# Burn Stress Pseudodiabetes *

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IN 1854, Goolden reported that a transient glycosuria accompanied by a diuresis occurred with relative frequency following injury.[15] Hyperglycemia following traumatic shock was observed by Cannon,[5] in 1918 and by Aub and Wu,[3] in 1920. Thomsen [29] in 1938, found this phenomenon more frequently in patients under 30 years of age, but it was more transient in this group than in older patients. Howard [16] observed that soldiers wounded in the Korean conflict had a diabetic response to the glucose tolerance test and a decreased sensitivity to insulin. Both responses were proportional to the extent of trauma.

Hyperglycemia following thermal burns has been reported by several investigators.[21, 22, 30] Taylor *et al.*[28] observed a direct relationship between the extent of the burn injury and the hyperglycemic response. The insulin sensitivity of these patients was normal and the hyperglycemia persisted from 12 hours to a few days. In 1951, Evans and Butterfield [11] described the syndrome of burn stress pseudodiabetes manifested by hyperglycemia, glycosuria without acetonuria, acute dehydration, shock, coma, and renal failure. This phenomenon was a contributing factor in the death of two patients and was observed in less severe forms in other patients. It appeared prior to the tenth postburn day and was thought to have been aggravated by forced feeding.

The syndrome of burn stress pseudodiabetes may complicate the postburn course more often than is realized. The entity may escape recognition because of a lack of appreciation of the typical features. Failure to recognize and correct the early manifestations resulted in the development of the full-blown syndrome in two patients at this installation. The clinical course of these patients is presented in detail.

## Case Reports

**Case 1.** On 18 February 1955, this 24-year-old white man sustained burns which involved 26 per cent of the body surface in third degree with a total burn of 56 per cent. The injury occurred when a blow torch ignited fluid being used to lay linoleum. He was admitted to the sick bay at the local naval base where resuscitative therapy was started. Twelve hours following injury he was transferred to this installation.

Physical examination on admission to the Surgical Research Unit revealed burns of the face, both upper extremities, both lower extremities, and posterior trunk. There were no other significant findings. His past history during the two years preceding injury was noncontributory except that his weight had increased from 171 to 221 pounds. He responded well to resuscitative therapy. His temperature on admission was 39.5° C. but decreased to 38.0° C. on the second postburn day. The burn wounds were treated by the exposure method.

From the third through the sixth postburn days the patient complained bitterly of thirst. During this period he was given water and liquid feedings by mouth in addition to continued intravenous infusions of 5 per cent dextrose in water and the urinary output ranged from 1,500 to 2,500 cc. per day. The caloric intake from the second through the sixth postburn day ranged from 3,000 to 4,500. There was little change in weight. He had continuous fever which on one occasion rose to 41.0° C., but repeated blood cultures were negative. Laboratory determinations performed during

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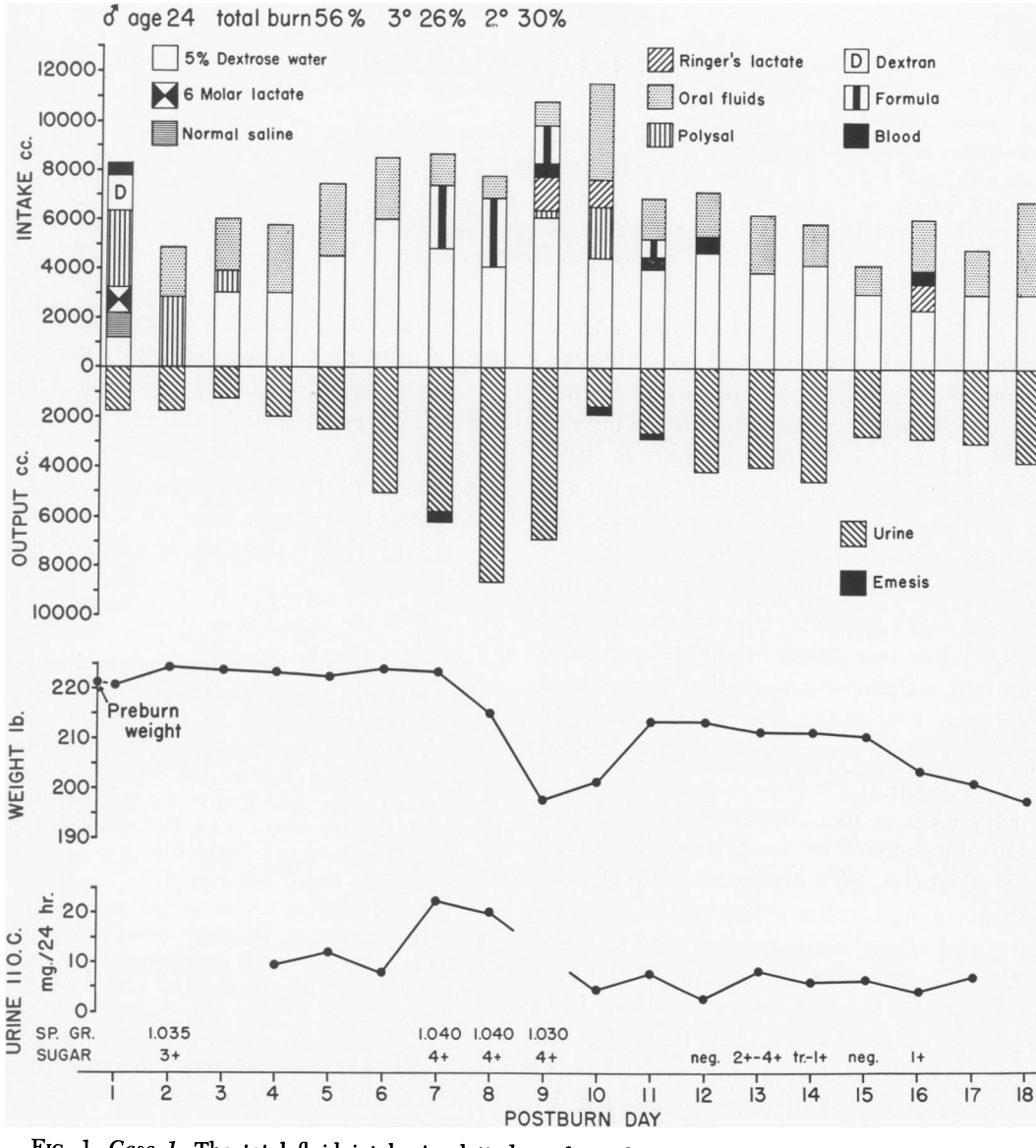


FIG. 1. *Case 1.* The total fluid intake is plotted up from the zero line and the measured fluid output is plotted down from the zero line. The weight, urinary 11-oxycorticoids, urinary specific gravity, and glycosuria are shown. The high caloric formula feeding was started on the 7th postburn day.

this period were normal except for a plasma sodium varying between 148 and 154 mEq./L. and a mild elevation of the plasma $CO_2$ and NPN. The only urinalysis recorded was on the second postburn day and showed 3 + glycosuria and specific gravity of 1.025.

This patient was selected for inclusion in a study designed to determine the nitrogen requirements for equilibrium during the postburn course. Metabolic balance studies were started at 0800 hours on the seventh postburn day. The 24-hour oral intake was given as a liquid formula which furnished 6,650 calories and contained 59 Gm. protein, 233 Gm. fat and 1,080 Gm. carbohydrate. The total caloric intake was increased to 7,590 by the administration of 4,700 cc. of 5 per cent dextrose in water. Blood chemistry values and hematologic studies at 0800 hours were within normal limits. The temperature ranged between 37.0° C. and 38.5° C., and his general condition appeared to be satisfactory. The formula was accepted well. Late in the day a profuse diarrhea developed which

was readily controlled with paregoric. The total fluid intake for the 24-hour period was 8,340 cc. and the urinary output was 5,805 cc. Urinalysis showed 4 + glycosuria and specific gravity of 1.040 but no acetonuria. The daily fluid intake and output, weight, urinary 11-oxycorticoids, urinary specific gravity and degree of glycosuria are shown in Figure 1. The blood NPN and glucose are shown in Figure 2 and the blood Na, K, Cl and $CO_2$ in Figure 3.

At the beginning of the eighth postburn day the patient's general condition was unchanged but his weight had decreased from 223½ lbs. to 215 lbs. The laboratory determinations did not differ significantly from those of the previous day. The formula was tolerated well and he had no further diarrhea. The total fluid intake was 7,740 cc. This included 4,050 cc. of 5 per cent dextrose in water intravenously which provided an additional 202 Gm. of carbohydrate. The urinary output of 8,670 cc. exceeded the intake by over 900 cc. Urinalysis again showed a 4 + glycosuria, a specific gravity of 1.040, and no acetonuria.

A rapid deterioration was noted early in the morning of the 9th postburn day. He was disoriented for the first time since admission, semicomatose, his temperature had fallen to 35.0° C., and there were physical findings of marked dehydration. There had been a further loss of weight from 215 to 197 lbs. Laboratory determinations on blood taken at 0800 hours were as follows: Na 156 mEq./L.; Cl 114 mEq./L.; K 4.9 mEq./L.; $CO_2$ 28 mEq./L.; NPN 60 mg. per cent; hemoglobin 16 Gm. per cent; hematocrit 42 and the white blood cell count 21,500/cubic millimeter. Between 0800 and 1100 hours when the above laboratory results were reported he was given 1,300 cc. of Ringer's lactate solution intravenously. Intravenous therapy was changed to 5 per cent dextrose in water and water by mouth was encouraged. At 1600 hours, the serum sodium was 160 mEq./L. and at 2000 hours it was 153 mEq./L. The hemoglobin was 12.3 Gm. per cent and the hematocrit 33. The total fluid intake for the 24-hour period was 10,745 cc. This included the intravenous administration of 6,150 cc. of 5 per cent dextrose in water, 1,300 cc. of Ringer's lactate solution, 500 cc. of whole blood, and 275 cc. of polysal; and the oral administration of 1,030 cc. of water and 1,490 cc. of formula. The urinary output for this period was 7,040 cc. The 4 + glycosuria persisted with a specific gravity of 1.040, but the urine remained negative for acetone.

There had been little change in the patient's general condition by 0800 hours on the tenth postburn day. The physical signs of extreme dehydration persisted; he remained semicomatose and the temperature remained at 35.0° C. The weight had increased from 197 to 201 lbs. Laboratory determinations at 0800 hours were as follows: Blood sugar 1,180 mg. per cent; NPN 75 mg. per cent; Na 162 mEq./L.; Cl 110 mEq./L.; K 3.9 mEq./L.; $CO_2$ 21 mEq./L.; hemoglobin 13.3 Gm. per cent; and the hematocrit 39. The intravenous administration of 5 per cent dextrose in water was continued and 100 units

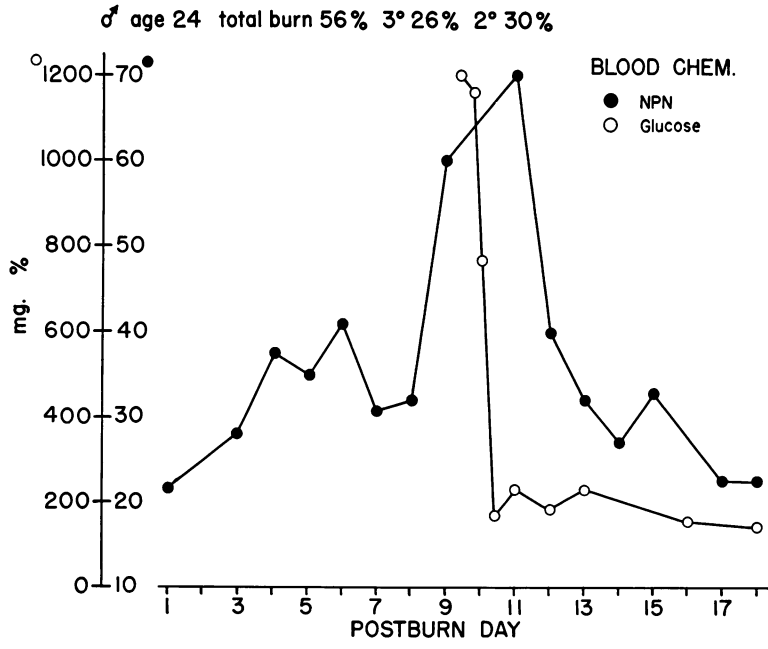


FIG. 2. *Case 1.* The blood nonprotein nitrogen and blood glucose determinations are plotted and show their direct relationship.

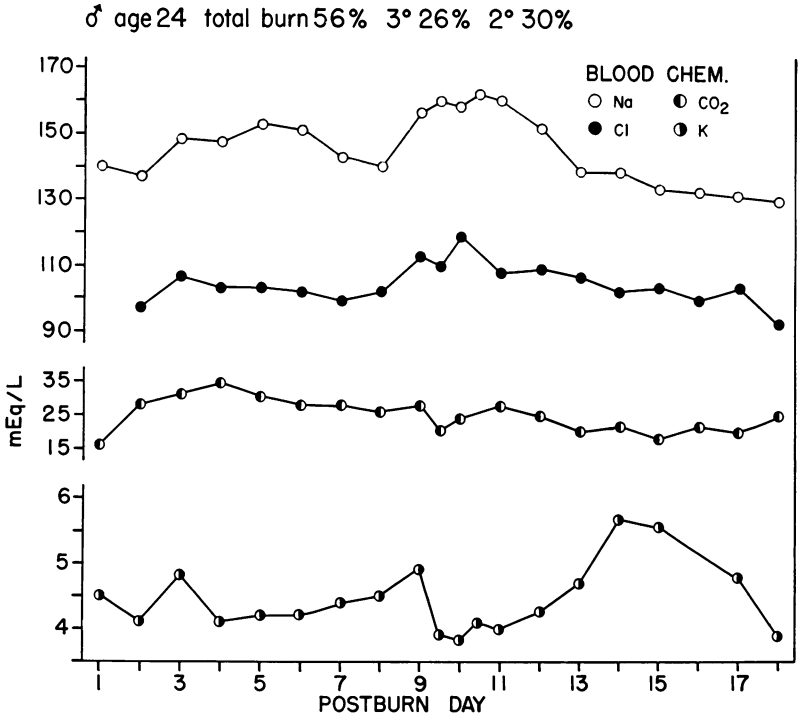


FIG. 3. *Case 1.* The blood Na, Cl, K, and $CO_2$ determinations are plotted and show the relationship of the changes observed.

of regular insulin were added to each 1,000 cc. An additional 200 units of regular insulin were given intramuscularly. The total fluid intake for the 24-hour period was 11,525 cc., including 4,500 cc. of 5 per cent dextrose in water, 1,000 cc. of Ringer's lactate solution, 2,000 cc. of polysal, and 4,025 cc. of oral fluids. One Gm. of calcium gluconate and 100 mEq. of potassium acetate were added to the 5 per cent dextrose in water. The total urinary output was 1,780 cc. At 1400 hours, the blood sugar was 740 mg. per cent, at 1600 hours, 440 mg. per cent, and at 1700 hours, 280 mg. per cent. By 1800 hours there was marked improvement in his general condition, although his temperature remained subnormal. The 4 + glycosuria persisted, but the urinary output had decreased to 25 cc. per hour. At 2000 hours the blood sugar was 137 mg. per cent; at 2230 hours 50 mg. per cent; at 0300 hours 118 mg. per cent, and at 0500 hours 204 mg. per cent. With the decrease in blood sugar, the glycosuria disappeared but the plasma sodium remained between 158 and 161 mEq./L. throughout this 24-hour period.

By 0800 hours on the 11th postburn day, the improvement in the patient's general condition was striking. He appeared rational but the temperature remained subnormal. His weight had increased from 201 to 213 lbs. Laboratory determinations at 0800 hours were as follows: blood sugar 278 mg. per cent; NPN 65 mg. per cent; plasma Na 152 mEq./L.; Cl 108 mEq./L.; K 4 mEq./L.; and $CO_2$ 28 mEq./L.; hemoglobin 12.2 Gm. per cent and the hematocrit 38. During the morning there was a gradual increase in the urinary volume and a reappearance of the 4 + glycosuria. By 1300 hours, he was again disoriented. The blood sugar at 1330 hours was 504 mg. per cent. Twenty units of regular insulin were added to each 1,000 cc. of 5 per cent dextrose in water. At 1830 hours, the blood sugar was 532 mg. per cent and an additional 35 units of regular insulin were given intramuscularly. At 2130 hours, the blood sugar was 364 mg. per cent. The total fluid intake for the 24-hour period was 6,880 cc. including the intravenous infusion of 4,000 cc. of 5 per cent dextrose in water containing 100 mEq. of potassium acetate, 500 cc. of whole blood, and an oral intake of 1,740 cc. of water and 640 cc. of formula. The urinary output was 2,500 cc.

On the 12th postburn day formula intake was discontinued. Fifteen units of regular insulin were added to each 1,000 cc. of 5 per cent dextrose in water. Laboratory determinations at 0800 hours showed a blood sugar of 187 mg. per cent and an NPN of 40 mg. per cent. The plasma Na was 145 mEq./L.; Cl 109 mEq./L.; K 4.3 mEq./L. and $CO_2$ 25 mEq./L. The patient appeared to be well hydrated but was intermittently disoriented.

The total fluid intake for the 24-hour period was 7,300 cc., including the intravenous infusion of 4,850 cc. of 5 per cent dextrose in water and 500 cc. of whole blood, and an oral intake of 1,375 cc. of water and 620 cc. of other liquids. The urinary output was 4,200 cc.

From the 12th through the 18th postburn days, his temperature ranged between 34.0° C. and 35.0° C. but his general condition appeared to be satisfactory. He was given a low carbohydrate diet. Apart from moderate elevation of the blood sugar and an intermittent glycosuria, laboratory determinations during this period were within normal limits. Small doses of regular insulin were given at intervals based on the degree of glycosuria. From the 19th to the 22nd postburn day there was little change in his general condition apart from a rise in temperature from 35.0°C. to 38.0° C. on the morning of the 20th postburn day.

On the 22nd postburn day, the temperature rose to 39.5° C. and a blood culture taken at this time was positive for *Micrococcus pyogenes*. Antibiotic therapy consisted of Chloromycetin 3 Gm. daily, Erythromycin 2 Gm. daily, and Bacitracin 300,000 units daily, but subsequent blood cultures remained positive. The ensuing clinical course was one of progressive deterioration. The fever persisted with occasional spiking to 40.5° C. The blood sugar remained within normal limits and the glycosuria did not reappear. The plasma sodium was 125 mEq./L. on the 25th postburn day, and despite replacement therapy did not return to normal levels. The burn wounds, which had progressed in a satisfactory manner, became necrotic with the disappearance of normal granulation tissue. A blood culture obtained on the 29th postburn day was positive for *Pseudomonas aeruginosa* as well as *Micrococcus pyogenes*. In addition to the above antibiotics he was given 200 mg. of Polymyxin B daily. There was no response to therapy and the patient expired on the 34th postburn day.

**Autopsy Findings.** The distribution and extent of the burn wounds were as described in the clinical summary. Sections of the burned skin revealed inflamed adipose tissue, dark reddish in color, with multiple small abscesses. Well demarcated abscesses measuring, on the average, 2 cm. in diameter were scattered throughout the unburned skin. These abscesses extended to the fascia of the underlying muscles. Small abscesses were found scattered throughout both lungs as well as in the myocardium of the left ventricle. The remaining findings did not differ from those usually seen following death due to septicemia in burned patients. The pancreas appeared completely normal on gross as well as on microscopic examination.

**Case 2.** This 21-year-old Negro man sustained burns which involved 21 per cent of the body surface in third degree with a total burn of 34 per cent. The injury occurred in Germany, when an ammunition truck in which he was riding overturned and caught fire. He was immediately hospitalized at a U. S. Army Hospital. The response to resuscitative therapy was satisfactory. On the seventh postburn day air evacuation to this installation was started, and the patient arrived on the evening of the ninth postburn day. Laboratory studies done during the first nine postburn days consisted of repeated blood chemistries, hematologic studies, and urinalyses. The results obtained were not remarkable but it should be noted that there was no glycosuria and that no blood sugar determinations had been done.

On admission to this installation, his general condition was satisfactory. History and physical examination were pertinent only as related to the burn injury. The burn wounds involved the face, neck, both forearms and hands, the right upper arm, and both lower extremities. The initial treatment of the burn wounds had included occlusive dressings and these were continued.

The patient was selected for inclusion in a study designed to determine the optimum calorie-nitrogen ratio of the intake for burned patients. Metabolic balance studies were started at 0800 hours on the 11th postburn day. The 24-hour oral intake was given as a liquid formula which furnished 6,650 calories and contained 180 Gm. protein, 232 Gm. fat, and 965 Gm. carbohydrate. The total 24-hour caloric intake was increased to 7,250 by the daily administration of 3,000 cc. of 5 per cent dextrose in water. The nonprotein calorie-nitrogen ratio was 230. Laboratory determinations at the beginning of the study were as follows: plasma Na 138 mEq./L.; Cl 96 mEq./L.; K 4.3 mEq./L.; $CO_2$ 29 mEq./L.; NPN 26 mg. per cent; hemoglobin 13.3 Gm. per cent, and hematocrit 41. The fasting blood sugar was 117 mg. per cent and the urinalysis was normal. The formula was taken without difficulty except for a diarrhea beginning on the second day of study. This was satisfactorily controlled by paregoric and codeine sulfate. The intake was maintained from the 11th through the 18th postburn days with a small amount of emesis occurring on each of the last five days of this period. The daily fluid intake and output, weight, urinary 11-oxycorticoids, urinary specific gravity and degree of glycosuria are shown in Figure 4. The blood

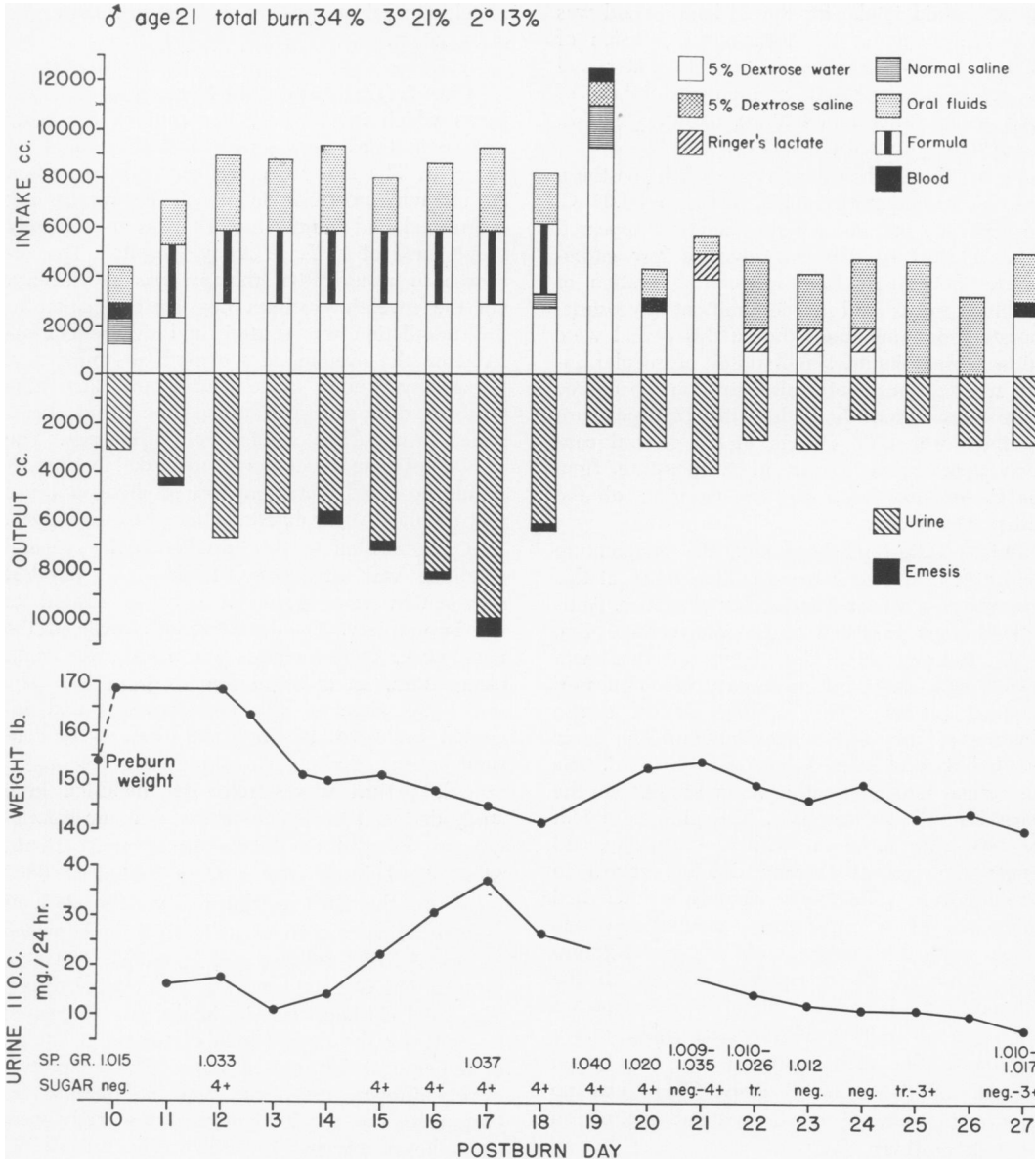


FIG. 4. *Case 2.* The total fluid intake is plotted up from the zero line and the measured fluid output is plotted down from the zero line. The weight, urinary 11-oxycorticoids, urinary specific gravity, and glycocuria are shown. The high caloric formula feeding was started on the 11th postburn day.

NPN and glucose are shown in Figure 5 and the blood Na, K, Cl, and $CO_2$ in Figure 6.

The 24-hour fluid intake from the 11th through the 18th postburn day ranged from 8,000 to 9,000 cc. The urinary output increased from 4,500 cc. on the 11th postburn day to 10,070 cc. on the 17th postburn day, but decreased to 6,370 cc. on the 18 postburn day. A persistent thirst was first noted on the 12th postburn day. At this time urinalysis revealed a 4+ glycosuria and a specific gravity of 1.037. The glycosuria and elevated urinary specific gravity persisted but there was no acetonuria. As the urinary volume increased, the body weight decreased from 169½ lbs. on the 12th postburn day to 141 lbs. on the 18th postburn day. The daily urinary 11-oxycorticoids increased from 15.8 to 36.9 mg.

During the afternoon and evening of the 18th postburn day, the patient became disoriented and the temperature which had ranged from 38.5° C. to 39.0° C. rose in the late evening to 40.5° C.

He was, nevertheless, able to complete the formula intake by 2400 hours. By the end of the 18th postburn day he was comatose, the rectal temperature was 41.0° C., and there were physical findings of extreme dehydration. Urinalysis revealed a 4 + glycosuria and a specific gravity of 1.040, but no acetonuria. Laboratory determinations on blood taken on the beginning of the 19th postburn day showed a blood sugar of 890 mg. per cent and an NPN of 60 mg. per cent. The plasma Na was 161 mEq./L.; Cl 119 mEq/L.; K 3.5 mEq./L.; $CO_2$ 29 mEq./L.; and Ca 3.0 mEq./L. The hemoglobin was 16.1 Gm. per cent, the hematocrit 49, and the white blood cell count was 23,200. From 0800 to 1100 hours, when the above chemical results were available, he was given 1,750 cc. of normal saline intravenously. At 1100 hours, the intravenous infusion of saline was discontinued and 5 per cent dextrose in water started. One hundred units of regular insulin and 40 mEq. of potassium chloride were added to each 1,000 cc. of 5 per cent dextrose in water. Laboratory determinations at 1200 hours showed a blood sugar of 600 mg. per cent and an NPN of 65 mg. per cent. The plasma Na was 187 mEq./L.; Cl 139 mEq./L.; K 2.8 mEq./L.; $CO_2$ 24 mEq./L.; and Ca 2.7 mEq./L. The hemoglobin was 15.4 Gm. per cent and the hematocrit was 45. Between 1100 hours and 1730 hours he was given 5,000 cc. of 5 per cent dextrose in water. By 1730 hours, the coma appeared to be less deep and the patient could be temporarily aroused. The physical findings of dehydration were less striking and the urinary output was decreasing in volume. The 4 + glycosuria persisted and the temperature remained at 40.5° C.

The laboratory determinations at 1730 hours showed a blood sugar of 370 mg. per cent and an NPN of 56 mg. per cent. The plasma Na was 155 mEq./L.; Cl 139 mEq./L.; K 4.2 mEq./L.; $CO_2$ 23 mEq./L.; and Ca 3.6 mEq./L. The hemoglobin was 14.3 Gm. per cent and the hematocrit was 32. Between 1730 hours and 2300 hours he was given 3,000 cc. of 5 per cent dextrose in water. The urinary output during this interval averaged 25 cc. per hour. The glycosuria decreased from 4 + to 1 + and the specific gravity from 1.040 to 1.033.

By 2300 hours, clinical improvement was striking. The temperature was 38.5° C., the pulse rate had slowed from 160 to 144 per minute, and the physical findings of dehydration had disappeared. He was no longer comatose but was irrational. Between 2300 hours and 0800 hours he received 1,300 cc. of 5 per cent dextrose in water, 1,000 cc. of 5 per cent dextrose in saline, and 500 cc. of whole blood. The total fluid intake for the 24-hour period was 12,550 cc. and consisted of 1,750 cc. of normal saline, 500 cc. of whole blood, 9,300 cc. of 5 per cent dextrose in water, and 1,000 cc. of 5 per cent dextrose in saline. In the last 3,000 cc. of 5 per cent dextrose in water given, the regular insulin was decreased from 100 units to 50 units per 1,000 cc. and 40 mEq. of potassium acetate was substituted for the 40 mEq. of potassium chloride. Eight hundred and sixty five units of regular insulin, 280 mEq. of potassium chloride and 80 mEq. of

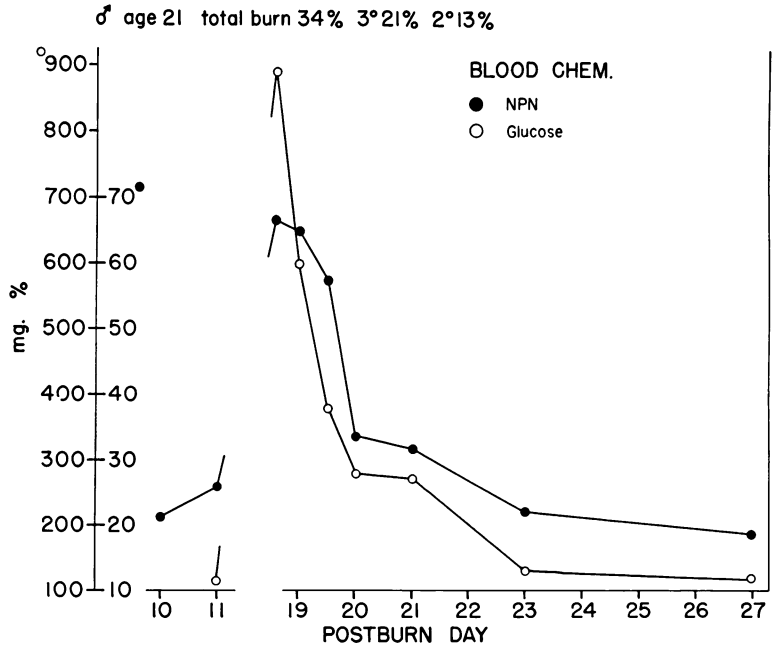


FIG. 5. *Case 2.* The blood nonprotein nitrogen and blood glucose determinations are plotted and show their direct relationship.

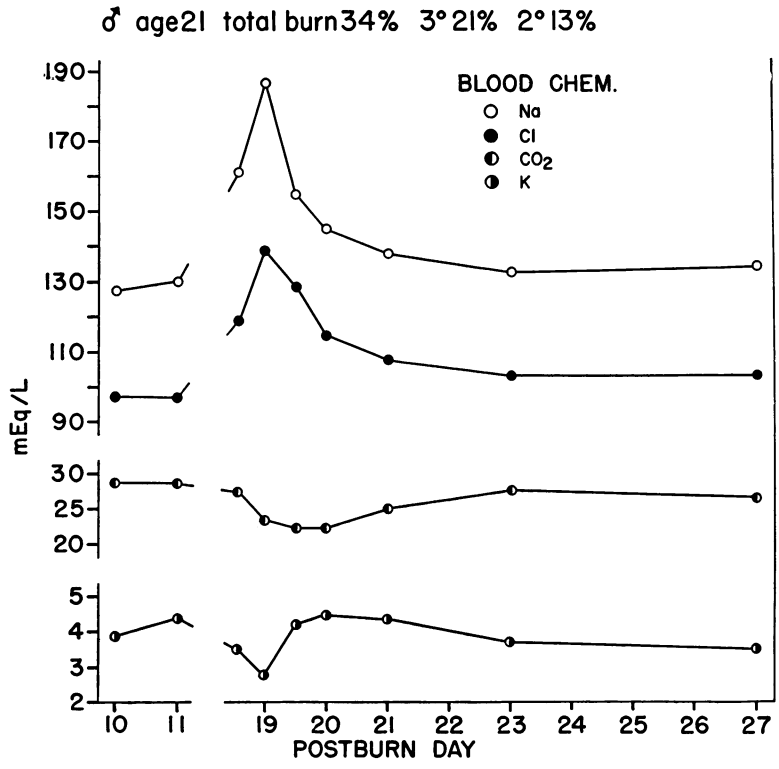


FIG. 6. *Case 2.* The blood Na, Cl, K, and $CO_2$ determinations are plotted and show the relationship of the changes observed.

potassium acetate were given during the 24-hour period. One Gm. of calcium gluconate was given at 1400 and at 0600 hours in an attempt to control a generalized muscle twitching. This resulted in only moderate improvement. During the same period two million units of crystallin penicillin and one Gm. of terramycin were given intravenously. Blood cultures taken at 0730 hours and 1730 hours were negative.

By 0800 hours, the beginning of the 20th postburn day, there was a dramatic improvement. The temperature was 37.5° C. and the mental status had returned to normal. His weight was 153 lbs. as compared to a weight of 141 pounds 48 hours previously. Throughout the day he remained rational and began to take oral fluids without difficulty. Laboratory determinations at 0800 hours showed a blood sugar of 275 mg. per cent and an NPN of 34 mg. per cent. The plasma Na was 145 mEq./L.; Cl 115 mEq./L.; K 4.4 mEq./L.; $CO_2$ 23 mEq./L. and Ca 3.6 mEq./L. The hemoglobin was 12.3 Gm. per cent and the hematocrit was 39. The urine showed a trace to a 4+ glycosuria and a specific gravity ranging from 1.011 to 1.033. Thirty-five units of regular insulin were given during this day.

On the 21st postburn day, except for a blood sugar of 262 mg. per cent, blood chemistries were normal. The glycosuria was still present. At 0900 hours he was given 25 units of regular insulin intramuscularly and in one hour the glycosuria had cleared. No insulin was given after this day.

From the 22nd through the 30th postburn day he was given a regular hospital diet. This diet contained an average of 115 Gm. protein, 200 Gm. fat, 380 Gm. carbohydrate, and had a caloric value of 3,700. On the days of surgery the caloric intake decreased to approximately 2,000. The fasting blood sugar was 135 mg. per cent on the 23rd postburn day, 135 mg. per cent on the 27th postburn day, and 193 mg. per cent on the 28th postburn day and there was an intermittent glycosuria.

Laboratory determinations at 0800 hours on the 31st postburn day were normal except for a fasting blood sugar of 177 mg. per cent. At this time, the regular diet was discontinued and an oral formula intake was started. The formula given each day furnished 5,775 calories and contained 206 Gm. protein, 199 Gm. fat, and 790 Gm. carbohydrate. The nonprotein calorie nitrogen ratio was 150. This feeding was continued for 48 hours. During this period a persistant 4+ glycosuria developed and the urinary specific gravity increased to 1.041. There was moderate dehyration and disorientation. The urinary 11-oxycorticoids did not increase during this 48-hour period. Laboratory determinations at the beginning of the 33rd postburn day were normal except

for a fasting blood sugar of 216 mg. per cent and a 4+ glycosuria. The regular diet was again started and was well tolerated. An intermittent glycosuria was present throughout the 47th postburn day.

The clinical course subsequent to this second attempt to give a high intake was not remarkable. Except for small areas on the fingers of both hands skin cover was achieved by the 48th postburn day. Subsequent therapy consisted of physical rehabilitation. An oral glucose tolerance test performed on the 56th postburn day using the standard 100 Gm. of glucose showed a diabetic response. An intravenous glucose tolerance test performed on the 57th postburn day, giving 0.5 Gm. of glucose per kilogram as a 20 per cent solution in 30 minutes showed a normal response (Fig. 7). A repeat oral glucose tolerance test performed on postburn day 68 showed a normal response.

## Discussion

The manifestations of burn stress pseudodiabetes are strikingly similar in these two cases even through the patients were dissimilar in several respects. The burn wounds were not comparable. The burn index, expressed as the per cent third-degree burn plus one-quarter of the per cent second-degree burn [25] was 33 in Case 1 and 24 in Case 2. Case 1 was overweight having gained 50 pounds in the two years preceding injury while the preburn weight of Case 2 was slightly below the ideal. The burn stress pseudodiabetes was recognized on the tenth postburn day in Case 1 and the nineteenth postburn day in Case 2. This was due to the difference in the feeding regimen employed. Case 1 had an average calorie intake of 3,700 from the second through the sixth postburn day.[6] On the seventh postburn day this intake was increased to 7,150 calories. Case 2 was started on an intake of 7,250 calories on the eleventh postburn day having previously received a relatively low intake. During the period of maximum dehydration, Case 2 developed a hyperpyrexia whereas Case 1 become hypothermic and continued to have a subnormal temperature for several days. This difference cannot be satisfactorily explained but may in part be attributed to the exposure treatment of the burn wounds in Case 1 and the use of occlusive dressings in Case 2.

A 4+ glycosuria was first noted on the second postburn day in Case 1 and on the twelfth postburn day in Case 2. In both

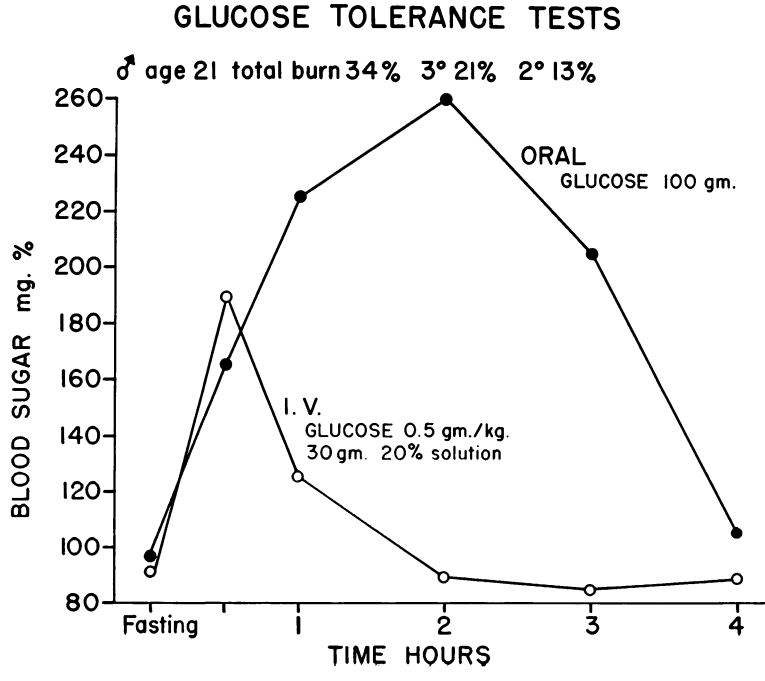


FIG. 7. *Case 2.* An oral glucose tolerance test performed on postburn day 56 shows a typical diabetic response. An intravenous glucose tolerance test performed the following day shows a normal response.

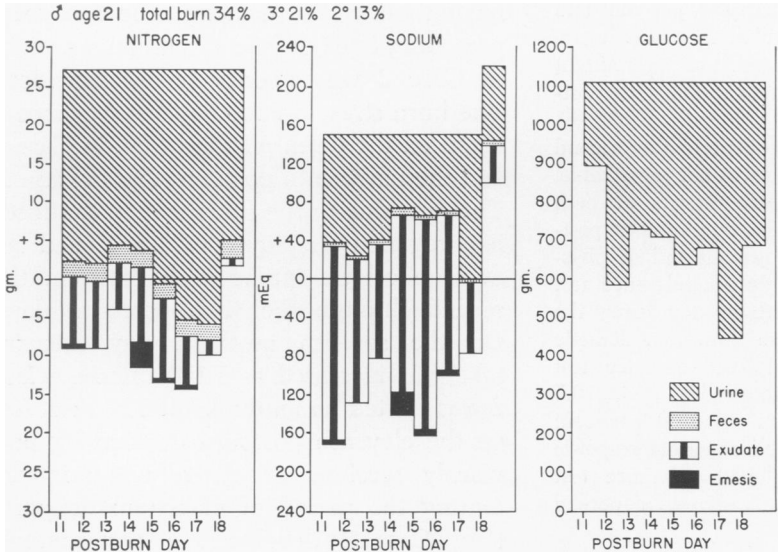


FIG. 8. *Case* 2. Nitrogen, sodium and glucose balance charts plotted in the conventional manner. The intake is plotted up from the zero line and the output is plotted down from the intake line. The nitrogen and sodium balances are similar to those usually seen in comparable burned patients. The glucose balance chart shows that more than one-half of the amount given was excreted in the urine.

instances the glycosuria was attributed to the intravenous infusion of 5 per cent dextrose in water, and blood sugar determinations were not done. A persistent thirst, present in both cases, was not regarded as an unusual occurrence. The total fluid intake consisted of water *ad libitum,* formula feedings, and the intravenous administration of 5 per cent dextrose in water. During the early postburn period the intravenous administration of 5 per cent dextrose in water is a part of the routine in patients on balance study because it has been found necessary for the maintenance of an adequate fluid intake in most patients. The large urinary output was attributed to the volume of the intake and to the diuresis normally seen during this postburn period[26] and the weight loss to the combined effects of the diuresis and the catabolic response to the burn injury.

The significance of these observations was not appreciated prior to the appearance of extreme dehydration. The inability of the patients to utilize the high caloric intake had resulted in marked hyperglycemia, glycosuria, and an intense osmotic diuresis. Both patients became irrational and then comatose. The clinical course of these two patients appears typical of the syndrome of burn stress pseudodiabetes described by Evans and Butterfield.[11] Two burned patients reported by them developed hyperglycemia, glycosuria, acute dehydration, shock, coma, renal failure, and died.

The osmotic diuresis and dehydration occurring in the absence of acidosis resulted in an elevation of the plasma Na and Cl in our cases. In both cases these changes were aggravated by inappropriate therapy. Balance data on Case 2 (Fig. 8) show a negative sodium balance during the period of development of the severe dehydration. The negativity of the balance was largely due to the exudate losses and was not as great as that seen in diabetic acidosis. It was not different from that usually seen during this postburn period in patients with burn wounds of comparable extent.

The progression of the manifestations of burn stress pseudodiabetes could have been interrupted by discontinuing the high-carbohydrate, high-caloric intake in both cases. The severe dehydration was not recognized as an almost pure water deficiency and the initial attempts at rehydration consisted of the intravenous administration of physiologic electrolyte solutions. A pure water deficit must be cor-

rected and in the comatose patient this can be accomplished by the intravenous administration of 5 per cent dextrose in water. Sufficient regular insulin must be given to correct the hyperglycemia and comparable amounts were necessary in both of these cases.

In Case 2 approximately one-half of the administered carbohydrate was metabolized. This is illustrated in Figure 8 where the carbohydrate balance has been obtained by subtracting the carbohydrate lost in the urine from the total intake. Utilization of carbohydrate is further confirmed by the absence of acidosis. The nitrogen balance of these two patients was no more negative than those seen during this postburn period in the average patient with a comparable injury.

The elevated nonprotein nitrogen, hemoglobin, and hematocrit were secondary to dehydration. If therapy had not been effective, shock might well have eventuated with secondary renal failure and death from hyperkalemia as described by Evans and Butterfield.[11] Moyer [23] described a strikingly similar syndrome consisting of uremia, hypernatremia, hyperpyrexia, and disorientation in burned patients who were forced fed. He attributed these manifestations to an excessive protein intake but made no statement as to the presence or absence of hyperglycemia or glycosuria.

The preceding discussion concerns the clinical courses, complication, and therapy of two patients in whom burn stress pseudodiabetes developed. The hyperglycemia and glycosuria that occur transiently following injury have been reported by many observers.[3, 5, 15, 16, 21, 22, 28-30] A decreased insulin sensitivity has been observed by some [16] and denied by others.[28] According to Ingle [17] the adrenal cortical hormones play a permissive role in the development of hyperglycemia but are not etiologically responsible. He concludes that the hyperglycemic response to trauma is dependent on a liver store of glycogen since it will develop in adrenalectomized rats if they have been fed or if they have been supported by replacement corticoid therapy. Steroid diabetes cannot be made to develop in a fasting rat but it will develop in a rat fed an *ad libitum* intake regardless of the distribution of fat and carbohydrate in the diet.[18] The adrenal glucocorticoids have been shown to affect the metabolism of carbohydrate by increasing the gluconeogenesis from protein and by inhibiting peripheral utilization of glucose.[6] The decreased carbohydrate tolerance observed during a stressing experience such as surgery, trauma, or infection has been attributed to an increased adrenal cortical activity. In the cases presented, the forced feeding could have replaced the necessity for a store of liver glycogen. There was an elevated urinary excretion of 11-oxycorticoids which further increased during the development of the burn stress pseudodiabetes. This may be attributed to an increased stress imposed by dehydration. The urinary 11-oxycorticoid excretion returned to the pre-forced feeding levels subsequent to restoration of the patients to a normal state of hydration.

Administration of ACTH, cortisone, or hydrocortisone to subjects with normal carbohydrate metabolism has been shown to produce temporary fasting hyperglycemia, a decreased glucose tolerance, glycosuria, and a relative resistance to insulin.[4, 8, 14, 27, 32] This diabetic state is reversible and carbohydrate metabolism becomes normal when hormone administration is discontinued. With continued administration of ACTH or glucocorticoids the disturbance will gradually subside in most cases but in some it persists and may become more severe.[7] This individual variation may be due to the fact that many diabetics have nondiabetic relatives who demonstrate decreased carbohydrate tolerance when challenged with ACTH or cortisone.[13] Case 1 had a family history of diabetes but not Case 2. The intake of

these two cases has been used for other individuals with no detected incidence of carbohydrate intolerance. The intake of Case 1 was given to a normal control subject and two patients with burn indices of 25 and 36, and that of Case 2 to a normal control subject and two patients with indices of 18 and 21. The levels of urinary 11-oxycorticoids of the patient with a burn index of 25 were determined and were comparable to the levels seen in both Case 1 and Case 2 prior to the development of burn stress pseudodiabetes. This further suggests that there is some predisposing factor in the patients who develop burn stress pseudodiabetes.

Hyperglycemia and glycosuria have been observed in eight other burned patients. All of these patients were receiving more than 5,000 calories per day and seven of them were on metabolic balance study. Five of the eight patients had a family history of diabetes mellitus. Four of the patients who had a family history of diabetes developed dehydration. This was corrected by decreasing the caloric intake and continuing water *ad libitum*. In the other four patients the glycosuria persisted through the 10-day period of high caloric intake but was not sufficient to cause dehydration. Six of these patients survived and none had a demonstrable carbohydrate intolerance subsequent to healing of the burn wounds.

The development of hyperglycemia depends on the overproduction or underutilization of glucose. In patients who are forced fed both the exogenous supply and the decreased tissue utilization can be responsible for hyperglycemia, and this can be aggravated by a continued endogenous overproduction of glucose. However, gluconeogenesis from protein [9] is not sufficient as measured by the negative nitrogen balance following induced steroid diabetes to account for the loss of carbohydrate tolerance. The decreased carbohydrate tolerance must therefore be assumed to be due to an impaired utilization of carbohydrate by the cells. This can be due to inhibition of insulin activity at the cellular level or to depressed production of insulin.[2] Decreased insulin sensitivity is not always demonstrable in ACTH or cortisone-induced diabetes [20, 24, 32] and has been questioned in patients with Cushing's Syndrome.[12] In the early phase of induced diabetes there may be insufficient augmentation of insulin secretion to compensate for the diabetogenic action of glucocorticoids. The large functional reserve of insulin-producing cells is usually sufficient to compensate, eventually, for the diabetogenic action of cortisone and to prevent clinically significant impairment of carbohydrate tolerance.[31]

The participation of the islets of Langerhans in the adaptation to the diabetogenic action of adrenal corticoids is supported by animal experiments. ACTH-induced diabetes in rats results in hyperplasia of the islets of Langerhans and degranulations of the beta cells.[1] It has been demonstrated in rats [18] and suggested in man [11] that steroid diabetes is more likely to develop with frequent forced feeding than when an equivalent amount of food is taken *ad libitum*. In the cases presented here it appears that the production of insulin was temporarily inadequate. Following the acute episode Case 2 was able to tolerate a regular hospital diet without difficulty. Twelve days later, the thirty-first postburn day, he was given a higher intake which was discontinued after two days because of the reappearance of hyperglycemia and glycosuria. On the fifty-sixth postburn day an oral glucose tolerance test showed a decreased carbohydrate tolerance but an intravenous glucose tolerance test performed on the fifty-seventh postburn day was normal. This difference in response may be due to an increased rate of glucose absorption from the gastro-intestinal tract. However, an oral glucose tolerance test performed on the sixty-eighth postburn day

was normal. In Case 1 death resulted from septicemia before further studies could be obtained. Neither case required insulin subsequent to control of the acute episode.

The severe dehydration in burn stress pseudodiabetes is due to the intense glycosuria and osmotic diuresis. This is secondary to hyperglycemia, but it should be noted that glucocorticoids may cause a glycosuria due to decreased tubular reabsorption of glucose.[19] Glycosuria has been observed in the presence of a normal glucose tolerance test following the administration of ACTH or cortisone.[10]

Burn stress pseudodiabetes is a potential threat in any burned patient being forced fed. Only by awareness of the syndrome can early recognition and prevention of extreme dehydration be accomplished. The syndrome appears to be rare, but its occurrence may be more frequent than is generally realized. It may have been a contributing factor in some previously unexplained deaths with the clinical picture attributed to other causes. However, this complication is not considered to be of such frequency or to have such dire consequences to warrant any less vigorous feeding of burned patients. This is particularly true in studies designed to clarify the metabolic alterations and to define the nutritional requirements of these patients.

## Summary

The syndrome of burn-stress pseudodiabetes occurring in two patients in the early postburn course is presented in detail. In both instances the syndrome occurred during periods of balance study at which time a high-carbohydrate, high-calorie intake was being given.

The clinical and laboratory manifestations of this syndrome are, in the order of appearance, hyperglycemia, glycosuria without acetonuria, high urinary specific gravity, and an intense osmotic diuresis. This results in severe dehydration with elevation of the nonprotein nitrogen, hemoglobin and hematocrit as well as a high serum Na and Cl. A marked increase in the urinary output is the most striking early clinical manifestation.

The syndrome has been seen most frequently in patients who have a family history of diabetes mellitus. When recognized early it has been aborted by discontinuing forced feeding. If it becomes fully developed, appropriate therapy consists primarily of vigorous water replacement and sufficient amounts of insulin to control the hyperglycemia.

The metabolic alterations pertaining to the etiology of the syndrome are discussed.

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