HYPERGLYCAEMIA IN BURNS

BY

B. N. BAILEY, F.R.C.S.*Senior Registrar, Stoke Mandeville Hospital,
Aylesbury, Bucks*

Hyperglycaemia due to burning may be: (1) an exacerbation of existing diabetes or activation of a pre-diabetic state; (2) an adrenal medullary response to burning; or (3) an adrenal cortical response to burning.

In the past year we have treated 112 cases of burns and scalds, 12 of which became hyperglycaemic. Four of these cases are reported in detail and the significance of the hyperglycaemia is discussed.

A common pitfall in the diagnosis of glycosuria after burns is that the sugar may be lactose. When penicillin in lactose powder is used locally on burns the lactose is readily absorbed and appears in the urine, giving a misleading impression of gross lactosuria (Baar and Bull, 1952). No lactose, however, was used in these cases.

Case 1

A man aged 74 was admitted to the Nuffield Burns Unit one-and-a-half hours after burning himself with ignited wax. The burns were deep partial-thickness, distributed over face, head, and forearms, and were assessed as 10% body surface.

His general condition was good, and his fluid requirements were met by copious oral intake. The first specimen of urine which he passed four hours after burning contained 1% sugar (on the "clintest" scale) and a trace of acetone. He was given the ordinary hospital diet, and for the ensuing week all his urinary specimens contained 1-2% sugar, with or without a trace of acetone.

A glucose-tolerance test (50 g. of glucose by mouth) 48 hours after burning showed a diabetic curve with a normal renal threshold. His eosinophil count was 30/c.mm.; after 72 hours it rose to 137/c.mm., and subsequently stayed at or above that level. A glucose-insulin-tolerance test (50 g. of glucose orally, 5 units of insulin intravenously) 72 hours after burning showed the diabetes to be insulin-sensitive.

The burns healed uneventfully with exposure. During the second week after burning he was restricted to a 1,000-calorie diet and his blood sugar varied between 150 and 210 mg./100 ml. on random sampling. He had urinary acetone on three occasions. During the third week after burning, the maximum random blood sugar was 140 mg./100 ml. and the urine showed an occasional 0.5% sugar with no acetone.

Since his discharge he has reverted to a full diet and recorded his urinary sugar tests, which showed 0.5% on Christmas Day and Boxing Day. For the past five months he has had no urinary sugar, although a recent glucose-tolerance test shows a diabetic curve.

Case 2

A girl aged 2½ was admitted two hours after being scalded with boiling water. The scalds were distributed over her back and buttocks, were partial-thickness, and covered 15% of her body surface.

Her condition on admission was good and the development of shock was prevented by the intravenous administration of 600 ml. of dextran and 200 ml. of blood in the 48 hours after burning. Her metabolic fluid requirements were given as milk and water orally.

From the time of admission until 18 hours after burning, half-hourly urinary specimens all contained 1% sugar. None of the specimens contained acetone. Her blood sugar six hours after burning was 181 mg./100 ml., and her eosinophil count was 40/c.mm.

The burns were treated by exposure, and healed within 10 days. A high-protein, high-calorie diet of milk and "casilan" (2,000 calories, with 100 g. of protein) was begun 48 hours after burning, but no further hyperglycaemia or glycosuria occurred.

We have treated eight other patients for this early hyperglycaemia in the past year. The ages of the patients ranged from 1 year to 65 years, and the area of burn from 10 to 60%. In all cases the glycosuria of 1 or 2% developed within eight hours of burning, and was usually present in the first specimen of urine obtained. Acetonuria did not occur in any case, and the glycosuria disappeared in 48 hours in all cases.

Case 3

Miss A was admitted after sustaining 45% full-thickness burns of the trunk and both legs when her clothing was ignited by a domestic boiler. In view of a previous history of hydronephrosis culminating in nephrectomy five years previously, the burned area was excised and homografted six hours after admission.

Her haematocrit was maintained at 40% with intravenous plasma and blood. Intravenous therapy was discontinued 48 hours after the burning. Her blood-pressure and urinary output remained good during the period of threatened shock. She began to take oral fluids a few hours after operation, and by the fifth day had progressed to a 4,000-calorie diet containing 250 g. of protein.

Despite rapid loss of weight her general condition remained good, and there was never any significant alteration in her serum electrolytes or blood-urea level. On the sixth and twentieth days after burning, Thiersch grafts were cut from the unburned parts of her back and chest and applied as strips, alternating with further homografts to the back, abdomen, and legs. These grafts took well, and on the twenty-seventh and thirty-ninth days further grafts were cut from the healed donor sites and applied to the remaining raw areas.

Intermittent glycosuria up to 1% was present from the tenth day after burning till the fifty-fourth. Her general condition remained good until the twenty-ninth day, when she developed an acute psychotic state in which her mood swung between extreme elation and uncontrollable terror. She had hallucinations and systematized delusions of persecution. Her blood sugar at this time was 793 mg./100 ml., but there was no acetonuria. Her eosinophil count remained below 40 c.mm. from the time of burning until the fiftieth day, when its rapid increase coincided with diminution of hyperglycaemia and general recovery. At the time of the mental disturbance she was apyrexial, had no evidence of systemic infection, and the granulating area, which was less than 5%, was clinically and bacteriologically clean. Liver-function tests were within normal limits (with the exception of reversal of the albumin/globulin ratio). Tests of pancreatic function were normal.

Attempts to reduce the hyperglycaemia with a four-hourly Jocelyn regime were unsuccessful, no drop in blood sugar being obtained with doses of up to 200 units a day, and after 10 days insulin treatment was stopped. At no time did she have acetonuria.

Her mental condition became better after the thirty-fifth day, and her blood sugar gradually fell to normal levels by the fifty-fourth day. Her glucose-tolerance test six months after burning was normal.

Case 4

A man aged 28 was admitted two hours after sustaining burns of the arms, trunk, and legs in a paraffin fire. The burns were 30% partial thickness and 15% full thickness.

The phase of threatened shock was controlled by plasma and blood transfusion, but as he refused to take adequate

oral fluids a drip of glucose-saline was continued up to the end of 72 hours. His general condition was good despite an exacerbation of chronic bronchitis. Glycosuria of 1% appeared after 48 hours, at which time his serum biochemistry was normal except for a blood sugar of 240 mg./100 ml. Insulin sensitivity tests showed no response. His eosinophil count was 40 c.mm. and did not rise above this level during the course of his illness.

The burns were exposed and the chest condition was treated vigorously. On the fourth day he had transient haemoglobinuria, and on the sixth day he developed a psychotic picture similar to that described in Case 3. Glycosuria and hyperglycaemia persisted from the third day, and tube-feeding with a 4,000-calorie diet containing 250 g. of protein was started on the fifth day. On the twelfth and twenty-sixth days slough was removed from the arms and legs and replaced with Thiersch grafts from the unburned thighs.

By the end of the second week he had lost all his body fat and most of his muscle bulk, despite continued tube-feeding. From this time his chest condition deteriorated rapidly, and on the thirty-third day he died, with about 5% unhealed burns.

Post-mortem examination revealed a left bronchopneumonia and empyema, toxic myocarditis, fatty degeneration of the liver, and cloudy swelling of the kidneys. A section of the pancreas removed one-and-a-half hours after death was stained for islet tissue; the pancreatic acini appeared normal, but there was a great reduction in islet cells.

Discussion

Pre-existing Diabetes and Prediabetes

Major trauma, whether mechanical or thermal, often exacerbates an existing diabetic state. The diet-controlled diabetic may need insulin after burning, and the insulin requirements of those already using it are often greatly increased (Root, 1945).

Case 1 shows the gradual transition from normality to diabetes. We cannot be sure that this patient did have a diabetic curve before burning, but in view of the development of mild diabetes after a minor burn, and of the persistence of the normal blood-sugar response, it seems highly probable. We have traced the medical records of a previous admission to hospital, and find that eight months before burning he did not have glycosuria.

This stress-induced diabetes in a subject whom we might (loosely) label prediabetic differs from the other two types of hyperglycaemia seen after burning. The exacerbated diabetic or the precipitated prediabetic shows the normal type of disease with ketone formation and insulin-sensitivity. When hyperglycaemia occurs after burning in a previously normal subject there is no ketone formation, and the hyperglycaemia is either very transient or, if persistent, insulin-resistant.

Adrenal Medullary Hyperglycaemia

This phenomenon may follow any severe injury. Out of 112 cases of burns admitted over the past year we have found that nine had glycosuria and hyperglycaemia without acetoneuria, associated with eosinopenia, within a few hours of burning. Case 2 is a typical example.

The mechanism of this type of hyperglycaemia seems to be an increased output of adrenaline. Hartman *et al.* (1926) demonstrated an increase in the circulating adrenaline after burning. Blum (1901) showed the hyperglycaemic effect of adrenaline to be partly due to increased breakdown of liver glycogen to glucose. Cori and Cori (1927) demonstrated the breakdown of muscle

glycogen to lactic acid after intravenous adrenaline. Clark and Rossiter (1944) have demonstrated hyperglycaemia in burned rats. This was accompanied by a depletion of muscle glycogen and a raised blood-lactate level. Adrenalectomy before burning prevented the development of hyperglycaemia.

There seems to be little clinical importance in this type of response, which is probably more widespread than is realized. We have not performed blood-sugar estimations on all our burned cases, and so have noticed the hyperglycaemia only in cases where it has been high enough to give a noticeable glycosuria. Taylor *et al.* (1944) found that 15 out of 35 burned patients had blood-glucose levels of over 160 mg./100 ml.

This transient stress hyperglycaemia does not seem to contraindicate high calorie intake. We have given the indicated high-calorie, high-protein diet to all cases that merited it, and in none of them has the hyperglycaemia persisted for more than 48 hours. None of our cases of adrenal medullary hyperglycaemia has gone on to the more formidable adrenal cortical hyperglycaemia. Conversely, neither of the cases of adrenal cortical hyperglycaemia appears to have passed through a phase of medullary hyperglycaemia.

Adrenal Cortical Hyperglycaemia

By this we mean a transitory state of hyperglycaemia after burning, usually of several weeks' duration, characterized by insulin resistance, lack of ketosis, and followed by spontaneous resolution. This condition has been described by Butterfield (1955) as the pseudodiabetes of burns. We see no reason to doubt that the pseudodiabetic response to burning is caused by an increased output of adrenal steroids.

Injection of A.C.T.H. produces hyperglycaemia for the duration of its administration (Conn *et al.*, 1948). A.C.T.H. produces many of the effects seen in the pseudodiabetic patient: eosinopenia (Wight *et al.*, 1953), raised plasma level of 17-hydroxycorticosteroids (Hume and Wittenstein, 1950), increased urinary potassium loss (Prunty, 1950), increased urinary 17-ketosteroids (Evans and Butterfield, 1951), and depletion of adrenal cortical lipid (Symington and Davidson, 1956).

The complete combustion of fat requires the simultaneous oxidation of carbohydrate, and we might reasonably expect to find ketosis in the presence of the high blood sugar of pseudodiabetes. Joslin *et al.* (1952) suggest that the site of antagonism between adrenal steroids and insulin is at the hexokinase level. Complete blockage at this level would stop all carbohydrate metabolism, since phosphorylation is a necessary step before glucose can be synthesized to glycogen or broken down to CO_2 and H_2O . Ketosis must occur in the absence of oxalo-acetic acid from carbohydrate metabolism, and, since ketosis does not occur, we suggest that the mechanism of the hyperglycaemia is not a hexokinase block.

Adrenal extracts produce a marked gluconeogenesis from protein, and we suggest that the likely cause of hyperglycaemia is an increased protein breakdown and not a block in carbohydrate metabolism. A negative nitrogen balance is present in most large burns, but the rapidity of weight loss and extreme emaciation in Cases 3 and 4 is far greater than any we have seen in burns of equal magnitude.

The insulin resistance of pseudodiabetes is a puzzling feature and no convincing reason for this has been suggested. It parallels the insulin resistance of A.C.T.H.-

produced diabetes, and to that extent is further suggestive evidence that the pseudodiabetic state is due to overactivity of the adrenal cortex.

We do not believe that there is a cause-and-effect relation between forced feeding and pseudodiabetes as suggested by Butterfield (1955). Although hyperglycaemia followed high-protein feeding in Case 3, this may well have been *post hoc* and not *propter hoc*. In Case 4 hyperglycaemia appeared after 48 hours and forced feeding was not begun until the fifth day. It might be suggested that the hyperglycaemia in Case 4 was initially of the medullary type, and changed into pseudodiabetes only after forced feeding had been started. In none of our other cases of adrenal medullary hyperglycaemia has there been a time lag in its development (in Case 4 there was a time lag of 48 hours); nor has the hyperglycaemia persisted for more than 48 hours. Had the hyperglycaemia in Case 4 been initially of the medullary type, it must have persisted for three days, even if we assume the pseudodiabetes to have started the instant after forced feeding began.

Dohan and Lukens (1948) state that pancreatic islet cells were depleted by the constant overstimulation of high carbohydrate intake. If the hyperglycaemia of pseudodiabetes were due to islet exhaustion we would expect replacement therapy with insulin to be effective, but this has not been the case.

Richardson (1940) states that injection of pituitary extract causes β -cell degeneration, and that it can be averted by the simultaneous administration of insulin.

At post-mortem examination Case 4 showed considerable loss of islet tissue. If insulin does protect the islet cells from damage it cannot be due to lowering of the blood sugar, either in corticosteroid-induced diabetes or in pseudodiabetes. A more central mechanism must be postulated if the peripheral stimulus to β -cell activity (high blood sugar) is not reduced by the administration of insulin.

Butterfield (1955) states that insulin resistance, which is most pronounced within three weeks of burning, gradually diminishes over the succeeding weeks, and if hyperglycaemia persists after 13 weeks it is responsive to insulin. This might fit in with Dohan and Lukens's (1948) suggestion, and in the early stages of pseudodiabetes insulin-resistant hyperglycaemia is caused by corticosteroid oversecretion. As the state of stress diminishes, the initial cause of the hyperglycaemia wears off, leaving depleted β -cells as a result of the prolonged hyperglycaemia. At this stage insulin sensitivity reappears as one might expect. This suggests that β -cell exhaustion is a result, and not the primary cause, of the hyperglycaemia in pseudodiabetes.

We believe it reasonable to give the burned patient the indicated high-calorie and high-protein diet, as it does not appear to precipitate the pseudodiabetic state. Once the condition has developed, it seems the more important to give this type of diet in the hope of sparing as much protein catabolism as possible. The usefulness of insulin seems doubtful, but in view of Richardson's (1940) opinion it may be wise to administer it, as it might have a protective action on the islet cells.

Summary and Conclusions

Four cases of hyperglycaemia after burning are described in detail. The chief causes of hyperglycaemia due to burning are (a) pre-existing diabetes and the activation of the prediabetic state; (b) adrenal medullary

hyperglycaemia and (c) adrenal cortical hyperglycaemia—known as the pseudodiabetes of burns.

Adrenal medullary hyperglycaemia is a transient condition of early onset, with disappearance within 48 hours. It is associated with the expected eosinopenia, and is a measure of the stress to which the patient has been subjected.

Adrenal cortical hyperglycaemia is a more severe condition appearing several days after burning. The hyperglycaemia is marked, is not associated with ketosis, and is resistant to insulin. The disease is accompanied by rapid emaciation and, in the two cases described, by severe psychotic upset.

We find no evidence that either of the adrenal types of hyperglycaemia is caused by high calorie intake, and it does not appear that adrenal medullary hyperglycaemia is a precursor of cortical hyperglycaemia.

We thank Mr. J. P. Reidy, under whose care these patients were admitted, for permission to publish this report.

REFERENCES

- Baar, S., and Bull, J. P. (1952). *Lancet*, **1**, 978.
 Blum, F. (1901). *Disch. Arch. klin. Med.*, **71**, 146.
 Butterfield, W. J. H. (1955). *Lancet*, **1**, 489.
 Clark, E. J., and Rossiter, R. J. (1944). *Quart. J. exp. Physiol.*, **32**, 269, 279.
 Conn, J. W., Louis, L. H., and Johnston, H. W. (1948). *Proc. Amer. Diabetes Ass.*, **8**, 213.
 Cori, G. T., and Cori, C. F. (1927). *J. biol. Chem.*, **72**, 615.
 Dohan, F. C., and Lukens, F. D. W. (1948). *Endocrinology*, **42**, 244.
 Evans, E. I., and Butterfield, W. J. H. (1951). *Ann. Surg.*, **134**, 588.
 Hartman, F. A., Rose, W. J., and Smith, E. P. (1926). *Amer. J. Physiol.*, **78**, 47.
 Hume, D. M., and Wittenstein, G. J. (1950). *Proc. First. Clin. A.C.T.H. Conf. 1949*, edited by J. R. Mote. Blakiston, Philadelphia.
 Joslin, E. P., Root, H. F., White, P., and Marble, A. (1952). *The Treatment of Diabetes Mellitus*, 9th ed. Kimpton, London.
 Prunty, F. T. G. (1950). *J. clin. Path.*, **3**, 87.
 Richardson, K. C. (1940). *Proc. roy. Soc. B*, **128**, 153.
 Root, H. F. (1945). Quoted in *The Treatment of Diabetes Mellitus*, edited by E. P. Joslin, H. F. Root, P. White, and A. Marble, 1952, 9th ed. Kimpton, London.
 Symington, T., and Davidson, J. N. (1956). *Scot. med. J.*, **1**, 15.
 Taylor, F. H. L., Levenson, S. M., and Adams, M. A. (1944). *New Engl. J. Med.*, **231**, 437.
 Wight, A., Raker, J. W., Merrington, W. R., and Cope, O. (1953). *Ann. Surg.*, **137**, 175.

Preliminary Communications

"Virugon" ("Flumidin"): No Benefit in Two Respiratory Diseases

A good deal of publicity has recently been given to the compound N¹,N¹-anhydrobis (β -hydroxyethyl) biguanide hydrochloride, marketed as "virugon" (formerly as "flumidin"), for the prophylactic and therapeutic treatment of influenza and a surprisingly large number of other virus diseases. A report of its failure to produce any effect upon two non-bacterial infectious diseases of the respiratory tract therefore may also be of value.

ADENOVIRUS TYPE 3

Between September, 1959, and February, 1960, I attended 33 children with a characteristic upper-respiratory infection (Watson, 1960a) from 15 of which adenovirus type 3 was isolated. From January 14, 1960, the last 11 of these were included in a controlled trial of the therapeutic effect, if any, of flumidin. Six children were treated. In five the recommended dose of 200 mg. was given thrice daily, and, in the youngest, 100 mg.