in an office practice when a clinical laboratory is not accessible; values in the low range could be construed as reasonable evidence against diabetes in normals or good control in diabetes, while those above 100 mg. per 100 ml., as determined by the test, would require checking by other methods. Presumably this could be done on the residue of the blood sample taken for the enzyme strip test, as the results would be immediately known. Undoubtedly the strips could distinguish clearly between hypoglycemic and diabetic coma, and might be so used if a urine specimen were not available for a strip test. Their use for monitoring patients in diabetic acidosis or coma might be useful when laboratory services are not immediately available. In view of the considerable error in reading these tests by experienced technicians, one has little confidence in using them for self-testing by patients; testing of urine is much simpler and probably equally useful when done often enough. The strips should not be used for detecting hypoglycemia.

With the advent of the AutoAnalyzer, it is difficult to see how the use of enzyme strips could be justified in hospital practice. Determinations of blood glucose by clinical laboratories not having the AutoAnalyzer are still relatively simple and inexpensive when done in quantity. Perhaps the greatest use of the strips might be made by physicians in their office practice, as part of a screening procedure.

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BRIEF NOTES AND COMMENTS

Early and Intensive Potassium Replacement in Diabetic Acidosis

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SUMMARY

A patient with diabetic acidosis is described who nearly died from potassium deficiency developing ninety minutes after starting therapy with insulin. The patient received 715 mEq. of potassium chloride intravenously during the first twenty-four hours of treatment, 364 mEq. being given in the first nine hours to maintain life. Attention is drawn to the limitations of current recommendations regarding potassium repletion in diabetic acidosis. DIABETES *15*:694-96, September, 1966.

Diabetic acidosis is today an uncommon cause of death among diabetics in Western countries, but in many developing populations it continues to exact a heavy toll.[1] Among Johannesburg Bantu, for example, acidosis still has a mortality rate of about 50 per cent and accounts for about two thirds of all Bantu diabetic deaths.[2] In the following case death would have occurred if not for the early recognition of potassium deficiency successfully treated with 715 mEq. of potassium intravenously in twenty-four hours.

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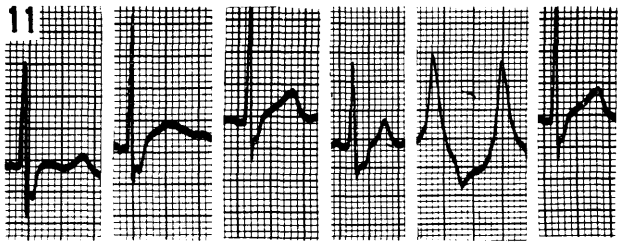
CASE REPORT

A forty-two-year-old Bantu manual laborer was admitted to hospital in coma. His wife stated that three days previously he became drowsy, and that he lost consciousness about six hours prior to admission. On examination he was deeply comatose, markedly dehydrated and acidotic. The blood pressure was 130/90 mm. Hg. and the pulse rate ninety per minute. Muscle tone was judged normal, and the reflexes were present and equal. Urinalysis revealed 4+ glycosuria together with large amounts of acetone and diacetic acid. The blood sugar was 423 mg. per 100 ml., urea 52 mg. per 100 ml., serum potassium 3.3 mEq./L., sodium 135 mEq./L., chloride 100 mEq./L., and carbon dioxide content less than 5 mEq./L. (These results, like those of the other biochemical investigations quoted in this report, only became available about three to four hours after blood was sampled.)

Treatment was begun with 200 units of soluble insulin intravenously, and infusion of 0.5 per cent saline containing 50 mEq./L., of sodium bicarbonate. Sixty minutes later the patient was given a further 100 units of soluble insulin intravenously, and by the ninetieth minute he had received four liters of the saline bicarbonate infusion. At this time his coma was lessening, his state of hydration was improved, and his breathing was much less acidotic. The blood sugar had fallen to 259 mg. per 100 ml. and the urea to 34 mg. per 100 ml.; the serum potassium was 2.9 mEq./L., sodium 130 mEq./L., chloride 101 mEq./L., and carbon dioxide content 5.5 mEq./L. At this point his condition suddenly deteriorated. He became comatose, completely flaccid and areflexic, and he perspired freely. His breathing was infrequent, irregular and gasping, and the blood pressure 60/0 mm. Hg. Hypoglycemia was suspected, but the blood glucose estimated at the bedside using "Dextrostix" was more than 250 mg. per 100 ml., and intravenous administration of glucose produced no response. Electrocardiography revealed the features of hypokalemia (figure 1), and because the patient appeared to be dying, he was given 80 mEq. of potassium intravenously within fifteen minutes with continuous electrocardiographic monitoring. The response was striking with a return of consciousness, improvement of respiration and muscle tone almost to normal, and an increase in blood pressure to 110/80 mm. Hg. The electrocardiogram also returned to normal, but at the fifteenth minute there was evidence of hyperkalemia (figure 1). This was corrected by infusing potassium at half the rate, the patient receiving 95 mEq. of potassium during the next thirty-



Time p.m.

a. 12:10 b. 12:18 c. 12:22 d. 12:24 e. 12:25 f. 12:30

FIG. 1. a. E.C.G. showing hypokalemia with absent T wave and prominent U wave.
b. After 45 mEq. potassium intravenously, T wave returning.
c. After 65 mEq. T wave normal.
d, e. After 78-80 mEq. appearance of signs of hyperkalemia—peaked T wave and widening of QRS.
f. Slowing of potassium infusion with return of tracing to normal.

five minutes. The serum potassium at this point was still only 2.1 mEq./L. The carbon dioxide content was 8.5 mEq./L., and the serum sodium and chloride and the blood urea were normal. During the following five hours 50 mEq. of sodium bicarbonate and 54 mEq. of potassium were infused bringing the total amount of potassium given over a period of six hours to 229 mEq. (17 gm. potassium chloride). That this was still inadequate was shown by the fact that at this time he again developed the clinical and electrocardiographic signs of severe potassium deficiency noted earlier. He was therefore given 135 mEq. of potassium intravenously over the next ninety minutes and the response was as prompt and complete as before. The serum potassium at the fifteenth minute of this infusion was 2.8 mEq./L. The blood urea and serum electrolytes were normal and the blood sugar 78 mg. per 100 ml. During the following fifteen hours he was given a further 351 mEq. of potassium intravenously. At the end of the twenty-four-hour period he had received a total of 715 mEq. of potassium (53 gm. potassium chloride) and was clinically, electrocardiographically and biochemically normal with a serum potassium of 4.9 mEq./L. He also received in this period a total of 410 units of soluble insulin, mainly intravenously, 400 mEq. of sodium bicarbonate and 12.5 L. of fluid. His course was thereafter uneventful and he was eventually stabilized on forty units of Lente Insulin daily. Investigation revealed no cause other than diabetes for the potassium depletion. His weight on discharge from hospital was 65 kg.

COMMENT

In most standard texts it is stated that in the management of diabetic acidosis, potassium should not be replaced until three to four hours after treatment with insulin has started. Earlier administration is avoided because the serum potassium level may be normal or high and the glomerular filtration rate depressed. It is also generally advised that the rate of parenterally administered potassium should not exceed 10 to 25 mEq. per hour, and that the total amount infused in twenty-four hours should not be greater than 200 mEq. These recommendations, however, are largely based on experience with cases of average severity. They are not necessarily applicable to the more severe cases, which for largely socio-economic reasons, may be common in developing populations such as the Bantu. Danowski[3] showed that the deficit in total body potassium in American patients with ketoacidosis varied between 3.2 and 11.7 mEq. per kilogram body weight. It is probable that the deficits in advanced coma are commonly in the region of, or even higher than, the upper figure quoted. This means that the deficit in our 65 kg. patient was of the order of 750 mEq. or more. In addition, the vigorous fluid replacement and large doses of intravenous insulin, which in our view are mandatory in the treatment of comatose patients, must often result in early and precipitous falls in the serum potassium level. This is particularly likely if the level is low or normal to start with as in the present case. Nor is this uncommon in the Bantu for among our last thirty-seven cases of advanced coma, 24 per cent had serum potassium levels on admission which varied between 2.6 and 4.0 mEq./L., and 38 per cent between 4.0 and 5.4 mEq./L. The severe potassium deficiency nearly caused the death of the present patient as early as ninety minutes after starting treatment with insulin. Furthermore, six hours later he again developed the signs of hypokalemia despite having received more than 200 mEq. of potassium intravenously. It is possible that many of our deaths from diabetic coma, especially those occurring within the first twenty-four hours, may have resulted from inadequate administration of potassium.

We now advocate in severe cases a much more intensive and flexible approach: During the first twelve to twenty-four hours electrocardiography is done every fifteen to thirty minutes. Blood for serum potassium estimation is taken hourly and arrangements made with the laboratory to obtain the result

within fifteen to thirty minutes. Results obtained hours after blood sampling may be too late to prevent disaster. The amount, rate and timing of potassium repletion must be determined from consideration of all the clinical, electrocardiographic and biochemical circumstances, including the degree of azotemia and urinary output. We suggest that some cases will need replacement within one to two hours after treatment with insulin has been started, and at infusion rates greater than those usually recommended. With careful supervision, which must include continuous electrocardiographic monitoring, high infusion rates in patients with large potassium deficits are not dangerous.[4,5] As an additional precaution, agents such as intravenous sodium bicarbonate or calcium gluconate should be on hand to treat hyperkalemia, if this develops and persists despite slowing or discontinuing the infusion.

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EDITORIAL

ALTERED NERVE METABOLISM IN DIABETES

As pointed out in the comprehensive review by Colby,[1] the neurological disorders of diabetes represent an important aspect of the disease from both the practical and theoretic points of view. To the practitioner, they are a common source of problems in therapy; to the medical scientist, they must be accounted for in any discussion of the nature and pathogenesis of diabetes mellitus.

Much discussion and not a little controversy have been generated in the groping for a reasonable hypothesis of pathogenesis and postulated theories can be grouped under two major mechanisms:

a. vascular insufficiency of nervous system structures.
b. derangements of molecular metabolism in the cord and peripheral nerves dependent on the diabetic state.

To many of the students of the subject, the variability of clinical manifestations and elegant demonstrations of arteriolar lesions in nerves from diabetics by Fagerberg[2] suggest the concept of multiple participating mechanisms of etiology.

Direct investigation of the metabolism of cords and peripheral nerves from alloxan diabetic animals has provided evidence of unequivocal biochemical changes in these tissues. Employing paired incubations of excised sciatic nerves from rabbits, Field and Adams[3] demonstrated that normal nerves fulfilled the criteria of responsivity to physiologic amounts of insulin. Insulin added in vitro enhanced glucose uptake, increased production of C-14-O_2 from glucose-C-14, and increased lactate production. The response phenomenon was associated with evidence of enhanced permeability not only to glucose, but also to nonutilizable pentoses and hexoses with the characteristic stereospecificity of insulin-action as described by Levine et al.[4] Nerves from diabetic animals differed in that they contained no detectable glycogen and whereas normal nerves without added insulin released glucose, there was a basal uptake in the diabetic tissue which could be enhanced threefold by incubation with additional insulin.

In situ neurectomy and degeneration experiments in both normals and diabetics established that the insulin responding capacity disappeared within twelve to twenty-four hours after section and gave proof that the effect was not dependent on adherent adipose tissue or Schwann cells which survived and proliferated. It was concluded that the capacity to respond to insulin was dependent on an intact axon and myelin sheath. A positive influence of insulin on peripheral nerve oxygen consumption had been noted by Heller.[5]

The prominence of myelin pathology in descriptions of nerves from clinical cases of neuropathy[6] prompted investigation of nerve lipid metabolism.[7] Despite unimpaired insulin enhanced glucose uptake by alloxan diabetic nerves, it was found that in vitro insulin failed to produce any enhancement of labeled glucose or labeled acetate incorporation into the nerve lipid. In