, 349, 538). The related effects of thyroid hormone on epinephrine hyperlacticacidemia should be investigated. Since the Cori lactic acid cycle is very important in the hyperglycemic effect and since Lundholm's (370) hypothesis relates the calorigenic effect to the hyperlacticacidemia, the influence of thyroid hormone on the hyperglycemia and the calorigenic effects of epinephrine might thus be explained.

The calorigenic effect of epinephrine was greatly diminished by thyroidectomy (2, 146, 541) and was increased by thyroid administration (146, 147). The calorigenic effect of epinephrine was greatest in hyperthyroid patients and least in hypothyroids (272). De Visscher (146) suggested that the calorigenic effect of epinephrine was limited by the availability of thyroid hormone. Epinephrine caused greater increases in the rate and oxygen consumption of thyroxine-treated terrapin hearts (377). In white rats diiodotyrosine also increased the effect of epinephrine on oxygen consumption (147).

Comsa (94, 95) found that thyroidectomy reduced and thyroid administration increased the following responses to epinephrine: increased creatine excretion, reduction of blood cholesterol, and hyperglycemia.

Brewster *et al.* (58) postulated that many of the effects which occur after the administration of thyroxine were merely sensitizations to adrenergic stimuli. This concept was based upon the experimental observation that when total sympathetic blockade was produced by epidural injection of procaine, the oxygen consumption, heart rate, cardiac index, and mean arterial pressure of thyroxine-treated dogs were reduced to the values observed in euthyroid dogs with similarly produced sympathetic blockade. In these animals the infusion of epinephrine or of levarterenol restored the oxygen consumption and the cardiovascular functions of the thyroxine-treated dogs with sympathetic blockade to the level of the thyroxine-injected animals with normal sympathetic activity. Consistently greater effects of epinephrine were observed in thyrotoxic dogs than in euthyroid dogs. They concluded that cardiovascular and calorigenic signs of thyrotoxicosis were not due to direct effects of thyroxine *per se*, but were due to an augmenta-

tion by thyroxine of the physiological effects of epinephrine and norepinephrine. Additional support for this point of view comes from an early observation that sympathetic denervation of the heart produced considerable protection against thyroid intoxication (328). It has been observed, and confirmed, that an adrenergic blocking agent, dibenzyline, prevented the calorigenic effect of low doses of thyroxine (269, 451). Although it has not been determined whether dibenzyline interferes with the calorigenic action of epinephrine, some related haloethylamine derivatives, including dibenamine, did reduce the effects of epinephrine and levarterenol on oxygen consumption (564a).

Effects of epinephrine on iodine metabolism and thyroid function. This subject was reviewed briefly by Money (398) and by Barker (19). A reasonably consistent picture of the effect of epinephrine on the thyroid and on iodine metabolism has emerged from the results of several groups of investigators. Chronic administration of epinephrine to dogs induced hyperplasia and hypertrophy of the thyroid, followed by some regression of these histologic changes. The changes in blood thryrotropic hormone in epinephrine-treated, thyroidectomized dogs were a rise and then a fall in a time sequence consistent with the histologic changes in the epinephrine-treated intact animals (508).

Epinephrine diminished the I^{131} uptake by the thyroids of normal or of adrenalectomized rats (50, 207, 559, 588). Soffer *et al.* (507) observed this response in intact rats, but they found that epinephrine increased the I^{131} uptake in adrenalectomized rats. Despite the conflicting evidence, Verzár (559) concluded that the depression of I^{131} uptake was not mediated by an epinephrine-induced release of adrenal cortical hormones. Levarterenol was less than ¼ as effective as epinephrine in reducing the thyroidal I^{131} uptake (207). The thyroidal uptake of I^{131} was increased by epinephrine in normal humans, but was not influenced in patients with Addison's disease or with panhypopituitarism (458). In this case the difference between the responses of humans and of rats may not be a species difference, but rather a difference in dosages. The smallest dose which reduced I^{131} uptake by the thyroid in rats was approximately 0.1 mg/kg (50); in man, the dose which increased I^{131} uptake was approximately 4 μg/kg (458).

Within the first few hours after a single injection of epinephrine, organically bound I^{131} of the thyroid diminished (49, 50, 588), but with repeated injections of epinephrine, started 16 hours after the administration of the I^{131}, there was a reduced loss of I^{131} from the thyroid (207).

Protein-bound iodine of the serum was reduced by epinephrine in intact or in thyroidectomized animals (49, 191, 588). Therefore, it was suggested that epinephrine increased the rate of peripheral utilization of thyroxine and may increase the release of corticotropin through this action, as well as by an action directly on the pituitary.

The oxygen consumption of thyroid tissue *in vitro* was increased by epinephrine (5).

Viale and Kurie (562) reported that extirpation of thyroid and parathyroid glands, or of only the parathyroids, prevented epinephrine hyperthermia.

VIII. MISCELLANEOUS EFFECTS OF EPINEPHRINE

1. Blood clotting. It is an old established fact that the administration of epinephrine (566) reduces the clotting time of blood, but the mechanism of this effect is poorly understood. This subject was reviewed by Seegers (495).

There have been several investigations of the mechanism of this action of epinephrine. Wakim *et al.* (567) sought the answer in the prothrombin activity, but this was unchanged. Sen *et al.* (497) correlated the clotting effect with the increased platelet count induced by epinephrine. They further supported this relationship by showing that, in rabbits in which the spleens had been excluded from the general circulation, epinephrine caused neither a decrease in the clotting time nor an increase in the platelets of the blood.

When relatively low concentrations of epinephrine or of levarterenol were added to whole blood *in vitro*, Waldron (574) observed a shortening of blood clotting time. He explained the negative findings of Cannon and Gray (70) as a consequence of collecting whole blood in uncoated glass tubes which now are known to accelerate the clotting of blood.

Epinephrine did not reduce the clotting time of blood in hypophysectomized turtles (364), but epinephrine was effective in decapitated cats (70).

Macht and Golden (380) reported that amphetamine was more effective than either *d*-amphetamine or methamphetamine in promoting clotting. Since amphetamine reduced the prothrombin time (380) and epinephrine did not (567), the mechanisms of the shortening of clotting time by the two drugs obviously differ.

2. Bleeding time. Derouaux (138) reported a shortening of the bleeding time after the administration of epinephrine or of one of several closely related compounds in his series of sympathomimetic drugs. The potencies of the catechol derivatives for the hemostatic effect correlated well with their pressor potencies. In the total group of sympathomimetic agents there was some general resemblance between the potencies for the effects on blood pressure and on bleeding time, but too many exceptions occurred to attribute the decreased bleeding time solely to the vasoconstrictor action.

Shortening of the bleeding time occurs rapidly after less than 10 μg/kg of epinephrine and the effect persists for more than 70 minutes, a duration that far exceeds any vascular effects (331). Kuschinsky and Schimassek (331) attribute this effect of epinephrine on bleeding time to the liberation of histamine (*vide infra*), since pre- or post-treatment with antihistaminics antagonized the action of epinephrine. Since adrenergic blocking activity is common with larger doses of several antihistaminic compounds (298a, 322, 530), blockade of epinephrine effects with compounds of this group does not necessarily implicate histamine in the mediation of the effect. It would be of interest to determine the time course of the blood platelet changes (497), referred to above, with the temporal changes in bleeding time.

3. Appetite. In relatively small doses, epinephrine was found to lessen food

intake in rabbits (66). This kind of action is better known for sympathomimetic amines structurally related to amphetamine.

4. Release of histamine by epinephrine and related amines. Increased blood histamine was found following the administration of epinephrine (24). The increased histamine was not related to the epinephrine-induced leukocytosis (24). The correlation of the elevated histamine and the increased platelets (497) should be investigated since the platelets contain most of the blood histamine (465).

Some related sympathomimetic amines have been found to increase plasma histamine (24). Cobefrine was about as effective as epinephrine; norepinephrine was only about $\frac{1}{5}$ as effective; and sympatol was about $\frac{1}{600}$ as effective.

5. Effects of vitamins and metabolites on the metabolic effects of epinephrine. Epinephrine hyperglycemia was increased by the administration of vitamin C and was reduced in vitamin C-deficient animals (501).

In riboflavin-deficient dogs, epinephrine produced an exaggerated, prolonged hyperglycemia, and liver glycogen recovered very slowly toward the normal level (13). This modified response to epinephrine may be caused by a reduced rate of assimilation of lactate and glucose by the liver and other tissues in the riboflavin-deficient animal. Evidence for this interpretation was the excessive postabsorptive hyperlacticacidemia in riboflavin-deficient animals.

Nicotinic acid (399) or nicotinamide (223) potentiated epinephrine hyperglycemia. Some potentiation of epinephrine hyperglycemia was produced also by thiamine (60).

Hepatic ascorbic acid, unlike adrenal ascorbic acid, was not reduced by epinephrine (480), but blood ascorbic acid was reduced (224).

The report that epinephrine caused a mobilization of vitamin A from the liver into the blood could not be confirmed (232). The difference in results was partially explained by the finding that in about 50% of a series of tests epinephrine increased blood vitamin A, but the average of all tests indicated no change in blood vitamin A (264).

Giertz and Iurna (220) reported that methyl-donor compounds potentiated norepinephrine hyperglycemia more than epinephrine hyperglycemia. They injected intravenously amounts of the amines which caused small elevations of blood sugar. The large variations of response at this level reduce the significance of the changes they observed.

6. Tolerance to epinephrine. Development of tolerance to various effects of epinephrine has been reported repeatedly. Abderhalden and Gellhorn (2) observed that mice, which had become tolerant to epinephrine, would show a good calorigenic response to doses of epinephrine which would reduce the oxygen consumption of, or kill, non-tolerant mice. These investigators also noted a greater tolerance toward epinephrine in the thyroidectomized mice. Essex (192) reported that a tolerance to the lethal effect of epinephrine developed in dogs. Repeated epinephrine-hyperglycemia tests led to reduced responses. A diet high in carbohydrate also reduced the average hyperglycemic response to epinephrine (9). Bennett (30) recorded the hyperthermic response to daily administration of epi-

nephrine in rabbits and found that no tolerance developed over a period of two weeks.

7. Miscellaneous effects of epinephrine and related compounds on cell-free preparations and on enzymes. The hypothesis that central nervous system stimulation by certain sympathomimetic amines depends on the inhibition of amine oxidase was tested by comparing stimulating potency and inhibition of amine oxidase. The results were in part consistent with the hypothesis, but there were sufficient exceptions to weaken the foundation of this hypothesis (201).

Neither arginase nor acid phosphatase activity of the rat liver was influenced by the injection of epinephrine. The arginase activity, however, was increased by adrenal cortical hormones (319). Amino acid oxidase of the liver was inhibited by epinephrine both *in vivo* and *in vitro* (65). Protease activity of rabbit liver was increased after epinephrine administration (296).

Ungar and Hummel (553) reported some interesting observations on the inhibition by sympathomimetic and sympatholytic substances of salicylaldehyde oxidation in liver extract. Although low concentrations of the drugs were inhibitory, the relative activities were not consistent with pharmacological potencies. For example, epinine and kephrine were more potent than epinephrine. Nevertheless, the broad generalizations were interesting: the catechol derivatives were more potent than the phenolic compounds; ephedrine and other phenylalkylamines and alkylamines were inactive. The sympatholytics were quite potent. Dibenamine produced irreversible inhibition, whereas inhibition by epinephrine was reversible.

Govier *et al.* (234) studied an isolated oxidation system with which they attempted to determine the biochemical mode of action of sympathomimetic amines. They discovered that α-tocopherol would inhibit their succinoxidase system. Epinephrine and other amines reduced the effect of α-tocopherol on the system. Since epinephrine was required in amounts equivalent to, or greater than, α-tocopherol, and since ascorbic acid and cysteine would relieve the α-tocopherol inhibition, epinephrine could be acting as a reducing agent. This, however, would not account for the activities of amphetamine and phenylethylamine. The same investigators (235) observed that, in pigeon liver slices, certain sympathomimetic amines activated cocarboxylase synthesis from thiamine. The mechanism of this activation has not been studied further, nor has the effect been related to other effects of sympathomimetic amines on liver. A somewhat related esterification, which was reported to be stimulated by epinephrine, was the synthesis of acetylcholine by brain homogenates (544).

Inhibition of cholinesterases by epinephrine and ephedrine has been reinvestigated by Benson (31, 32). These amines had very weak inhibitory activity: similar degrees of inhibition were produced by 3×10^{-3} M epinephrine, 3×10^{-3} M ephedrine, and 1×10^{-7} M eserine. It is evident that no epinephrine effects in intact animals should be attributed to cholinesterase inhibition.

Since epinephrine produces positive inotropic effects on muscle, it is interesting that Straub *et al.* (524) found that epinephrine activates the transformation of actin-G to actin-F. The high concentration of epinephrine which was used in

these experiments makes it unlikely that this effect plays a role in the action of epinephrine on muscle function.

Epinephrine injections in rats did not affect the hexokinase activity of muscle (90). Therefore, inhibition of glucose uptake by muscle must be explained by secondary changes such as the increase in muscle glucose-6-phosphate.

Tryptophan peroxidase activity of rat liver was increased by epinephrine in intact, but not in adrenalectomized, rats (318).

Randall (452) found that even relatively large amounts of epinephrine did not inhibit anaerobic glycolysis in rat brain homogenates. Adrenochrome was a fairly potent inhibitor in his test system.

Adenosinetriphosphatase could control tissue oxygen consumption by making more adenosinediphosphate available. Epinephrine was found to have no effect on adenosinetriphosphatase either in slices or homogenates of rat heart (77).

IX. CONCLUDING REMARKS

The most exciting segment of the literature included in this review is undoubtedly the recent progress toward unraveling the mechanism of the glycogenolytic effect of epinephrine. Epinephrine appears to control the cellular concentration of active phosphorylase, the enzyme which catalyzes the reversible reaction glycogen + phosphate $\rightleftharpoons$ glucose-1-phosphate. "The concentration of active phosphorylase . . . represents a balance between inactivation (dephosphorylation) by inactivating enzyme (phosphorylase phosphatase) and reactivation by dephosphophosphorylase kinase . . . [and] . . . epinephrine displace[s] this balance in favor of the active phosphorylase" (449). This action of epinephrine has now been demonstrated in the absence of intact cells.

Since the first step in glycogenolysis is the slowest and, thus, the rate-limiting reaction, epinephrine, by increasing the level of active phosphorylase, causes an increased glycogenolysis, which, in turn, causes an increase in the cellular concentrations of glucose-1-phosphate and glucose-6-phosphate. In the liver the increased concentration of glucose-6-phosphate accelerates the rate of glucose liberation and thus causes hyperglycemia. In muscle there is a more rapid formation of lactic acid, as well as an increase in glucose-6-phosphate. The lactic acid liberated from the muscle is the major cause of the hyperlacticacidemia. The blood lactate is rapidly utilized by the liver to support an enhanced production of glucose and a prolonged hyperglycemia. Since epinephrine elevates muscle glucose-6-phosphate concentration, and since glucose-6-phosphate at concentrations found in muscle does inhibit hexokinase, these facts explain the depression of glucose utilization by epinephrine. According to some investigators, the calorigenic effect of epinephrine may be caused by the hyperlacticacidemia. Although this proposed mechanism requires extensive corroboration, it must be granted that this proposal has more in its favor than the suggested, but poorly substantiated, direct effects of epinephrine on tissue oxygen consumption.

Some effects of epinephrine on protein and lipide metabolism have been adequately demonstrated, but there is little information on the cellular mechanisms which are affected. Several observations indicate that protein catabolism and fat

catabolism occur when liver glycogen is severely depleted by epinephrine. This would tend to support a suggestion by Cori (99) that possibly all the metabolic effects of epinephrine are the result of primary glycogenolytic action. Since there have been several reports that epinephrine increased fatty acid catabolism in liver slices and in liver homogenates, an analysis of the mechanism of the effect of epinephrine on lipide metabolism may be forthcoming.

The effects of epinephrine on electrolyte and water exchange are varied and complex. Potassium changes in liver and voluntary muscle in response to epinephrine have been under investigation for decades, and there is a growing interest in the effects of epinephrine on the potassium of cardiac and smooth muscles. Epinephrine action on the liver results in a large, transient loss of potassium followed by an increased uptake of potassium. The epinephrine-induced loss of potassium from the liver ordinarily occurs in association with glucose liberation, but several observations indicate that glucose liberation and potassium loss from the liver may be dissociated. The effects of epinephrine on muscle potassium are the reverse of the effects on liver potassium; the effect in muscle is a retention of potassium followed by an increased loss. Potassium retention by muscle in response to epinephrine has been attributed to the associated increase in the concentrations of the hexosemonophosphates. Although information on the effects of epinephrine on cardiac and smooth muscle potassium are scanty, the data suggest that epinephrine causes a loss of potassium from muscles in which activity is increased (heart, blood vessel, rabbit uterus) and that epinephrine causes an uptake of potassium by muscle in which activity is reduced (guinea pig taenia coli). An investigation of a large variety of smooth muscles will be needed in order to determine whether the pharmacological effects and potassium changes are indeed related.

Sodium and water extrusion by frog skin is markedly accelerated by epinephrine. The mechanism of this interesting action of epinephrine may have to await the discovery of the systems which normally control intracellular electrolyte concentration. There is, nonetheless, an urgent need for further exploration of the manner in which electrolyte distribution is affected by epinephrine, as well as a need for exploring the importance of the electrolyte shifts in the pharmacological actions of epinephrine.

The reduction of serum phosphate during epinephrine hyperglycemia is accompanied by an increased transfer of phosphate into muscle and liver. There is an increased phosphate gradient between extracellular and intracellular compartments as a result of the reduction in intracellular inorganic phosphate which is organically bound in the increased amounts of hexosemonophosphates. An additional factor which leads to a reduction in serum phosphate is the action of insulin secreted in response to epinephrine hyperglycemia.

The interactions of epinephrine and the hormones are quite complex. Some light is being shed on the detailed mechanism of insulin-epinephrine antagonism. Thyroxine appears to regulate the degree of response to epinephrine but the intimate mechanisms of these interactions are not yet known. The adrenocortical hormones profoundly influence the actions of epinephrine on the metabolism of

carbohydrate, lipide, protein, and potassium. In the absence of the adrenal gland many of the typical responses to epinephrine are severely diminished or entirely absent.

Epinephrine and the sympathomimetic amines appear to influence many phases of organic and inorganic metabolism. With the exception of the effects on carbohydrate metabolism, little is known of the cellular mechanisms of the many metabolic responses to epinephrine. The advances have been great in recent years and much more detailed knowledge concerning cellular mechanisms may be expected in the near future. There are two general questions which deserve the attention of investigators interested in these important physiological and pharmacological agents. 1) Can the large variety of metabolic responses to epinephrine be the result of a single, primary effect on cells, such as the glycogenolytic effect, or does epinephrine induce independent catalytic effects on each kind of metabolism which it affects? 2) Are the changes in the activities of muscular tissues, nervous tissues, etc. in response to epinephrine the result of a single primary metabolic action or are these effects also independent, dissociated responses to epinephrine?

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