Plasma Norepinephrine and Epinephrine in Untreated Diabetics, During Fasting and After Insulin Administration

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SUMMARY

Employing a precise and sensitive double-isotope derivative technic, plasma norepinephrine and epinephrine were measured in twenty-three normal subjects and fourteen diabetics during various metabolic conditions. Patients with poorly controlled diabetes showed a rise in norepinephrine, which correlated with the degree of metabolic derangement, during resting conditions. High epinephrine values were seen only in patients with moderate to severe ketoacidosis. During exercise, diabetic patients with ketosis demonstrated large increments in plasma catecholamines as compared to normals. During insulin treatment, when good control had been achieved, plasma catecholamine levels were similar to those in normal subjects.

During prolonged fasting, plasma norepinephrine rose from 0.18 to 0.40 ng. per milliliter in four normal nonobese subjects. No change was observed in plasma epinephrine.

During insulin hypoglycemia, high plasma epinephrine levels were seen only in subjects in whom the blood glucose concentration declined to values below 20 mg. per 100 ml. Plasma norepinephrine rose as blood glucose concentrations decreased even in diabetics in whom values had not reached hypoglycemic levels. No correlation was observed between plasma epinephrine and increase in pulse rate during hypoglycemia. DIABETES *23*:1-8, January, 1974.

The recent development of a sensitive and precise double-isotope derivative technic for determination of plasma norepinephrine and epinephrine has made it possible to obtain reliable measurements of the small amounts of catecholamines present in plasma during basal conditions. Such measurements constitute one way in which information can be obtained about the integrative control of the adrenergic system in man. The interpretation of the results is complicated, however, because the sympathetic division of the autonomic nervous system participates in both circulatory and metabolic control. We have previously reported that the rise in plasma norepinephrine during standing and exercise can be divided into two components called CAP and CAH.[2] The CAP component is probably derived from adrenergic vasoconstrictor nerve fibers, especially those of the lower extremities.[2] CAH is correlated with cardiac acceleration,[2] and a recent study suggests that this component represents norepinephrine released from the heart.* In diabetics with neuropathy, CAH remains normal while the CAP component is decreased.[2]

The present study represents an attempt to obtain some basic information about plasma norepinephrine and epinephrine concentrations during conditions where major changes in the metabolic state are present. Diabetic patients were studied during ketoacidosis as well as after treatment with insulin. Nondiabetic patients were examined during a three day period of starvation. In addition the significance of decreasing blood glucose concentrations was evaluated in some subjects.

METHODS

For measurement of total plasma catecholamine concentration, i.e. the sum of norepinephrine and epinephrine, and for the separate determination of these two catecholamines the double-isotope derivative technic described by Engelman and Portnoy[1] was employed with minor modifications. This method permits determination of the catecholamine content of a plasma sample without the use of standard solutions. In order to insure continuous control of the method we have, however, included in each assay one or two samples containing a known amount of catecholamine, 0.8 ng.

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per milliliter of norepinephrine in the determination of total plasma catecholamine concentration and 0.6 ng. per milliliter of both norepinephrine and epinephrine in the separate determination. Aliquots of 10 ml. of the samples were used in these determinations.

The precision of the method was calculated on the basis of nineteen double determinations performed on nineteen consecutive days. The samples contained 0.8 ng. per milliliter of norepinephrine, and 10 ml. of this sample was used in each analysis. The standard deviation of the determinations was ± 0.03, or 4 per cent. The mean recovery was 99 ± 8 per cent (standard deviation of the single recovery). Results of recovery studies at lower concentrations of catecholamines have been presented elsewhere.[3,4]

Blood glucose concentration was assayed employing a glucose oxidase method.[5] Free fatty acids in serum were determined employing the spectrophotometric method of Laurell and Tibling.[6] Other laboratory procedures included determination of hemoglobin, total carbon dioxide in plasma, serum sodium, serum potassium and serum creatinine concentrations.

PATIENTS

A total of thirty-seven subjects were examined, some of whom were re-examined.

1. Nine normal subjects, three females and six males, with a mean age of thirty-one years (range twenty-one to seventy-five years) were examined while they rested in the supine position. Seven of them were less than thirty years of age. None had cardiovascular or endocrine diseases.

2. Ten diabetics, five females and five males, were studied when admitted to the hospital with varying degrees of ketoacidosis. None of them had infectious diseases and none were comatose. The mean age was twenty-eight years (range fourteen to sixty-six years). Seven were less than thirty years old. Six were re-examined after several days of treatment with insulin and diet. Most of the patients had diabetes mellitus of recent onset. None had retinopathy or neuropathy.

3. Two diabetic males, ages nineteen and forty years, were examined at rest and during exercise in the supine position. The results were compared with data obtained from five nondiabetic males (mean age thirty years, range eighteen to forty-six years). One of the diabetics was examined before treatment with insulin and the other after withdrawal of insulin, and both were again studied after several days of treatment with insulin and diet. Both subjects had ketosis and slight acid-base abnormalities when diabetes was untreated.

4. Four young nonobese subjects, two females and two males, without diabetes were examined during three days of fasting. The ages ranged between twenty-one and thirty-five years.

5. Two male diabetics (ages sixteen and sixty-one) with recently diagnosed diabetes were studied during experimental hypoglycemia. For comparison, similar experiments were performed in five young healthy subjects (aged twenty-five or twenty-six years, two females and three males).

PROCEDURE

Blood samples of 10 to 20 ml. were collected from an antecubital vein via an indwelling catheter. At least fifteen minutes elapsed between insertion of the catheter and withdrawal of the first blood sample. In the exercise experiments arterial blood was obtained via an indwelling catheter in the brachial artery. Most of the experiments were performed in the morning with the subjects in a fasting state. Smoking was prohibited, but water intake was not limited. When the diabetics were studied during ketoacidosis, the blood samples were obtained shortly after admission to hospital. The diabetics were examined before treatment with insulin and sodium chloride solutions were started.

In the exercise experiments arterial blood was obtained before, during, and after a twenty minute period of exercise. The working load was 450 kg. per minute. In the fasting experiments blood samples were obtained every morning before and during the three day period of food privation. In the experiments with decreasing blood glucose concentrations crystalline insulin (LEO) was given intravenously.

All experiments were performed after the subjects had rested in the supine position for at least thirty minutes.

RESULTS

For control subjects in the supine position, plasma norepinephrine and epinephrine levels averaged 0.18 ng. per milliliter and 0.06 ng. per milliliter respectively (table 1).

Clinical and laboratory data pertaining to the diabetic patients admitted to hospital with various degrees of ketoacidosis are given in table 2. The pulse rate was increased in all patients, as expected, while the blood pressure was normal or slightly increased. Plasma norepinephrine was elevated in all of the diabetic subjects during untreated states (table 3), with values ranging

TABLE 1

Plasma norepinephrine and epinephrine in normal subjects in the supine position

Number	Sex	Age (years)	Plasma norepinephrine ng./ml.	Plasma epinephrine ng./ml.
9	3 F 6 M	31 (21-75)	0.18 ± 0.06* (0.10-0.32)	0.06 ∓ 0.07 (0.00-0.19)

* Standard deviation of the single determination.

from 0.36 to 4.19 ng. per milliliter. The large variance is partly explained by the different degrees of metabolic derangement in these patients. Figure 1 shows the correlation between the plasma norepinephrine concentration and the degree of metabolic disturbance expressed as total carbon dioxide in plasma (p less than 0.02). Plasma norepinephrine also correlated with the pulse rate in the untreated diabetics (p less than 0.001) and with the blood glucose concentration (p less than 0.01).

The plasma epinephrine values obtained in the ketotic diabetic subjects are somewhat conflicting. Four of the values are extremely high, ranging from 0.72 to 1.58 ng. per milliliter while the others are within normal range. The metabolic status was slightly worse in the patients with the high epinephrine values. Mean total carbon dioxide in plasma was 11 mEq. per liter in the four patients with the elevated epinephrine concentrations in plasma and 14 mEq. per liter in those with normal values; blood glucose concentrations averaged 528 mg./100 ml. and 348 mg./100 ml. respectively.

Figure 2 shows the plasma norepinephrine and epinephrine concentration in a patient admitted with rather severe ketoacidosis. Several samples were obtained during initial treatment with insulin and fluids. It can be

TABLE 2

Pertinent clinical and laboratory data in ten diabetic patients admitted to hospital with ketoacidosis

Number	Sex	Duration (years)	Age (years)	Glucose in blood mg./ 100 ml.	Total CO_2 in plasma mEq./L.	Sodium in serum mEq./L.	Potassium in serum mEq./L.	Pulse rate (min.)	Blood pressure (mm. Hg)
Untreated (n = 10)	5 F 5 M	4 (0-14)	28 (14-66)	423 (310-922)	13 (8-18)	135 (126-142)	4.3 (3.7-5.1)	103 (140-88)	143/73 (160/80-120/60)
Treated (n = 6)	3 F 3 M	5 (0-14)	29 (14-66)	211 (120-326)	26 (22-33)	142 (138-148)	3.9 (3.5-4.4)	68 (56-80)	123/68 (160/80-110/60)

TABLE 3

Plasma norepinephrine and epinephrine in diabetic subjects in the supine position before and after treatment with insulin

Case	Plasma norepinephrine ng./ml. untreated	Plasma norepinephrine ng./ml. treated	Plasma epinephrine ng./ml. untreated	Plasma epinephrine ng./ml. treated
1	4.19	0.26	0.72	0.04
2	0.36	0.10	0.02	0.03
3	1.55	0.19	0.14	0.04
4	1.12	0.13	1.58	0.05
5	0.78	0.24	1.54	0.05
6	0.67	0.17	0.78	0.09
7	1.78		0.09	
8	1.26		0.05	
9	0.48		0.08	
10	0.48		0.06	
Mean	1.27	0.18	0.51	0.05
∓ SD	1.13	0.06	0.62	0.03

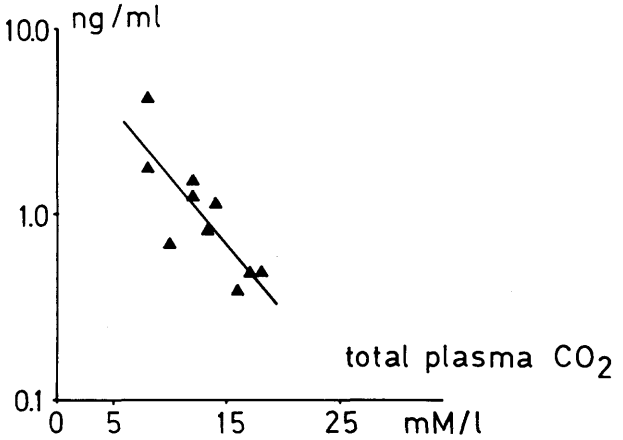

FIG. 1. Correlation obtained in ten diabetics between plasma norepinephrine and total carbon dioxide in plasma.

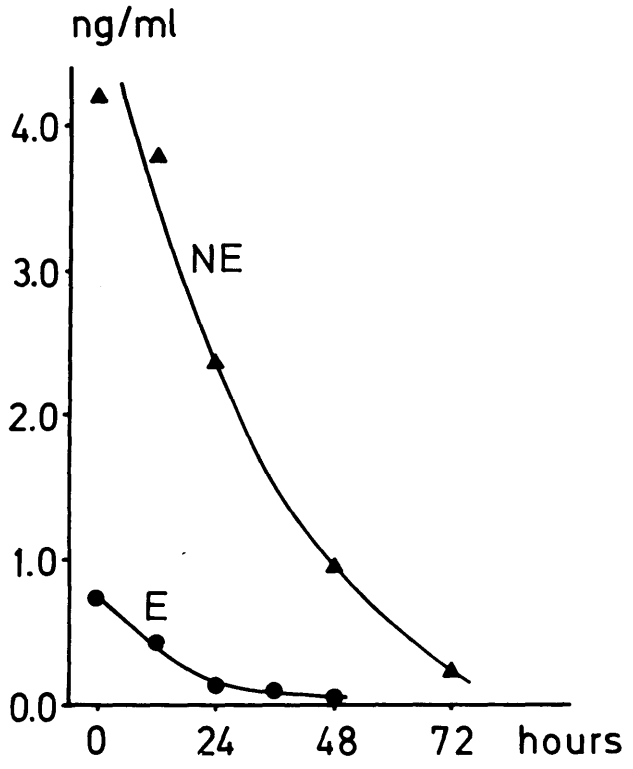

FIG. 2. Plasma norepinephrine (NE) and plasma epinephrine (E) in a diabetic patient with severe ketoacidosis during the course of treatment with insulin.

seen that both norepinephrine and epinephrine are considerably elevated during ketoacidosis, but plasma epinephrine becomes normal rather quickly and much earlier than plasma norepinephrine concentration.

It appears from table 3 that when the diabetics were examined during good control after several days of treatment with insulin and diet, the mean catecholamine values were similar to those obtained in the control subjects.

Figure 3 shows the total plasma catecholamine concentration (the sum of norepinephrine and epinephrine) measured in arterial plasma samples obtained before, during, and after a twenty minute period of exercise performed in the supine position in two diabetics and in five non-diabetic control subjects. The diabetics were studied while they exhibited ketosis and slight acid-base abnormalities and again after a period of treatment with insulin and diet. In the normal subjects the plasma catecholamine concentration rose from 0.31 ng. per milliliter at rest to 0.59 ng. per milliliter at the end of the exercise period and declined to resting values shortly after cessation of exercise. During ketosis the diabetics demonstrated elevated resting values, and during exercise large increments occurred. When good control had been achieved the values in the diabetics were similar to those in normal subjects. The systolic blood pressure of the controls rose during exercise from 120 mm. Hg to a maximal value of 160 mm. Hg at ten and twenty minutes. The same increase in blood pressure was found in the diabetics in both metabolic conditions. As expected, the resting pulse rate was elevated in the ketotic patients; mean rate per minute was 108 as compared with 69 in the controls. Maximal pulse rate during exercise was higher in the diabetic patients than in the controls (mean rate 168 against 124 in the controls).

Figure 4 shows results obtained in four normal non-obese subjects during three days of fasting. The free fatty acids show the expected rise during fasting, and the blood glucose declined from a mean value of 75

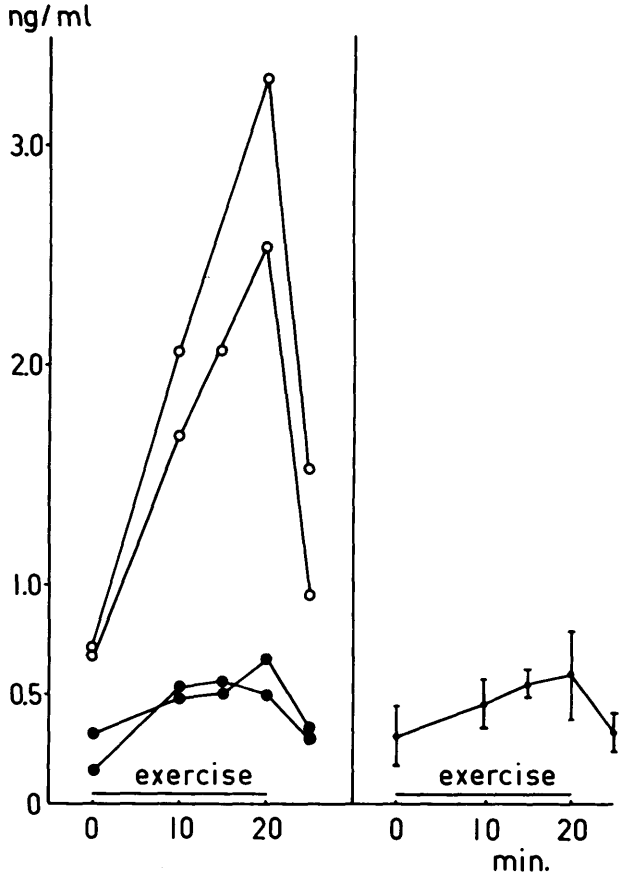

FIG. 3. Plasma catecholamines in subjects at rest and during and after exercise in the supine position. Right: average values from five controls ± S.D. Left: two diabetics; 0-0-0 untreated; ●-●-● treated.

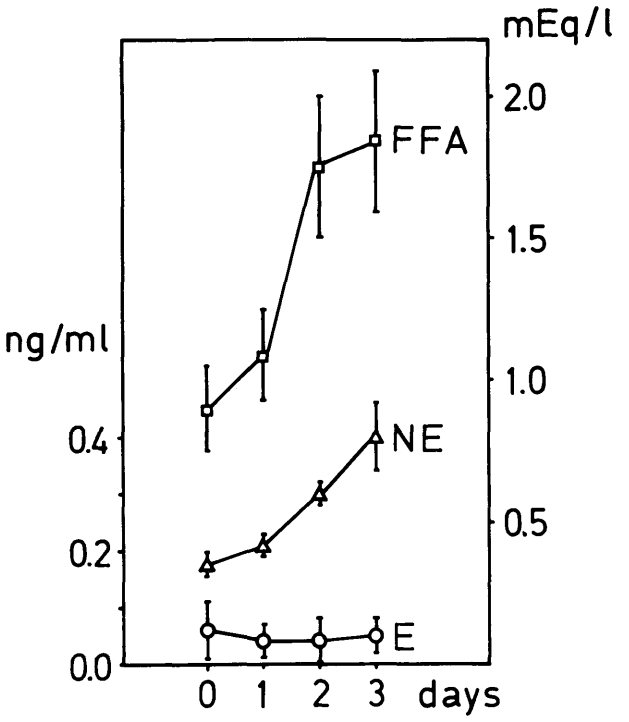

FIG. 4. Changes in free fatty acids (FFA) in serum, plasma norepinephrine (NE), and plasma epinephrine (E) in four normal subjects during three days of fasting. Mean values ± S.E.

mg./100 ml. to 56 mg./100 ml. The mean norepinephrine concentration rose from 0.18 to 0.40 ng. per milliliter (p less than 0.05) during the course of three days. No changes were observed in plasma epinephrine. Pulse rate and blood pressure remained unchanged during the experimental period.

Table 4 shows blood glucose concentrations, plasma norepinephrine and epinephrine in five normal subjects and in two diabetics after intravenous injection of crystalline insulin. One of the normal persons (case 5) received a very small dose of insulin and might be regarded as a person who has received a sham injection of insulin.

As expected plasma epinephrine increased during hypoglycemia. However, patients in whom the blood glucose level was just above 30 mg./100 ml. showed a modest rise in epinephrine, while large increments occurred in two subjects with values below 20 mg./100 ml. (figure 5).

There was no change in plasma epinephrine in the two diabetic subjects examined.

One unexpected finding was the increase in plasma norepinephrine which was observed in the diabetics as well as in the control subjects, although the change in case 4 is questionable. The magnitude of the response was similar in the diabetics and in the normal subjects (figure 6). In the diabetic patients there was no change in pulse rate and in blood pressure during the decline in blood glucose concentration.

The pulse rate increased suddenly in all of the normal subjects (excluding case 5) twenty to thirty minutes after the injection of insulin. There was no correlation between change in pulse rate and the epinephrine concentration. The largest rise in pulse rate was seen in patient 4, who showed a doubled epinephrine concentration only. Furthermore, the change in pulse rate was transient and declined to normal values despite sustained and very high plasma epinephrine concentrations (cases 1 and 2) (figure 7).

DISCUSSION

This study shows that plasma catecholamines are elevated in untreated diabetics. The characteristic change is an elevation of plasma norepinephrine paralleling the degree of metabolic derangement. The pulse rate was also elevated in the ketotic diabetics, as expected, but it should be emphasized that the plasma norepinephrine level in the diabetics is much higher than could be expected from the changes in pulse rate even were

TABLE 4

Plasma norepinephrine (NE) ng./ml., plasma epinephrine (E) ng./ml. and blood glucose concentration (G) mg./100 ml. in two diabetics and in five normal subjects after intravenous injection of insulin

		0	15	20-30 (min.)	30	45
Nondiabetics						
Case 1	NE	0.21	0.18	0.29	0.35	0.35
(8 units)	E	0.14	0.09	0.53	1.46	1.81
	G	66	32		16	41
Case 2	NE	0.10	0.11	0.22	0.31	0.32
(8 units)	E	0.08	0.10	0.82	1.51	1.87
	G	87	30		17	34
Case 3	NE	0.17	0.17	0.23	0.26	0.28
(2 units)	E	0.04	0.04	0.08	0.11	0.20
	G	80	43	33	36	56
Case 4	NE	0.15	0.15		0.18	0.18
(4 units)	E	0.03	0.04		0.23	0.23
	G	74	49		30	51
Case 5	NE	0.12	0.13		0.12	0.14
(0.3 units)	E	0.04	0.03		0.02	0.03
	G	76	76		68	69
Diabetics						
Case 6	NE	0.14	0.14		0.22	0.26
(8 units)	E	0.04	0.03		0.05	0.06
	G	269	195		149	121
Case 7	NE	0.13	0.14		0.30	0.27
(8 units)	E	0.06	0.06		0.08	0.08
	G	250	195		134	127

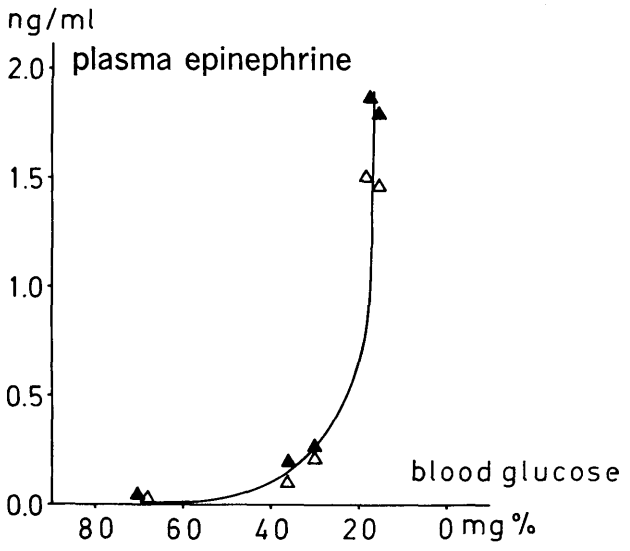

FIG. 5. Abscissa: the lowest blood glucose concentration obtained after intravenous injection of various doses of insulin. Ordinate: plasma epinephrine: △ thirty minute value; ▲ forty-five minute value.

it assumed that the tachycardia is due solely to sympathetic stimulation of the heart. We have earlier demonstrated a linear relationship between a rise in pulse rate and an increase in plasma norepinephrine in normals.[2]* Based on these data the rise in plasma norepinephrine in the diabetics exhibiting a mean increase in pulse rate of 35 beats per minute is expected to be approximately 0.30 to 0.35 ng. per milliliter. This value is considerably less than the measured value which averaged 1.09 ng. per milliliter. Analysis of the results obtained in the ketotic diabetics during exercise permits a similar conclusion. It is likely that the additional rise in plasma norepinephrine in ketoacidosis reflects adrenergic adjustment to volume depletion as well as increased lipolysis. The complicated circulatory and metabolic situation in a ketotic diabetic makes it impossible, however, to separate the rise in plasma norepinephrine into a circulatory and a metabolic component.

The finding of elevated plasma catecholamines in untreated diabetics is in accordance with other studies indicating increased sympathetic nervous activity in such patients. Thus it has been shown that the mobilization of free fatty acids, mediated via the adrenergic system, in response to exercise is increased in such patients.[7] Ganglion-blocking agents lower the increased level of free fatty acids in diabetic dogs,[8] and the increased responsiveness of growth hormone to exercise in poorly controlled diabetics can be completely abolished by alpha-receptor blocking agents.[9]

Porte has presented some experiments suggesting that adrenergic adjustment to volume depletion in diabetics may aggravate the metabolic status in these patients.[10] Although the level at which circulating norepinephrine directly influences the adrenergic receptors has not been completely elucidated, a plasma concentration of 1.50 ng. per milliliter corresponds roughly to an infusion rate of 10 μg. per minute in man.[11] In normal subjects this infusion rate is accompanied by a large rise in blood pressure as well as an increased level of free fatty acids in the blood.[12]

Havel has suggested that autonomic neuropathy in diabetics may protect them from the development of ketosis.[8]

We have shown earlier[13] that circulatory changes present in ketotic diabetics cannot be explained solely

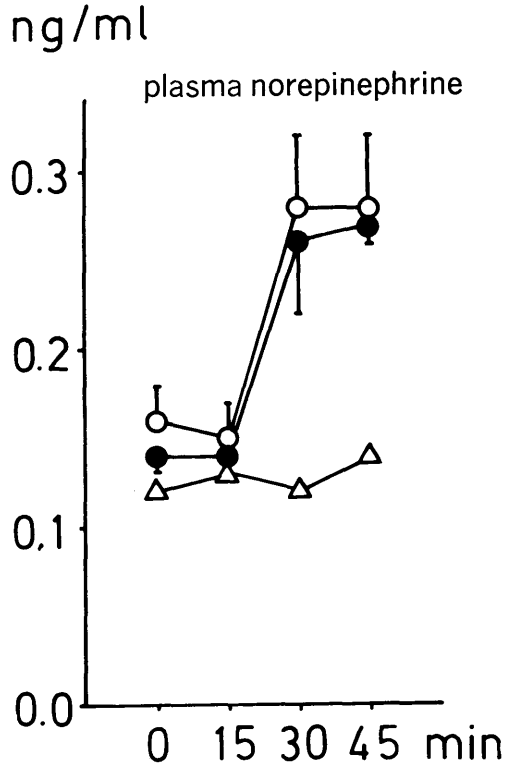

FIG. 6. Abscissa: time after the injection of insulin. Ordinate: plasma norepinephrine; O mean values ± S.E. in four normal subjects; ● mean values ± S.E. in two diabetic patients; △ case 5, who received a very small dose of insulin.

*Christiansen, N. J., and Brandsborg, O.: Eur. J. Clin. Invest. 3:299-306, 1973.

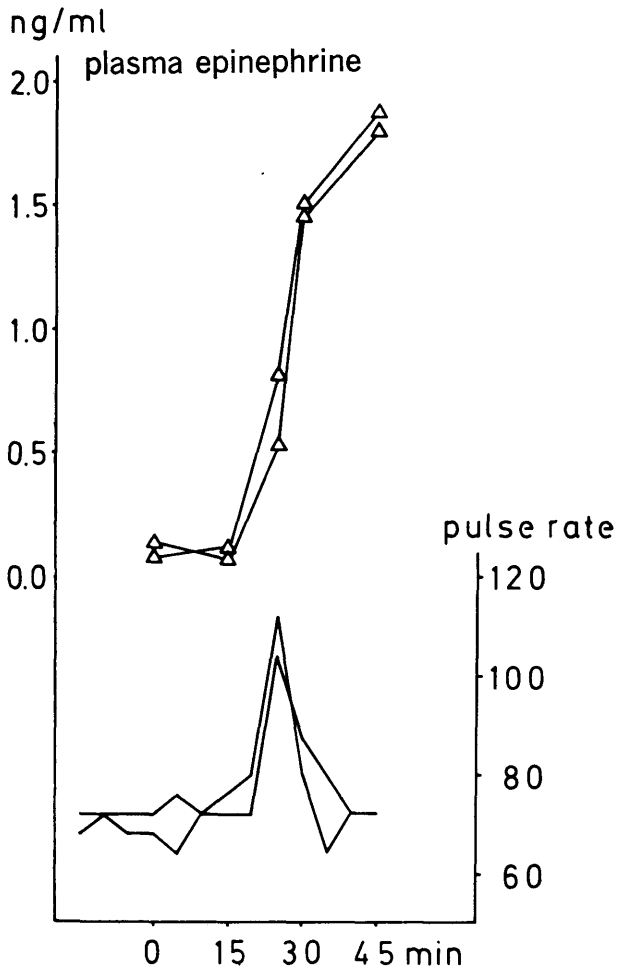

FIG. 7. Abscissa: time after injection of 8 U. of insulin in two normal subjects. Ordinate: Left: plasma epinephrine; Right: pulse rate per minute.

on the basis of dehydration. In the forearm epinephrine-like circulatory changes are consistently seen even in patients with very slight degrees of ketosis. Similar alterations are present in healthy fasting subjects.[14] Although these changes are similar to those seen after infusion of epinephrine it is clear from the present findings in ketotic diabetics and in fasting nondiabetics that these changes are not caused by circulating epinephrine. High levels of epinephrine were seen only in diabetic patients with a rather severe degree of ketoacidosis.

During prolonged fasting nondiabetic subjects showed in all cases an increase in plasma norepinephrine. This result is in accordance with previous studies which have shown that the mobilization of free fatty acids, the rise in plasma growth hormone, and the suppression of insulin secretion during fasting are at least partially mediated via an adrenergic mechanism.[15-18] No change was observed in plasma epinephrine in fasting subjects.

The rise in plasma epinephrine in response to hypoglycemia is well known.[11] Although our data are limited, they indicate that this response to hypoglycemia is not an all-or-none phenomenon but increases tremendously at very low blood glucose concentrations. A number of authors have observed that changes in blood glucose concentration during insulin hypoglycemia do not differ in patients with and without intact epinephrine secretion.[19-21] These results suggest that increased epinephrine secretion is not responsible for the restoration of the blood glucose concentration during insulin hypoglycemia. It is apparent, however, that the blood glucose level attained in these experiments was not very low. Our study does not directly shed light on this problem of whether or not epinephrine is significant in the maintenance of glucose homeostasis during hypoglycemia but indicates that any effect of epinephrine is more likely to be significant at glucose concentrations below 20 mg./100 ml. The above-mentioned studies[19-21] including our own have all been performed after the injection of insulin. It is also possible that during physiologic conditions, even minor changes in epinephrine and norepinephrine secretion may have been sufficient to inhibit insulin release from the pancreas.

The rise in plasma norepinephrine during decreasing blood glucose concentrations has not been observed before. The magnitude of the response was similar in both diabetics and controls and seems to depend upon a relative rather than an absolute lack of glucose. There was no change in pulse rate and blood pressure in the diabetic subjects during the experiments, which decreases the likelihood that the rise in plasma norepinephrine reflected any circulatory adjustment to decreasing blood glucose concentrations. During hypoglycemia there is, in fact, a withdrawal of adrenergic vasoconstrictor tone in some tissues.[22] Luft et al. have observed a small increase in urinary excretion of norepinephrine in normal subjects after the infusion of very small amounts of insulin.[23]

One striking finding was the lack of correlation between plasma epinephrine and the change in pulse rate during hypoglycemia. In two of the normal subjects who received 8 U. of insulin the pulse rate declined to normal levels despite sustained and very high levels of plasma epinephrine. This result is, however, in accord-

ance with clinical experience that tachycardia is not a characteristic finding in patients admitted to hospital with hypoglycemia. French and Kilpatrick[19] observed a normal rise in pulse rate during insulin hypoglycemia in patients who previously had been treated with bilateral splanchnicectomy and removal of the sympathetic chain and in whom there was no increase in urinary excretion of epinephrine during hypoglycemia.[19] The main difference they observed between the sympathectomized subjects and the normal persons was a decline in systolic blood pressure in the operated patients during hypoglycemia while the systolic blood pressure increased in the normal subjects as expected. This suggests that the adrenergic system may be of importance in the maintenance of blood pressure homeostasis during insulin hypoglycemia.

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