Mechanisms and Management of Hyperosmolar Coma Without Ketoacidosis in the Diabetic

Robert D. Johnson, M.D., Jerome W. Conn, M.D., Calvin J. Dykman, M.D., Sumer Pek, M.D., and Jerome I. Starr, M.D., Ann Arbor

SUMMARY

The mechanisms involved in the production, maintenance and progression of the state of nonketotic, hyperosmolar coma of mild diabetic patients are discussed; and a method is outlined for both initial therapy (before insulin activity is sufficiently increased) and subsequent therapy. Factors involved in the development of the syndrome include: (1) Persistence of enough insulin production to prevent ketoacidosis but very severe suppression of insulin release in relation to the level of blood glucose. (2) Insidious development of extreme hyperglycemia, increasingly great osmotic diuresis, severe depletion of body water and *large* volumes of urine. (3) Lack of appropriate response of the thirst center as the sensorium becomes inadequate.

Because the mortality of this condition now approaches 50 per cent, careful attention to details of therapy is imperative. Delay in recognition and, therefore, of therapy leads to fatalities. DIABETES *18*:111-16, February, 1969.

Hyperglycemic nonketotic coma has emerged in the past decade as an unusual complication of diabetes mellitus. Although the syndrome was first recorded by Umber-Berlin[1] in 1924, the initial clinical description in the English literature is credited to Sament and Schwartz[2] in 1957. The syndrome is characterized by severe hyperglycemia, hyperosmolality and dehydration in the absence of ketoacidosis. Schwartz and Apfelbaum[3] in a recent review cited forty-one diabetic patients who demonstrated significant depression of consciousness in the absence of acidosis. Halmos et al.[4] have since reported eight cases, and Jackson and Forman[5] have described ten patients with this condition. Yet, despite increased recognition of this acute situation the mortality rate remains high. Delay in proper diagnosis and in the institution of appropriate treatment contributes significantly to the fatalities. The purpose of this paper is to discuss some details of two illustrative cases with emphasis upon pathophysiology and upon the indicated therapeutic procedures.

From the Department of Internal Medicine (Division of Endocrinology and Metabolism and the Metabolism Research Unit), University of Michigan Medical School, Ann Arbor, Michigan.

CASE REPORTS

Patient No. 1. The patient, a seventy-nine-year-old white male, a retired pastor, was admitted to the University of Michigan Medical Center on September 20, 1966, because of progressive lethargy, confusion and somnolence for three days. Diabetes mellitus had been discovered in January, 1963, and had been controlled exclusively by dietary means. Fasting blood sugar levels had varied between 90 and 120 mg. per 100 ml. Six weeks before admission there occurred the insidious onset of nocturia which progressed to the point of copious nocturia. (6×). The patient became unusually thirsty and drank ten to twelve glasses of half-strength frozen orange juice concentrate per day. He also admitted eating one pint of ice cream daily to relieve a constant dry mouth. Five days before admission, when he was evaluated by a physician during a routine clinic visit, he appeared to be well. During the three days preceding his admission, the patient's wife noted that he had become forgetful, less intellectually inquisitive and alarmingly erratic while driving his car. A coarse irregular tremor of the right arm appeared approximately six hours prior to his admission. This was followed by progressive hoarseness and deepening somnolence.

Hiatus hernia and duodenal ulcer had been treated medically in the past. He had suffered also from intermittent mild congestive heart failure. In 1960 a pericardiectomy had been performed. The surgical material was described as showing chronic productive pericarditis. Before the present admission his medications had been Digitoxin 0.1 mg. per day and Isoniazid 100 mg. t.i.d.

On physical examination the patient was found to be slightly obese, dehydrated and semicomatose. He was sporadically responsive to verbal commands. Blood pressure was 140/80, temperature 100.2; pulse 110/minute and regular; respirations were 28/minute and shallow. Funduscopic examination revealed retinal artery narrowing, distinct disc margins and spontaneous venous pulsations. The mucous membranes and skin were dry. Neck veins were flat. Systolic retraction was present at the apex of the heart and there was a sustained apex impulse. A short early systolic murmur was heard at the apex. The lungs were clear. There was bilateral depression of the deep tendon reflexes. Perioral and tongue fasciculations were noted together with bilateral coarse nonrhythmic tremors of shoulder and arm muscles. There were no localizing neurologic findings. Peripheral pulses were strong and no pitting edema was present.

On admission blood glucose was found to be 1,000 mg. per 100 ml. The urine showed 4+ sugar, no acetone, specific

gravity of 1.030, pH of 5.5, a trace of protein and no abnormal microscopic findings. The hematocrit was 54 per cent and the white blood cell count was 19,000 with 89 per cent polymorphonuclear neutrophils. The BUN was 53, serum creatinine 3.27 mg. per 100 ml., serum sodium 154, chloride 109, potassium 5.2 and CO_2 combining power 30 mEq./L. An electrocardiogram demonstrated left axis deviation and primary T wave changes which did not differ from a previous tracing dated January 5, 1965. Chest X ray revealed mild left ventricular enlargement with no evidence of active pulmonary disease.

Details of therapy together with progressive biochemical alterations are summarized in table 1. Treatment consisted primarily of intravenous hypotonic solutions and Regular insulin. The urine turned dark brown in color from the fourth to the eighth hour of treatment and subsequently cleared. As hydration improved a parallel improvement in his somnolence and stupor occurred. By the sixth hour of therapy he was able to respond with movement to verbal commands. Twelve hours after therapy had begun the patient was oriented, alert and taking oral fluids eagerly. At this point, after he had been given 5,800 cc. of intravenous fluid and 335 U. Regular insulin, the blood sugar was 68 mg. per 100 ml. At twenty hours the blood sugar had risen to 685 mg. per 100 ml. but the patient remained alert. An additional 60 U. Regular insulin subcutaneously reduced the blood sugar to 74 mg. per 100 ml. at the thirty-six-hour point (see table 1). Lente insulin was then begun and has been continued.

Coincident with rehydration, the hematocrit dropped from 53 to 40 with a corresponding gain of weight from 137 to 145 lbs. More vigorous oral fluid therapy was not advised because of the appearance of bilateral basilar rales and visible ankle swelling twenty-four hours after the beginning of treatment. These signs gradually disappeared.

TABLE 1

Laboratory data and therapy of Patient No. 1

					Data					
Time (hours)	0	2	4	6	8	10	12	20	36	96
Blood sugar (mg./100 ml.)	1,000	945	825		265		68	685	74	160
*Osmolality (mOsm./kg.)	364						322		318	303
BUN (mg./100 ml.)	53						44		38	
Creatinine (mg./100 ml.)	3.27								2.7	1.93
Na^+ (mEq./L.)	154		158				159		157	147
K^+ (mEq./L.)	5.2		3.8		4.2		4.3		4.8	4.6
Cl^- (mEq./L.)	102		109				109		112	107
CO_2 (mEq./L.)	30		26				30		27	29
Acetone (undiluted serum and urine)			uniformly negative							
Hct.	53						44			40
Body weight	137						145			143
					Therapy					
Time (hours)	0	*—* 2	4	6	8	10	12	20	36	96
Regular insulin (U.)	10 SC	50 IV 50 SC	50 IV 50 SC	50 IV 50 SC		25 SC		50 SC	60 SC	45 Lente/d.
Intravenous fluid intake	1,000	1,300	1,000	1,000	500	1,000	1,000	1,000	4,000	
Glucose (gm.)	25	7.5				50	50	25	175	
Na^+ (mEq./L.)	77	60	77	77	38	34	34	34	102	
K^+ (mEq./L.)			10	20	20	20	40		60	
Solution composition	2.5 per cent gluc. 0.45 per cent sal.	300 ml. 2.5 per cent gluc. 0.45 per cent sal. 1,000 ml. 0.22 per cent sal.	0.45 per cent sal.	0.45 per cent sal.	0.45 per cent sal.	5 per cent gluc. 0.2 per cent sal.	5 per cent gluc. 0.2 per cent sal.	2.5 per cent gluc. 0.2 per cent sal.	5 per cent gluc.	

*Osmolality (mOsm./kg.H_2O) $= 2 \times$ Na (mEq./L.) $+ \frac{\text{glucose (mg./100 ml.)}}{18}$

— Delay in recognition of situation at emergency station
SC = subcutaneous

The patient was discharged on the eleventh hospital day in good condition.

Patient No. 2. The second illustrative patient did not survive. Measurements of plasma insulin were made, however, before treatment was instituted. Such information has not been reported previously.

Peculiar behavior had been noticed by the family of this sixty-seven-year old female for several weeks. She had been obtunded for three to four days before admission to the hospital. The patient responded only to deep pressure pain, was extremely dehydrated, and had tachycardia, hypotension and gangrene of the right leg. Rectal temperature was 101.2° F. Laboratory studies included a blood sugar of 720, BUN—170, serum creatinine 6.1 and phosphorus 6.2 mg./100 ml., serum sodium 135, potassium 5.1, chloride 93 and CO_2 combining power 15 mEq./L. Plasma immunoreactive insulin was 29 μU./ml. Plasma acetone was not measurable and the urine contained neither sugar nor acetone. Glycosuria appeared later after hydration had been improved. The renal threshold for glucose was found to be high. The urinary tract was infected with *E. coli.* Despite administration of 6 L. of hypotonic fluid during the first eight hours, urinary output was less than 300 cc. The patient expired eighteen hours after admission to the hospital in spite of intensive therapy which brought her blood sugar down to 300 mg. per 100 ml. Electrolytes changed very little and the low CO_2 combining power, secondary to the renal insufficiency, persisted to the time of demise.

COMMENTS REGARDING PATIENTS No. 1 AND No. 2

In case No. 1, the admitting diagnosis was nonketotic diabetes with possible cerebrovascular accident. The initial insulin dose was small. When it was recognized, however, that the patient was suffering from "hyperosmolar coma," he was treated much more vigorously with insulin and hypotonic solutions. At the sixth hour, the muscle twitching ceased and he became hyporeflexic and flaccid. Serum potassium had fallen from 5.4 to 3.8 mEq./L., not low enough to cause such signs, but conceivably important in the presence of hypernatremia (158 mEq./L.).[6] He improved greatly over the next five hours concomitant with the administration of potassium, hypotonic saline and insulin. The blood sugar fell from 1,000 to 265 mg. per 100 ml. At this time fluid therapy was changed to 5 per cent glucose in 0.2 per cent saline.

We are not aware if hemolysis has been recorded as a complication of hyperglycemic, nonketotic coma. Table 2 summarizes data suggesting that this could have occurred in the present patient. The dark brown urine observed early in the course of treatment was accompanied by a uniform elevation of serum glutamate oxaloacetate transaminase (SGOT), lactate dehydrogenase (LDH) and alphahydroxybutyric dehydrogenase (SHBD). Kingsley et al.[7] have shown SGOT, SLDH and SHBD values increased linearly during hemolysis. Hemolysis of 0.3 per cent caused a rise of SGOT of 10 per cent and of SLDH and SHBD of 40 per cent. This correlates well with the relative increases in the respective enzyme determinations obtained in this patient after initial therapy which included one liter of 0.22 per cent saline intravenously. The serum bilirubin also showed a slight concurrent elevation. While other variables including congestive heart failure and myocardial damage could have contributed to the enzyme elevations, it seems that significant intravascular hemolysis was precipitated during the course of initial therapy. It is of interest that initial and continued elevation was also observed in serum creatine phosphokinase (CPK) although it is known that this enzyme is not measurable in normal erythrocytes or serum. Hess et al.[8] demonstrated a selective tissue distribution of CPK in skeletal and cardiac muscle. In the absence of electrocardiographic or clinical evidence of myocardial damage, it is likely that the CPK elevations were due to the effects of profound dehydration on skeletal musculature. Myoglobinuria is another possible cause for the appearance of dark urine, but definitive studies for its presence were not carried out in this patient. The absence of muscular pain, a prominent feature of acute myoglobinuria of diverse etiologies, and the elevation in serum bilirubin noted in this case would favor intravascular hemolysis and hemoglobinuria.

In Case No. 2, plasma insulin concentration was measured before treatment. Such data (plasma immunoreactive insulin in hyperosmolar nonketotic diabetic coma) have heretofore not been published, though a

TABLE 2

Enzyme data on Patient No. 1

	SGOT (units)	LDH (units)	SHBD (units)	CPK (units)	Bilirubin (mg./100 ml.) Total	Direct
Normal values	< 40	24-77	< 105	< 30	0.1-0.9	< 0.2
Pretherapy	90	85	97	110		
12th hr.	125	296	522	65	1.0	0.4
36th hr.	119	171	335	52		
60th hr.	81	200	385	24		
One month later	45	63	84	12	0.5	0.1

few reports of insulin and insulin-like activity are available from patients *with* diabetic ketoacidosis and coma.[9-12] In the latter cases, plasma concentration of immunoreactive insulin has been undetectable or very low as might be expected. Bioassays have also shown that the serum of such patients does not stimulate cellular uptake of glucose to any important degree.[11-13]

In the hyperosmolar nonketotic situation plasma concentration of immunoreactive insulin was found to be 29 μU./ml. when the blood sugar was 720 mg. per 100 ml. before therapy was instituted. It was learned from the family, however, that insulin had been received by the patient intermittently for short periods of time during the prior three years. None, however, had been given for at least two months before her last hospital admission. Since the presence of endogenous insulin antibodies would influence the result of the immunoassay for insulin, tests were carried out on the patient's serum for such evidence. No insulin antibodies were detected.

GENERAL DISCUSSION

The syndrome of hyperosmolar coma without ketoacidosis is much more common than was initially anticipated.[14] Variations in the clinical picture are observed but certain features are present in most cases. The condition arises, generally, in persons with "mild" diabetes of the "adult onset type." Diabetes has sometimes been undiscovered until the comatose episode arises. The onset is insidious and may cover many days and occasionally, weeks. The common sequence of events is polyuria, urine output exceeding fluid intake despite polydipsia; followed by profound dehydration, mental confusion, stupor and finally coma. A history of increased carbohydrate intake during the prodromal period is often obtained.[15,16]

Hyperosmolar nonketotic coma has also been reported as a complication of hemodialysis,[17] acute pancreatitis[18] and following extensive body burns.[19-20] During hypothermia administration of small amounts of glucose (65-75 gm. intravenously) has resulted in blood sugar levels as high as 1,040 mg. per 100 ml.[21,22] This is associated with no increase over fasting values of the plasma insulin levels.[23] One should be aware of the possibility of hyperosmolar coma under conditions of induced hypothermia. Fortunately, insulin secretion becomes normally responsive to hyperglycemia on rewarming the patient.[23]

With respect to the pathophysiology of hyperosmolar, nonketotic coma, we believe that the following points should be stressed: (1) absence of ketosis; (2) extreme hyperglycemia; (3) extreme dehydration, and (4) depression of sensorium. These points are discussed separately below.

1. *Absence of ketoacidosis.* This indicates that endogenous insulin activity exists, even though relatively small in amount for the level of blood glucose. Patient No. 2 exhibited a plasma level of immunoreactive insulin of 29 μU./ml. at a blood glucose level of 720 mg. per 100 ml. This level of insulin is about twice the normal fasting level but it is far below what would be expected at a blood sugar level above 700 mg. per 100 ml. On the other hand, inhibition of lipolysis has been shown to occur at this concentration of insulin.[24,25]

This syndrome is rarely seen in the young age group where dependency upon exogenous insulin is the rule. It occurs, however, among the "adult onset" diabetics who rarely become ketotic in the absence of exogenous insulin. Some of the patients have been unaware they were diabetic before the development of hyperosmolar coma. Most of them are easily controlled subsequently with diet alone. An exception regarding age of onset has been reported recently in an eighteen-month-old child with a blood sugar of 1,750 mg. per 100 ml.[26] The initial absence of ketones in the urine of this child suggests that some endogenous insulin activity was present at the onset. Absence of ketosis in the hyperosmolar syndrome *allows for a degree of protraction of the illness* not possible in diabetics with ketoacidosis. This additional time accounts for the more profound osmotic diuresis and dehydration observed in nonketotic coma cases.

2. *Extreme hyperglycemia.* Prolonged stimulation of insulin secretion in maturity onset diabetes by administration of intravenous glucose causes further deterioration of an already compromised insulin secretory mechanism.[27] This is associated with a steadily rising level of blood sugar. On the other hand, normal subjects respond to such stimuli by steadily increasing their levels of plasma insulin while their levels of blood sugar remain normal or only slightly elevated.[27] Thus, hyperosmolar nonketotic coma is associated with slow, prolonged and progressive deterioration of islet cell function but with persistence of enough insulin production to prevent ketosis and to allow time for the syndrome to develop.

3. *Extreme dehydration.* During the progressive and intense hyperglycemia that occurs in this condition, the increasing glycosuria induces severe osmotic diuresis and, unless water intake keeps up with output, severe dehydration ensues.[5] But water intake lags behind output

as soon as the sensorium begins to become clouded. A high incidence of pyelonephritis is observed in this condition and, in those cases, may also be important in reducing water conservation by the kidney.[16,28] As hemoconcentration progresses, further movement of water out of cells occurs. Intra- and extracellular osmotic balance is maintained at the expense of progressive and profound total body dehydration. In many such patients the intense thirst often leads to the use of large quantities of beverages containing carbohydrate, especially when the existence of diabetes is unknown, and blood sugar rises further. Sufficient insulin activity to avoid ketoacidosis gives the patient several extra days of grace during which he intensifies the degree of hyperosmolality. When depression of the sensorium begins, the sudden reduction in oral fluid intake precipitates the critical period.

4. *Central nervous system manifestations.* Tremors and muscle fasciculations are quite characteristic of hyperosmolar coma.[5] Some patients present with seizures.[29] Sotos and associates[30] have reported that hypertonicity due to sodium chloride, sucrose or glucose in rat brain slices reduces oxygen consumption and Krebs' cycle activity in that tissue. It seems likely that the degree and duration of hyperosmolality are important determinants of the onset of coma,[31,32] especially *duration,* since one can find in the literature wide discrepancies between sensorial depression and osmolality values as calculated from blood sugar and serum sodium levels.[33,34] In our patient No. 1 the sensorium had cleared considerably at 10.5 hrs. after use of hypotonic saline and insulin. At that time the serum had risen from 154 to 158 mEq./L. and the blood glucose had fallen from 1,000 to 265 mg. per 100 ml. The calculated serum osmolality had fallen from 364 to 331 mOsm/L., an osmolality still considerably above normal.

CONSIDERATIONS REGARDING THERAPY

Disagreement exists regarding the management of hyperosmolar, nonketotic coma. The need for insulin is clear to all. The need for water is also obvious, but there is disagreement concerning what should be in the water when intravenous therapy is *initiated.* Some writers advise the use of isotonic glucose,[4,35] some isotonic saline[36,37] and others[5,38-40] hypotonic solutions in early therapy. Those who use *isotonic glucose* argue that, since the major need is to provide replacement for the great deficit of total body water and since insulin is also given initially, free water will become available as the glucose is utilized. They object to the use of *isotonic saline* because it impedes the needed fall in plasma osmolality.[41,42] It is emphasized that 10 mEq./L. of serum sodium has equivalent osmolar activity to 360 mg. per 100 ml. of glucose.[35,40] Those who employ *isotonic saline* early in treatment realize that water must be made available quickly but they fear hemolysis from hypotonic solutions. They object to glucose, pointing out that episodes of shock, hypotension and sudden death have been observed during administration of glucose for treatment of this condition. They decry the accentuation of glycosuria, increased osmotic diuresis and further dehydration which is induced before insulin activity increases the disposal of glucose. In an effort to overcome these various objections, others,[5,38-40] employ hypotonic solutions, but attempt to avoid great hypotonicity and its attending hemolysis.

We believe that the management of the hyperosmolar nonketotic state of the diabetic should embody the following principles:

1. *Early recognition and prompt treatment.* Physicians must develop a diagnostic awareness of this possibility in considering the causes of stupor. Often the patient is not known to have diabetes. Further, the diagnosis of profound dehydration may be obscured by the fact that urinary output (osmotic diuresis) appears to be adequate. Delay in treatment can be fatal.

2. Soluble insulin in adequate amounts frequently.

3. Rapid infusion of hypotonic solutions* initially, followed later by the use of 5 per cent dextrose.

4. An appreciation that some depletion of body potassium has already occurred and that hypokalemia may be precipitated by the large amount of carbohydrate disposal which will attend the supply of adequate amounts of insulin.

A suggested outline for therapy of the hyperosmolar, nonketotic coma that occurs in mildly diabetic patients is given below:

I. Initial therapy
   (a) Soluble insulin—50 U. intravenously and 50 U. subcutaneously.
   (b) *Mixture* of 0.45 per cent saline and 2.5 per cent fructose—two liters rapidly intravenously.

II. Subsequent therapy
   (a) Insulin every two hours as initially (50 U. intravenously and 50 U. subcutaneously) until blood sugar is below 300 mg. per 100 ml.
   (b) When blood sugar falls below 300 mg. per 100 ml. discontinue saline-fructose mixture

*Initial use of a hypotonic solution of fructose has theoretical advantages.

and begin 5 per cent glucose.

(c) 6,000 to 16,000 ml. of fluid may be required.

(d) Potassium depletion of tissues is present. Insulin plus glucose may precipitate hypokalemia. Judicious potassium therapy is indicated.

ADDENDUM

Since this paper was submitted for publication Henry and Bressler have reported serum insulin levels in nonketotic hyperosmotic diabetes mellitus consistent with our findings. (Henry, II, D.P., and Bressler, R.: Serum insulin levels in nonketotic hyperosmotic diabetes mellitus. Amer. J. Med. Sci. *256*:150, 1968.)

REFERENCES

[1] Umber-Berlin, F.: Stoffwechselkrankheiten. II Der Diabetes mellitus. Munchen, Med. Wschr. *71*:1324, 1924.

[2] Sament,, S., and Schwartz, M. B.: Severe diabetic stupor without ketosis. South Afr. Med. J. *31*:893, 1957.

[3] Schwartz, T. B., and Apfelbaum, R. I.: Nonketotic Diabetic Coma. Yearbook of Endocrinology, (1965-66) p. 165, Chicago, Yearbook Medical Publishers, 1966.

[4] Halmos, P. B., Nelson, J. K., and Lowry, R. C.: Hyperosmolar nonketoacidotic coma in diabetics. Lancet *1*:675, 1966.

[5] Jackson, W. P., and Forman, R.: Hyperosmolar nonketotic diabetic coma. Diabetes *15*:714, 1966.

[6] Kernan, R. P.: Cell K, London, Butterworth & Co., 1965, pp. 108-09.

[7] Kingsley, D. P. E., Cook, J., and Vartan, A. E.: The effects of haemolysis on some plasma and serum enzymes in man. Clin. Chim. Acta *12*:489, 1965.

[8] Hess, J. W., MacDonald, R. P., Frederick, R. J., Jones, R. N., Neely, J., and Gross, D.: Serum creatine phosphokinase activity in disorders of heart and skeletal muscle. Ann. Intern. Med. *61*:1015, 1964.

[9] Bierman, E. L., Bagdade, J. D., and Porte, D., Jr.: A concept of the pathogenesis of diabetic lipemia. Trans. Ass. Amer. Physicians 79:348-60, 1966.

[10] Froesch, E. R., Bürgi, H., and Müller, W. A.: Plasma Insulin und Diabetes. Helv. Med. Acta 32:341-48, 1965.

[11] Fraser, R., Samaan, N., and Shaper, A. G.: Serum insulin studies in Bugandans, *In* Diabetes Mellitus. Edinburgh, University of Edinburgh 1965, p. 125.

[12] Froesch, E. R., Bürgi, H., Ramseier, E. B., Bally, P., and Labhart, A.: Antibody-suppressible and nonsuppressible insulin-like activities in human serum and their physiologic significance. An insulin assay with adipose tissue of increased precision and specificity. J. Clin. Invest. *42*:1816-34, 1963.

[13] Willebrands, A. F.: Serum insulin and anti-insulin activity in diabetic acidosis. Clin. Chim. Acta *5*:508, 1960.

[14] deGraeff, J.: Diabetic coma with ketoacidosis. Lancet *1*:1322, 1963.

[15] Danowski, T. S., and Nabarro, J. D. N.: Hyperosmolar and other types of nonketotic coma in diabetics. Diabetes *14*:162, 1965.

[16] DiBenedetto, R. J., Crocco, J. A., and Soscia, J. L.: Hyperglycemic nonketotic coma. Arch. Intern. Med. *116*:74, 1965.

[17] Potter, D. J.: Death as a result of hyperglycemia without ketosis—a complication of hemodialysis. Ann Intern. Med. *64*:399, 1966.

[18] Halmos, P. B.: Hyperosmolar non-ketoacidotic diabetic coma in a patient with necrotizing pancreatitis. Brit. Med. J. *2*:686, 1966.

[19] Sevitt, S.: Hyperglycemia after burning. Lancet *1*:566.

[20] Rosenberg, S. A., Brief, D. K., Kinney, J. M., Herrera, M. G., Wilson, R. E., and Moore, F. D.: The syndrome of dehydration, coma and severe hyperglycemia without ketosis in patients convalescing from burns. New Eng. J. Med. *272*: 931, 1965.

[21] Wynn, Victor: Electrolyte disturbances associated with failure to metabolize glucose during hypothermia. Lancet *2*:575.

[22] Wright, H. K., and Gaun, D. S.: Hyperglycemic hyponatremia in nondiabetic patients. Arch. Int. Med. *112*:334, 1963.

[23] Baum, D., and Porte, D., Jr.: Adrenergic regulation of the inhibition of insulin release in hypothermia. (Abstract) 28th Annual Meeting of the Amer. Diabetes Assoc., *17*:298, 1968.

[24] Zierler, K. L., and Rabinowitz, D.: Effect of very small concentrations of insulin on forearm metabolism. Persistence of its action on potassium and free fatty acids without its effects on glucose. J. Clin. Invest. *43*:950, 1964.

[25] Mahler, R., Stafford, W. S., Tarrant, M. E., and Ashmore, J.: The effect of insulin on lipolysis. Diabetes *13*:297, 1964.

[26] Ehrlich, R. M., and Bain, H. W.: Hyperglycemia and hyperosmolarity in an eighteen-month-old child. New Eng. J. Med. *276*:683, 1967.

[27] Seltzer, H. S., and Harris, J. L.: Exhaustion of insulinogenic reserve in mature onset diabetic patients during prolonged and continuous hyperglycemic stress. Diabetes *13*:6.

[28] Ward, F.: Diabetic coma without ketoacidosis. Lancet *1*:450, 1963.

[29] Maccario, M., Messis, C. P., and Vastola, E. F.: Focal seizures as a manifestation of hyperglycemia without ketoacidosis. Neurology *15*:195, 1965.

[30] Sotos, J. F., Rearick, P. D., Cahill, F. D., and Addanki, S.: Effect of hypertonicity on the metabolism of brain in vitro. Clin. Res. *14*:443, 1966.

[31] Mirsky, I. A., Franzblau, A. N. Nelson, N., and Nelson, W. E.: The role of excessive carbohydrate intake in the etiology of diabetic coma. J. Clin. Endocrinol. *1*:307, 1941.

[32] Evans, E. I., and Butterfield, W. J. H.: Stress response in severely burned. Interim report. Ann. Surg. *134*:588, 1951.

[33] Jarrett, E., and Bacon, G.: Hyperosmolarity and diabetic coma. Lancet *1*:891, 1963.

[34] Lucas, C. P., Grant, N., Daily, W. J., and Reaven, G. M.: Diabetic coma without ketoacidosis. Lancet *1*:75, 1963.

[35] deGraeff, J., and Lips, J. B.: Hypernatremia in diabetes mellitus. Acta Med. Scand. *157*:71, 1957.

[36] Sament, S.: Hyperosmolar coma in diabetes. Lancet *1*:1153.

[37] Haapenen, E.: Hyperosmolar coma in diabetes. Lancet *1*:1154, 1966.

[38] Feagin, O. T.: Hyperosmolar coma in diabetes. Lancet *2*:51, 1966.

[39] Nicholson, W. A., Shujjauddin, Patel, N. T., and Scott, W. J.: Diabetic coma without ketoacidosis. Lancet *1*:982, 1964.

[40] Nelson, J. K.: Hyperosmolar coma in diabetes. Lancet *1*:1376, 1966.

[41] Knowles, H. C., Jr.: Hypernatremia. Metabolism 5:508.

[42] Elkington, J. R., and Taffel, M.: Prolonged water deprivation in dog. J. Clin. Invest. *21*:787, 1942.