[51]Christensen, N. J.: Plasma noradrenaline and adrenaline in patients with thyrotoxicosis and myxedema. Clin. Sci. Molec. Med. *45*:163-71, 1973.

[52]Cryer, P. E.: Plasma norepinephrine and epinephrine in acromegaly. J. Clin. Endocrinol. Metab. *41*:542-45, 1975.

ABSTRACTS

(All are verbatim summaries)

Louis, W. J.; Doyle, A. E.; and Anavekar, S. N. (Univ. of Melbourne, Dept. of Med., Austin Hosp., Victoria, Australia): PLASMA NORADRENALINE CONCENTRATION AND BLOOD PRESSURE IN ESSENTIAL HYPERTENSION, PHAEOCHROMOCYTOMA AND DEPRESSION. Clin. Sci. Molec. Med. *48*:239, 1975.

1. Mean plasma noradrenaline concentration was elevated in forty-four patients with established essential hypertension. Eighteen of these hypertensive patients had resting plasma noradrenaline concentrations in the normal range.

2. Patients with endogenous depression had higher mean plasma noradrenaline concentrations but significantly lower blood pressure than patients with essential hypertension.

3. Patients with phaeochromocytoma had plasma noradrenaline concentrations twenty-eight times greater than those found in essential hypertension, but blood pressures were less than 20% higher.

4. It is concluded that excess of sympathetic drive only partly explains the level of the blood pressure in essential hypertension.

Ben-Jonothan, Nira; and Porter, John C. (Cecil H. and Ida Green Centr. for Reproductive Biology Sciences, the Dept. of Obstetrics and Gyn., and the Dept. of Physiology, the Univ. of Texas Health Science Centr. at Dallas, Southwestern Med. Sch., Dallas, Tex.): A SENSITIVE RADIOENZYMATIC ASSAY FOR DOPAMINE, NOREPINEPHRINE, AND EPINEPHRINE IN PLASMA AND TISSUE. Endocrinology *98*:1497, 1976.

A double-isotope, radioenzymatic assay for measuring dopamine, norepinephrine, and epinephrine in one sample is described. The assay procedure includes incubation, solvent extraction, and thin-layer chromatography. Dopamine, norepinephrine, and epinephrine were incubated with catechol-O-methyl transferase (COMT) and [^{3}H]S-adenosyl methionine ([^{3}H]SAM) and were converted to the O-methylated tritiated derivatives: [^{3}H]methoxytyramine, [^{3}H]normetanephrine, and [^{3}H]metanephrine, respectively. After several extraction steps, the O-methylated products were purified by means of two-dimensional, thin-layer chromatography using silica gel. The thin-layer chromatographic system using silica gel. The thin-layer chromatographic system resulted in complete separation of the three O-methylated compounds with an overlap of only 1-2%. The assay was linear from 0 to 5 ng for each catecholamine and had a sensitivity of 10-30 pg. The addition of large amounts of plasma reduced the activity of COMT, but increasing the magnesium concentration in the incubation mixture and the addition of EGTA to plasma samples improved the recoveries. Each sample was corrected for losses incurred during extraction and chromatography by using [^{14}C]methoxytyramine, [^{14}C]normetanephrine, and [^{14}C]metanephrine that were added at the end of incubation. Several catechol compounds known to be O-methylated by COMT were examined for cross-reactivity. Of the substances tested, only dihydroxyphenylalanine (DOPA) exhibited cross-reactivity. However, the apparent 30% cross-reactivity of DOPA with dopamine was due to the presence of decarboxylase activity in the COMT preparation. As little as 50 μl of trunk plasma from decapitated rats was sufficient for the determination of the three catecholamines.

De Champlain, Jacques; Farley, Lise; Cousineau, Daniel; and Van Ameringen, Marie-Reine (Centre de Recherche en Sciences Neurologiques, Dép. de Physiologie, Faculté de Médecine, Université de Montréal, Québec, Canada): CIRCULATING CATECHOLAMINE LEVELS IN HUMAN AND EXPERIMENTAL HYPERTENSION. Circ. Res *38*:109, 1976.

The radiometric enzymatic technique of Coyle and Henry (J. Neurochem. 21:61-67, 1973) was adapted to the measurement of serum catecholamines. This technique requires less time than other enzymatic techniques and is sensitive to quantities as small as 25 pg. In normotensive subjects lying supine for 20 minutes serum catecholamine levels averaged 0.218 ng/ml, with no obvious sex or age difference. Under these standardized conditions, the circulating catecholamine levels for a given individual are highly reproducible on different days over a period of several months. In 22 patients with essential hypertension, circulating levels were significantly higher, with an average of 0.370 ng/ml. More than 50% of the hypertensive patients had values greater than the highest value measured in normotensives. Systolic blood pressure and heart rate were significantly higher in the hypertensive group with elevated levels of circulating catecholamines than in the hypertensive group with normal levels. In one model of experimental hypertension, produced in the rat by administration of deoxycorticosterone acetate (DOCA) and saline for 4-8 weeks, serum catecholamines were significantly elevated. These findings suggest that the sympathetic system may play an important role in maintaining an elevated blood pressure in experimental hypertension and in a significant proportion of patients with essential hypertension.

Johnson, David G.; Henry, David P.; Moss, Jonathan; and Williams, Robert H. (Divisions of Endocrinology and Clinical Pharmacology, Dept. of Med., Univ. of Washington, Seattle, Wash.): INHIBITION OF INSULIN RELEASE BY SCORPION TOXIN IN RAT PANCREATIC ISLETS. Diabetes *25*:198, 1976.

Toxin purified from venom of the scorpion Leiurus quinquestriatus was used to release norepinephrine from adrenergic nerve terminals in isolated pancreatic islets perifused in vitro. Addition of toxin (10 μg./ml.) to the perifusion medium caused a sixfold increase in release of norepinephrine in the presence or absence of 3×10^{-5}M phenoxybenzamine. During 20 minutes of stimulation with toxin, the pancreatic islets released an average of 15 pg.

of norepinephrine per islet, which represented 20 per cent of the normal content of norepinephrine in islets. Insulin secretory rates in response to either 1.0 or 3.0 mg./ml. glucose were inhibited similarly by scorpion toxin. Addition of phenoxybenzamine abolished the inhibition of insulin release caused by scorpion toxin. Phenoxybenzamine alone did not affect release of insulin. Neither the enhanced release of norepinephrine nor the decreased release of insulin was reversed by a 20-minute wash-out period after infusion of toxin.

These results indicate that the sympathetic nerve terminals in the rat pancreatic islet contain considerable amounts of norepinephrine that can be released by scorpion toxin. The norepinephrine released from sympathetic nerve endings in the pancreatic islet can inhibit release of insulin through an alpha-adrenergic action that is blocked by phenoxybenzamine.

Neubauer, B.; and Christensen, N. J. (Second Clinic of Intern. Med., Kommunehospitalet, Aarhus, Denmark): NOREPINEPHRINE, EPINEPHRINE, AND DOPAMINE CONTENTS OF THE CARDIOVASCULAR SYSTEM IN LONG-TERM DIABETES. Diabetes *25*:6, 1976.

Norepinephrine, epinephrine, and dopamine concentrations were studied in the cardiovascular system of postmortem material obtained from six long-term diabetics and six control subjects.

Norepinephrine concentration was considerably reduced in the cardiovascular system of the diabetic patients. The mean norepinephrine concentration in the apex of the heart, the radial artery, the posterior tibial artery, and the femoral artery in the diabetics averaged 6, 9, 12, and 20 per cent, respectively, of the corresponding mean values in the controls.

Epinephrine was present in the cardiovascular system in the controls but in small amounts in comparison with norepinephrine. There was no correlation between the epinephrine and the norepinephrine concentrations in the tissue. In the diabetics the epinephrine concentration in the heart and in the arteries did not differ from the values obtained in the controls.

The dopamine concentration averaged 11 per cent of the norepinephrine concentration in the cardiovascular system in the controls. There was a strong correlation between tissue concentrations of dopamine and of norepinephrine. In the diabetics the dopamine concentration was reduced, but relatively less than that of norepinephrine, and constituted 53 per cent of the norepinephrine concentration.

It is suggested that the depletion of the norepinephrine stores in the heart in diabetic patients may in part be responsible for their reduced survival rate in acute myocardial infarction.

Cryer, Philip E.; Haymond, Morey W.; Santiago, J. V.; and Shah, Suresh D. (Metab. Div., Depts. of Med. and Pediatrics, Washington Univ. Sch. of Med., St. Louis, Mo.): NOREPINEPHRINE AND EPINEPHRINE RELEASE AND ADRENERGIC MEDIATION OF SMOKING-ASSOCIATED HEMODYNAMIC AND METABOLIC EVENTS. N. Engl. J. Med. *295*:573, 1976.

We studied the effects of cigarette smoking, sham smoking and smoking during adrenergic blockade in 10 subjects to determine whether smoking released the sympathetic neurotransmitter norepinephrine, as well as the adrenomedullary hormone epinephrine, and whether smoking-associated hemodynamic and metabolic changes were mediated through adrenergic mechanisms. Smoking-associated increments in mean (±S.E.M.) plasma norepinephrine (227 ± 23 to 324 ± 39 pg per milliliter, $P<0.01$) and epinephrine (44 ± 4 to 113 ± 27 pg per milliliter, $P<0.05$) were demonstrated. Smoking-associated increments in pulse rate, blood pressure, blood glycerol and blood lactate/pyruvate ratio were prevented by adrenergic blockade; increments in plasma growth hormone and cortisol were not. Since significant smoking-associated increments, in pulse rate, blood pressure and blood lactate/pyruvate ratio, preceded measurable increments in plasma catecholamine concentrations, but were adrenergically mediated, these changes should be attributed to norepinephrine released locally from adrenergic axon terminals within the tissues rather than to increments in circulating catecholamines.

Ziegler, Michael G.; Lake, C. Raymond; and Kopin, Irwin J. (Laboratory of Clinical Science, National Inst. of Mental Health, Bethesda, Maryland): DEFICIENT SYMPATHETIC NERVOUS RESPONSE IN FAMILIAL DYSAUTONOMIA. N. Engl. J. Med. *294*:630, 1976.

Norepinephrine concentration and dopamine-beta-hydroxylase activity were measured in the plasma of 10 dysautonomic patients and 10 normal subjects while they were reclining, standing and exercising. While reclining, dysautonomic patients had normal norepinephrine concentrations and blood pressure, but after standing they did not have a normal increase in their levels of norepinephrine ($P<0.005$), dopamine-beta-hydroxylase ($P<0.05$) or plasma protein concentration ($P<0.01$); they became hypotensive. In reclining dysautonomic patients there appeared to be a correlation between blood pressure and plasma norepinephrine concentration. These data support the view that hypertension and hypotension in dysautonomia are related to the rate of norepinephrine release.

Garber, Alan J.; Cryer, Philip E.; Santiago, Julio V.; Haymond, Morey W.; Pagliara, Anthony S.; and Kipnis, David M. (Metab. Divisions, Dept. of Med. and Pediatrics, Washington Univ. Sch. of Med., St. Louis, Mo.): THE ROLE OF ADRENERGIC MECHANISMS IN THE SUBSTRATE AND HORMONAL RESPONSE TO INSULIN-INDUCED HYPOGLYCEMIA IN MAN. J. Clin. Invest. *58*:7, 1976.

Sequential determinations of glucose outflow and inflow, and rates of gluconeogenesis from alanine, before, during and after insulin-induced hypoglycemia were obtained in relation to alterations in circulating epinephrine, norepinephrine, glucagon, cortisol, and growth hormone in six normal subjects. Insulin decreased the mean (±SEM) plasma glucose from 89 ± 3 to 39 ± 2 mg/dl 25 min after injection, but this decline ceased despite serum insulin levels of 153 ± 22 μU/ml. Before insulin, glucose inflow and outflow were constant, averaging 125.3 ± 7.1 mg/kg per h.; 15 min after insulin, mean glucose outflow increased threefold, but then decreased at 25 min, reaching a rate 15% less than the preinsulin rate. Glucose inflow decreased 80% 15 min after insulin, but increased at 25 min, reaching a maximum of twice the basal rate. Gluconeogenesis from alanine decreased 68% 15 min after insulin, but returned to preinsulin rates at 25 min, and remained constant for the next 25 min, after which it increased linearly. A fourfold increase in mean plasma epinephrine

was found 20 min after insulin, with maximal levels 50 times basal. Plasma norepinephrine concentrations first increased significantly at 25 min after insulin, whereas significantly increased levels of cortisol and glucagon occurred at 30 min, and growth hormone at 40 min after insulin.

Thus, insulin-induced hypoglycemia in man results from both a decrease in glucose production and an increase in glucose utilization. Accelerated glycogenolysis produced much of the initial, posthypoglycemic increment in glucose production. The contribution of glycogenolysis decreased with time, while that of gluconeogenesis from alanine increased. Of the hormones studied, only the increments in plasma catecholamines preceded or coincided with the measured increase in glucose production after hypoglycemia. It therefore seems probable that adrenergic mechanisms play a major role in the initiation of counterregulatory responses to insulin-induced hypoglycemia in man.

Robertson, R. Paul; Halter, Jeffrey B.; and Porte, Daniel, Jr. (Univ. of Washington Sch. of Med., and VA Hospital, Seattle, Wash.): A ROLE FOR ALPHA-ADRENERGIC RECEPTORS IN ABNORMAL INSULIN SECRETION IN DIABETES MELLITUS. J. Clin. Invest. *57*:791, 1976.

To determine whether endogenous alpha-adrenergic activity contributes to abnormal insulin secretion in nonketotic, hyperglycemic, diabetic patients, alpha-adrenergic blockade was produced in normal and diabetic subjects. The diabetics had a significantly ($P<0.01$) greater increase in circulating insulin 1 h after an intravenous phentolamine infusion than did the normal subjects. During the phentolamine infusion, there was also a significant augmentation of acute insulin responses to intravenous glucose (20 g) pulses in normal subjects ($P<0.05$) and diabetics ($P<0.02$); this augmentation was fivefold greater in the diabetics. Simultaneous treatment with the beta-adrenergic blocking agent, propranolol, did not alter these findings. Thus a role for exaggerated endogenous alpha-adrenergic activity in abnormal insulin secretion of the diabetic subjects is suggested. To determine whether this alpha-adrenergic activity might be related to elevated circulating catecholamines, total plasma-catecholamine levels were compared in normal and nonketotic diabetic subjects given intravenous glucose pulses. These levels were significantly greater ($P<0.02$) in the diabetic compared to the normal group before the glucose pulse, and increased significantly in both groups ($P<0.02$ and <0.001, respectively) after the pulse. These data suggest that excessive catecholamine secretion may lead to an abnormal degree of endogenous alpha-adrenergic activity, which contributes to defective insulin secretion in diabetic subjects.

Alberti, K. G. M. M.; Christensen, N. J.; Iversen, J.; and Orskov, H. (Faculty of Medicine, Chemical Pathology, Gen. Hosp., Southampton, and Second Clinic of Intern. Med., Kommunehospitalet, Aarhus, Denmark): ROLE OF GLUCAGON AND OTHER HORMONES IN DEVELOPMENT OF DIABETIC KETOACIDOSIS. Lancet 1:7920, 1975.

Blood concentrations of pancreatic glucagon, cortisol, noradrenaline, adrenaline, and growth hormone have been measured during the first 41 hours of insulin deprivation in six insulin-dependent diabetics to assess the importance of these hormones in the pathogenesis of diabetic ketoacidosis. Plasma-glucagon showed an early small significant rise and thereafter a slow increase to a plateau during the remaining experimental period. Plasma-cortisol increased only at the end of the insulin-deprivation period, while plasma-catecholamines and serum-growth-hormone concentrations did not change. In the three of the six patients who developed significant ketosis, plasma-glucagon showed a close correlation with blood-ketones and plasma-free-fatty-acids while for the whole group the change in glucagon concentration correlated significantly with the rise in ketone-body concentration. It is suggested that the excess of glucagon in addition to the insulin lack may be an important factor in determining the degree of hyperglycaemia and hyperketonaemia in the early stages of insulin deprivation.

Galbo, H.; Holst, J. J.; and Christensen, N. J. (Inst. of Med. Physiol. B., Univ. of Copenhagen, Dept. of Surg. A, Bispebjerg Hosp., Copenhagen; and Second Clinic of Intern. Med., Kommunehospitalet, Aarhus, Denmark): GLUCAGON AND PLASMA CATECHOLAMINE RESPONSES TO GRADED AND PROLONGED EXERCISE IN MAN. J. Appl. Physiol. *38*:70, 1975.

Eight men were studied during graded (47, 77, and 100% of maximal oxygen uptake) and prolonged (76%) exhaustive treadmill running. During graded exercise the glucagon concentration increased 35% from 81 ± 7 pg/ml (mean and SE) at rest to 109 ± 17 after the heaviest load. During prolonged exercise glucagon increased progressively to three times (226 ± 40) the resting value. Norepinephrine increased from 0.40 ± 0.06 ng/ml to 2.22 ± 0.39, epinephrine from 0.07 ± 0.01 to 0.42 ± 0.13 during graded, and to 1.51 ± 0.08 and 0.33 ± 0.04, respectively, during prolonged exercise. Insulin concentrations were depressed during work except for the heaviest load. Fatty acids rose throughout prolonged exercise, whereas blood glucose significantly diminished 30 min afterward. Glucagon concentrations correlated significantly with norepinephrine and epinephrine concentrations during prolonged and with epinephrine during graded exercise. Although increments in catecholamines were similar, the glucagon secretion was larger during prolonged than during graded exercise. While increments in catecholamines might explain increased glucagon secretion during graded exercise, they cannot account completely for the rise of glucagon during prolonged exercise.

Christensen, N. J.; Alberti, K. G. M. M.; and Brandsborg, O. (2nd Clinic of Intern. Med. and the Surg. Dept. of Gastro., Kommunehospitalet, Aarhus, Denmark, and Chem. Path., the Gen. Hosp. Southampton, Great Britain): PLASMA CATECHOLAMINES AND BLOOD SUBSTRATE CONCENTRATIONS: STUDIES IN INSULIN INDUCED HYPOGLYCAEMIA AND AFTER ADRENALINE INFUSIONS. Eur. J. Clin. Invest. *3*:299, 1973.

Plasma adrenaline-blood glucose interrelationships in insulin-induced hypoglycaemia in man have been studied using a sensitive double-isotope derivative method for adrenaline estimation. Plasma adrenaline reached a peak of 1.24 ng/ml at 45 minutes after insulin while blood glucose reached a nadir of 22 mg/100 ml at 30 minutes. There was a strong correlation both between the rise in adrenaline and the degree of hypoglycaemia and between the rise in adrenaline and the post-hypoglycaemic rise in glucose. Plasma noradrenaline rose from 0.29 to 0.59 ng/ml, the rise

correlating with the rise in adrenaline. Changes in pulse rate preceded and were unrelated to changes in plasma catecholamines. Fuel mobilisation in response to adrenaline infusion (6 μg/min. for 20 min.) in normoglycaemic man was also studied. Plasma adrenaline concentration rose from a mean of 0.02 ng/ml to 0.71 ng/ml while plasma noradrenaline concentration was unchanged. Blood glucose rose from 71 to 98 mg/100 ml while plasma insulin decreased from 11 to 8 μU/ml. Blood lactate rose by 0.85 mM while pyruvate concentration remained unchanged. Blood glycerol concentration rose twofold and ketone body concentration threefold but there was little change in the concentrations of the glucogenic amino acids, alanine, glutamate and glutamine. Both the 3-hydroxybutyrate/acetoacetate ratio and the lactate/pyruvate ratio rose implying a more reduced intracellular state due presumably to increased hepatic fatty acid oxidation. It is concluded that adrenaline enhances the recycling of lactate and spares glucose through the mobilisation of lipids but that amino acids are little affected.

Cryer, Philip E.; and Weiss, Stuart (Depts. of Med., Neurol., and Neurosurg., Washington Univ. Sch. of Med., St. Louis, Mo.): REDUCED PLASMA NOREPINEPHRINE RESPONSE TO STANDING IN AUTONOMIC DYSFUNCTION. Arch. Neurol. *33*:275, 1976.

In five patients having primary autonomic dysfunction with clinical manifestations including postural hypotension, the mean plasma norepinephrine concentrations were significantly lower than those of normal subjects after two and five minutes in the standing position. The mean (± SE) increment in the plasma norepinephrine concentration after two minutes standing was 123 ± 19 pg/ml in the normal subjects and 13 ± 4 pg/ml ($P<.001$) in the patients with primary autonomic dysfunction. After five minutes standing, the mean increment in plasma norepinephrine concentration was 244 ± 36 pg/ml in the normal subjects and 99 ± 51 pg/ml ($P<.05$) in the patients. There were no statistically significant differences in plasma epinephrine between the two groups.