DIABETIC KETOACIDOSIS AT THE KENYATTA NATIONAL HOSPITAL.

A PROSPECTIVE STUDY: 1981 - 1982.

"PRESENTATION, PRECIPITATING FACTORS, MORTALITY AND PROBLEMS OF MANAGEMENT"

By

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DECLARATION

This thesis is my original work, and has not been presented for a degree in any other university.

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This thesis has been submitted for examination with our approval as University supervisors.

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SUMMARY

30 patients presenting to the Kenyatta National Hospital in diabetic ketoacidosis were each subjected to a well tried regimen of therapy, namely "small dose-intramuscular insulin" regimen. Besides insulin every patient received intravenous fluids, intravenous potassium supplementation and a broad spectrum antibiotic as an adjunct to the general considerations of a very ill patient. The presentation of diabetic ketoacidosis at the Kenyatta National Hospital was found to be similar to that elsewhere. Infection was the precipitating factor in the majority of patients (60%). The small dose intramuscular insulin regimen was found to be simple, safe and effective. The mortality rate for diabetic ketoacidotic patients treated was 16.7% (Cf. 29% in 1975 and 33% in 1978-80). At the Kenyatta National Hospital laboratory backup was found to be very inadequate, a factor which in the author's opinion contributed to the high mortality figure.

INTRODUCTION

Definition:

It has been the tradition of the Joslin Clinic to classify any case of diabetic ketoacidosis as one of "diabetic coma" when the plasma bicarbonate concentration is 9 mEq per litre or less, regardless of the degree of sensorium alteration (1). Page defines diabetic ketoacidosis as a plasma concentration of total ketoacids in excess of 3 mmol per litre (normal: 0.15 mmol per litre) (2). Felig in a review of "current concepts" in diabetic ketoacidosis (3) points out that ketoacidosis is a condition characterized by an absolute or relative deficiency of insulin in which ketone acids accumulate in blood (generally to levels greater than 7 mmol per litre) so as to cause a fall in arterial pH to less than 7.25 or a decrease in serum bicarbonate to less than 10 mEq per litre or both. It is quite evident from the foregoing that definitions for ketoacidosis vary from centre to centre and from one diabetologist to another. K. Alberti (4) has aptly defined diabetic ketoacidosis as severe uncontrolled diabetes requiring emergency therapy with insulin and intravenous fluids and where total ketone body concentration is more than 5 mmol/L. The latter part of the definition is retrospective and is merely to distinguish

it from hyperosmolar non-ketotic coma (4). This latter definition is preferred in this study as it is a practical and pragmatic one directed at therapy.

Pathogenesis:

Hyperglycaemia and ketoacidosis result mainly from a relative or absolute lack of insulin (5). It has been suggested that a second prerequisite for the development of the ketotic state is the concomitant excess secretion of insulin - counter-regulatory hormones (such as glucagon, catecholamines, cortisol and growth hormone) in response to stress (5,6,7). A large body of literature emphasizing the presumptive role of each hormone in the production of ketoacidosis has been reviewed by Schade and Eaton (7). Until recently it was supposed that the early stages of ketoacidosis were characterized by insulin deficiency alone without any particular changes in the anti-insulin hormones, although it was known that in established ketoacidosis plasma levels of growth hormone, glucagon, cortisol and catecholamines were raised (8,9). It was shown by Gerich, Lorenzi, Bier et al (10) and Alberti, Christensen and Iversen (11) that upon insulin deprivation of insulin-dependent diabetic subjects there was an early rise in plasma glucagon. This rise correlated with the rise in concentrations of ketone bodies, non-esterified fatty acids and glucose. Moreover,

infusion of somatostatin which is a potent inhibitor of glucagon release markedly attenuated the rise in concentration of ketone bodies and glucose (10). Studies on pancreatectomized subjects lent support to the thesis that glucagon was very important in the early stages of the development of ketoacidosis (12). Here obviously pancreatic glucagon concentration did not rise significantly while ketone body and glucose concentrations rose less than in a control group of juvenile diabetics. As a result of the above observations great emphasis was put on glucagon excess as the second prerequisite to insulin lack as a cause of ketoacidosis. Barnes, Kohner and Bloom (13) have performed similar studies on hypophysectomized diabetics. When insulin was deprived in these subjects there was a 70 per cent decrease in the rate of rise of ketone bodies, and glucose concentrations compared with diabetics who had intact pituitary glands.

Studies of pancreatectomized patients who developed ketoacidosis upon insulin deprivation (12) albeit slowly, underscored the preponderant role of insulin lack as a cause of ketoacidosis. Unger and Orci however hold the view that in pancreatectomized patients glucagon is probably devired from the gut, where glicentin can be converted to glucagon by the removal of a few amino acids.

The full blown picture of diabetic ketoacidosis can be explained on the pathophysiologic dynamics of lack of insulin, i.e., stimulation of lipolysis, proteolysis and gluconeogenesis, coupled with inhibition of glycolysis and of fatty acid and glycogen synthesis (5).

Role of Glucagon:

Hepatic ketogenesis has been extensively studied and revised by McGarry and Foster (14,15). They have tried to elucidate the exact site of action of glucagon in relation to insulin, and to clarify how and where the hormonal signals were translated into biochemical events. Glucagon increases ketogenic activity in isolated liver preparations by increasing the level of cytoplasmic carnitine concentration. Carnitine is a substrate for the enzymes carnitine acyltransferase I and II which transport free fatty acids from the cytosol into the mitochondria where they are oxidized. An increase in glucagon, therefore raises the potential activity of these enzymes. The ketogenic liver so produced cannot form ketones as long as glycogen stores are present to provide the means for glycolysis and fatty acid synthesis to continue. On the other hand there will be ketone formation in conditions leading to glycogen depletion and lipolysis such as starvation and ketoacidosis, both accompanied by a low insulin/glucagon ratio.

Ketosis is viewed as the result of increased mobilization of free fatty acids from adipose tissue (site 1) to the liver (site 2) coupled with simultaneous enhancement of the liver's capacity to convert these substrates into acetone, acetoacetate and B-hydroxybutyrate (14). The former event is believed to be triggered by a fall in plasma insulin levels while the latter is considered to be effected primarily by the concomitant glucagon excess characteristic of the ketotic state. Although the precise mechanism whereby elevation of the circulating glucagon/insulin ratio stimulates hepatic ketogenic potential is not known, activation of the carnitine acyltransferase reaction is an essential feature (Figure 1). The opposing metabolic pathways, fatty acid synthesis and fatty acid degradation cannot be simultaneously active.

A step by step search for the "carbohydrate key" to the control of fatty acid oxidation and ketogenesis revealed that malonyl CoA, the first intermediate in the conversion of glucose into fat via acetyl CoA is the putative metabolic switch (Figure 1). Increased malonyl CoA as a result of increased glycolysis has been shown to be the most potent inhibitor of the enzyme carnitine acyltransferase at the mitochondrial membrane. Conversely a decreased level of malonyl CoA (decreased glycolysis) activates the enzyme and leads to fatty acid transport and oxidation. Once in the mitochndrion,

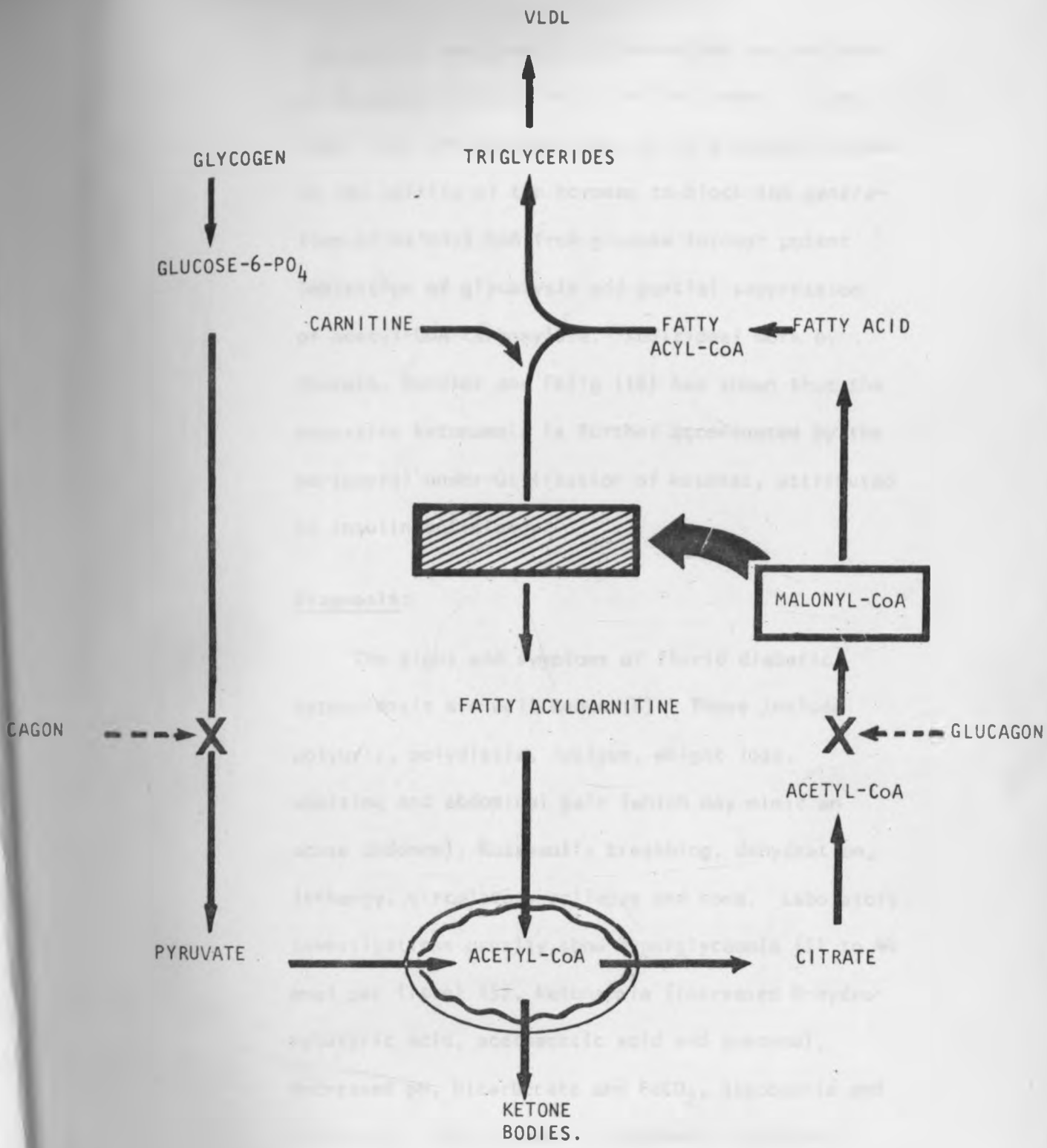

Fig. 1. Interrelations between the pathways of fatty acid synthesis and oxidation in liver.

Modified from McGarry J.D. New Aspects in the regulation of ketogenesis (Lilly Lecture) 1978. Diabetes, 28:517, 1979.

the rate of ketogenesis is determined by the rate of delivery of fatty acids to the liver. It was shown that the ketogenic action of glucagon resided in the ability of the hormone to block the generation of malonyl CoA from glucose through potent inhibition of glycolysis and partial suppression of acetyl-CoA carboxylase. Additional work by Sherwin, Hendler and Felig (16) has shown that the excessive ketonaemia is further accentuated by the peripheral under-utilization of ketones, attributed to insulin deficiency.

Diagnosis:

The signs and symptoms of florid diabetic ketoacidosis are well known (6). These include polyuria, polydipsia, fatigue, weight loss, vomiting and abdominal pain (which may mimic an acute abdomen), Kussmaul's breathing, dehydration, lethargy, circulatory collapse and coma. Laboratory investigations usually show hyperglycaemia (11 to 44 mmol per litre) (5), ketonaemia (increased B-hydroxybutyric acid, acetoacetic acid and acetone), decreased pH, bicarbonate and $PaCO_2$, glycosuria and ketonuria. Also present is azotaemia caused by increased protein breakdown and diminished renal clearance, hyperuricaemia as a result of diminished competitive urate clearance, increased serum free fatty acids and triglycerides because of accelerated lipolysis in adipose tissue and increased

production of triglycerides and very low density lipoproteins in liver (6). The metabolic emergency states that may present some clinical similarities to diabetic ketoacidosis are acute insulin hypoglycaemia, non ketotic hyperosmolar hyperglycaemic coma, alcoholic ketoacidosis and lactic acidosis. The differentiating features are dealt with extensively in the literature(1,4,5,6,17).

HISTORICAL

a) Global Overview

The earliest accounts of diabetes mellitus appeared in Egyptian papyrus writings (Ebers Papyrus, circa 1500 B.C.) (1). Many other accounts appeared in various parts of the world, Sushrutta in India in 400 B.C.. Celsus and Aretaus in Rome both in the first century of the Christian era (1). Descriptions of diabetes were made in Japanese, Chinese and Arabic writings. Through the centuries many aspects of diabetes were described by investigators and authors whose names are strongly linked with various aspects of diabetes today, e.g. Langerhans, Kussmaul and Joslin. The most remarkable step forward in diabetes mellitus came in 1921 when Banting and Best succeeded in extracting insulin from the pancreas (1). This epoch-making achievement which altered the outlook for patients with diabetes mellitus stimulated research immensely.

Of the serious metabolic diseases of man diabetes mellitus is the most common (17). The true prevalence in the general population is difficult to ascertain because of widely differing standards of diagnosis, but probably lies somewhere between 2 and 6 per cent (17). Diabetes occurs in all parts of the world (18a). Although comparison of data from different countries is unreliable, it appears to be common in some places (e.g. Malta), and rare in others, (e.g. Alaska and Greenland). The relationship of diabetes to age, sex, diet, obesity and inheritance seems to differ in various countries, as does the tendency to ketosis (18b).

Ketoacidosis was the main cause of death in diabetes before the discovery of insulin in the early 1920's (5,1). In the pre-insulin period between 1898 and 1914 ketoacidosis accounted for 63.8% of deaths in diabetics at the Joslin Clinic (1). During the early insulin period 1922 to 1929 the percentage of deaths due to ketoacidosis fell to 14.5% of all diabetic deaths. By the 1960's (1960-1966) the mortality due to ketoacidosis had fallen to 1.1%. Despite this precipitous decline over the past six decades the mortality for patients actually treated for diabetic ketoacidosis remains high, ranging from 5 to 15 per cent in specialized centres (18b). Mortality is much higher (20 to 30 per cent) in less specialized units and may go up to 50 per cent or more in elderly populations) (18b).

Insulin has no doubt contributed greatly to the increased survival in patients presenting in diabetic ketoacidosis but other aspects of therapy like the vigorous use of fluid replacement, electrolyte supplementation and antimicrobial agents have been of no lesser importance.

b) Kenyan Ketoacidosis

The prevalence of diabetes mellitus has increased considerably since 1962 when Tulloch (19) concluded that it was uncommon in Kenya. By 1966 the magnitude of the problem necessitated the establishment of a special diabetic clinic at the Kenyatta National Hospital. In the period between November, 1981 and October, 1982 (one year) 441 patients were admitted to Kenyatta National Hospital with diverse complications of diabetes mellitus, 41 of these being for ketoacidosis. Documentation of the early history of ketoacidosis in Kenya is scanty but Mngola, Radia and Shah (20) in a retrospective analysis of 34 patients in diabetic ketoacidotic coma seen in 1975 at the Kenyatta National Hospital gave a mortality rate of 29%. Meanwhile Thomas (21) (1978 to 1980) in her retrospective review of 74 patients in diabetic hyperglycaemic 'coma' at the Kenyatta National Hospital arrived at a mortality rate of 33%. (Only 2 patients were diagnosed as non-ketotic hyperosmolar hyperglycaemic coma). She came to the conclusion that the management of electrolyte and acid/base balance and the method

of insulin administration contributed greatly to the mortality. In Kenya like in many other places it was not until the 1970's that the "small dose insulin" regimen became popular in the treatment of diabetic ketoacidosis. This study is concerned with the application of this regimen to the treatment of ketoacidosis at Kenyatta National Hospital.

OBJECTIVES OF THIS STUDY

With a background of such a high mortality rate in the management of patients in diabetic ketoacidosis at the Kenyatta National Hospital a prospective study was designed, to collect and treat cases of ketoacidosis presenting to the Kenyatta National Hospital. A standard and uniform small-dose intramuscular insulin regimen was chosen and used in all the patients in this study (see Appendix I). The following aspects peculiar to Kenyatta National Hospital were analysed:-

i) Mode of presentation
ii) Precipitating factors
iii) Mortality.
iv) Problems in management.

PATIENTS AND METHODS

Selection of Patients

Doctors who were immediately involved in the care of acutely ill patients at the Kenyatta National Hospital were informed through a circular to contact the author as soon as they suspected a diagnosis of diabetic ketoacidosis. The majority of patients were selected from the acute casualty admissions and the rest chosen from the Adult Observation Ward and the medical wards. The duration of study was one year (November, 1981 to October, 1982). All patients who were correctly diagnosed as being in ketoacidosis and in whose management the author was involved were included in the study.

Methods:

1. Each patient was properly identified: age, sex and tribe were noted. Information as to whether the patient was a new or old diabetic was sought. The duration of symptoms of diabetes, the regularity of diabetic clinic attendance and the type of therapy the patient was receiving were detailed for the known diabetics.

2. a) The patient's symptoms were inquired into, particularly polyuria, polydipsia, fatigue, vomiting, abdominal pain, dysuria, cough, diarrhoea and any evidence of infection.

   b) The state of dehydration of the patient was estimated, the temperature taken and the respiratory and cardiovascular systems and the abdomen were fully examined. The mental status was labelled as alert, drowsy, confused, precoma or coma in order of diminishing consciousness. Fits were recorded as focal or generalized. Any neurological deficit was noted.

   c) Any pertinent physical findings that were thought to act as precipitating factors of ketoacidosis were sought for.

3. a) Urinary sugar and ketone bodies were estimated on admission or as soon as urine was obtained. These were estimated by the Uristix-Strip method (Ames or Boehringer Mannheim). Urinary microscopic examination and bacterial culture were performed in some of the patients.

   b) Venous blood samples were immediately collected for estimation of blood sugar and serum levels of sodium, potassium and urea.

Most blood sugar estimations were done at the "routine laboratory" using the Reflomat technique (Labra-Mannheim). Other patients had their initial blood sugar estimations done by the use of destrostix (Ames), and sometimes accuracy of colour reading was ascertained by the aid of a "Glucometer" reflactance meter (Ames). Serum sodium and potassium were done by the flame photometry method and the blood urea by the "Urastral strip" method (General and Diagnostics). Blood cultures were done whenever possible.

c) Estimation of the haemoglobin level and a white blood cell count including a differential count was performed on some of the patients.

d) Chest and other radiographs were taken when indicated.

e) Electrocardiograms were not performed routinely as it was felt these would not be cost effective. Moreover electrocardiographic facilities were not readily available as emergency procedure

f) Arterial blood analysis of pH $PaCO_2$, oxygen saturation, bicarbonate and base excess were done only when the Intensive Care Unit facilities were in use.

4. MANAGEMENT

The management of each patient was individualized, but the guidelines that were used in this study are appended (Appendix I).

a) Fluids

On admission all patients were given intravenous normal saline (0.9% sodium chloride). This was administered as stated in Appendix I. When the blood sugar level was approximately 14 mmol/L the regime was changed to isotonic saline alternating with 5% dextrose in water, given as half a litre in four hours. The infusion of fluid was changed to half normal saline if the serum sodium level was 155 mmol/L or higher.

b) Insulin

In the acute phase only short acting soluble (crystalline) insulin was used. Insulin therapy was started as soon as ketoacidosis was confirmed by glycosuria and ketonuria and hyperglycaemia. Twenty units of soluble insulin were administered as a stat dose. In the severely dehydrated patient, half of the total amount was given intravenously and half intramuscularly. Otherwise the total amount of 20 units of

soluble insulin was given by deep intramuscular injection into the gluteal muscles or into the thigh. Subsequently one hourly deep intramuscular doses of 5 units of soluble insulin were administered until the blood sugar level was about 14 mmol/L, when this was altered to a 2 hourly intramusclar dose. As soon as the acute symptoms were controlled, normoglycaemia achieved and the patient taking orally, a three times daily subcutaneous insulin regimen was commenced. Arbitrarly all patients were given 10 units of soluble insulin three times a day. Subsequently adjustments were made depending on urinary glycosuria and blood sugar estimation. Patients were discharged on long-acting insulin preparations or oral hypoglycaemic agents depending on individual characteristics.

c) Potassium

At the commencement of insulin therapy, potassium supplements were added to the intravenous fluids. 5 mls of 20 per cent potassium chloride (13 mmols) were added to each half litre of intravenous fluids. Usually this was the third or fourth half litre bottle of saline. If hyperkalaemia was detected, potassium supplementation was

suspended, or if no urine was passed in 3 to 4 hours caution was exercised in supplementation. After the acute phase potassium was continued orally.

d) Alkali

Sodium bicarbonate was only given when severe acidosis was present (pH less than 7.1). Sodium bicarbonate was administered over 30 minutes in aliquots of 50 to 100 mmols (approximately 50-100mls of 8.4% sodium bicarbonate) with additional potassium supplementation of 13 to 26 mmols (5 to 10 mls of 20% potassium chloride). In cases requiring alkali, the pH was measured regularly and further administration of alkali was discontinued as soon as the pH rose to 7.1 or above.

e) Antibiotics

In every case, a broad spectrum antibiotic was given.

f) Supportive Therapy

Comatose patients or those who were obtunded and vomiting were subjected to nasogastric intubation and stomach contents were aspirated regularly. Oxygen was administered as necessary. An indwelling bladder catheter was temporarily maintained for patients who could not pass urine spontaneously in the first 3 to 4 hours.

5. MONITORING

a) A half hour record of pulse, blood pressure and respiratory rate was maintained during the acute phase, later these were done one hourly.

b) An input and output chart was kept.

c) Blood sugar estimation was done one hourly for 2 hours, then 2 hourly (see Appendix I).

d) Serum sodium and potassium and the blood urea nitrogen were done 2 hourly for 4 hours then 4 hourly.

6. Results are given as Mean ± S.E.M. Statistical significance was assessed by the student t-test.

RESULTS

1. In the 12 month period, November 1981 to October, 1982, 441 patients were admitted to Kenyatta National Hospital with various complications of diabetes mellitus. 41 (9.3%) of these cases were managed as diabetic keto-acidosis. 30 (73.2%) of the 41 patients satisfied the criteria for the diagnosis of diabetic ketoacidosis (for this study) and were included in the study (Table 1). The male to female ratio was 1:1 i.e., 15 patients each. The mean age was 32.4 ± 2.8 years (range 13 to 79 years).

   Sixteen patients (53.3%) were new diabetics. Out of the 14 known diabetics 8 (57.1%) were on intermediate acting insulin-zinc suspension, U.S.P. (lente insulin). The remaining 6 patients were on oral hypoglycaemic agents; 5 on chlorpropamide and one on glibenclamide. The tribal distribution is shown in Table 2. The tribal distribution is compatible with the tribal breakdown of all admissions to Kenyatta National Hospital (Medical records department).

2. Symptoms (Tables 3 and 10)

   All patients in this study presented with polyuria, polydipsia and fatigue. Fifteen (50%) complained of vomiting, while abdominal pain and diarrhoea was each present in 3 (10%) patients. Cough was a symptom in 13 patients (43.3%).

Dysuria and "other complaints" was each given by 2 patients (6.7%). The mean duration of symptoms was 7.8±1.1 days in the 29 patients in whom it was obtainable (range 1 to 21 days).

3. Signs (Tables 4 and 11)

Dehydration was clinically evident in all patients on admission, 13 (43.3%) of them were severely dehydrated. Of the 18 patients who had evidence of infection, only 4 (22.2%) were febrile. Air hunger (Kussmaul's respiration) was evident in 26 (86.7%) of the cases. Chest signs were present in 10 (83.3%) of the 12 patients who eventually were shown to have respiratory tract infection. The state of consciousness on admission is shown in Table 11. Three (10%) of the patients were in coma, meanwhile 11 (36.7%) were in a clear state of consciousness on presentation to hospital. In all, 19 (63.3%) of the 30 patients in the study had some degree of impairment of consciousness (Table 11). One patient who was not previously an epileptic had focal seizures. A single patient was hypotensive, the admission blood pressure being 90/20 mm Hg. This patient eventually recovered. The rest of the presenting signs are shown in Table 4.

4. LABORATORY DATA

a) Initial Data (Table 5)

All patients had a glycosuria of at least 2+ (1%). Ketonuria was present in all cases. The initial blood sugar was above 20 mmol per litre in 26 (86.7%) of the patients. More precise estimation of the blood sugar was not possible as an emergency procedure. Only one patient had a serum sodium level equal to or above 155 mmol per litre (Case No. 8 with serum sodium of 155 mmol per litre). The mean admission potassium level was 4.9 ± 0.18 mmol per litre (range 3.0 to 6.5 mmol per litre). Hypokalaemia, that is a serum potassium level equal to or below 3.4 mmol per litre was present in 4 (13.3 per cent) patients. 12 patients (40 per cent) exhibited a blood urea nitrogen (BUN) above the Kenyatta National Hospital Laboratory upper limit of normal of 6.7 mmol per litre. Subsequently BUN estimations fell to normal except in patient No. 10 who eventually died. Patient No. 20 who had a BUN of 45.8 mmol per litre on admission was found to have benign prostatic hypertrophy. The BUN level fell to

normal when the obstruction was relieved by continuous bladder drainage. Blood gas analysis was performed on 3 patients. Patient No. 17 had a pH of 6.9 and a bicarbonate level of 3 mmol per litre. White blood cell counts were performed on 10 patients on admission, 8 of these had a leucocytosis (a white blood cell count of above 10×10^9 per litre). An absolute neutrophil leucocytosis was present in 6 of these patients, 3 (50 per cent) of whom had infection. Only 2 electrocardiograms were performed, both of which were within normal limits.

b) Treatment Laboratory Data (Table 6)

i) The mean time over which symptoms and signs of severe ketoacidosis were brought under control and blood sugar was brought below 14 mmol per litre was 11±1.0 hour (range 4 to 26 hours).

ii) The mean amount of soluble insulin used in the first 24 hours was 60.7±1 unit (range 30 to 145 units).

iii) A mean of 4220±210 mls of fluid was used in the first 24 hours (range 2,500 to 8,000 mls).

iv) The lowest blood sugar level estimation was a mean of 7.2±0.6 mmol per litre (range 3.0 to 15 mmol per litre). Taking 2.8 mmol per litre as the hospital laboratory lower limit of normal for blood sugar, no patient experienced hypoglycaemia during the period of treatment for ketoacidosis.

v) The lowest serum potassium estimation was a mean of 4.1±0.1 mmol per litre (range 3.0 mmol per litre to 5.4 mmol per litre). 6 patients (20 per cent) developed hypokalaemia during treatment (i.e. a serum potassium level of 3.4 mmol per litre or less). None of the latter, however, had a serum potassium below 3.0 mmol per litre.

5. Fatal Cases (Tables 6 and 7)

Five of the patients studied died, giving a mortality of 16.7 per cent. The pertinent symptoms, signs and laboratory data of the fatal cases are shown in Table 6. There were 4 female deaths and 1 male death (P = 16)(difference not statistically significant). The mean age of the fatal cases was 40.6±10.3 years (range 23 to 70 years). 3 (60%) of the deaths were of new cases. Of the two others, one was on lente insulin for 6 months prior to this fatal hospitalization and the other was on chlorpropamide.

Records of the latter show very poor control of glycaemia before he developed ketoacidosis. All the fatal cases had impairment of consciousness on admission, one of them was in coma. The lowest blood sugar and serum potassium estimations are shown in Figure 6. None of these cases developed hypoglycaemia (blood sugar below 2.7 mmol per litre) during treatment. 2 cases (40%) had hypokalaemia of 3.2 mmol per litre and 3.0 mmol per litre respectively. Infection was identified in all the fatal cases.

6. Precipitating Factors (Tables 5, 8 and 9)

Eighteen patients (60%) had infection as a precipitating cause for ketoacidosis. Of these, 12 (66.7%) patients had respiratory tract infection, including pulmonary tuberculosis in 2 patients. 3 (16.7%) patients had osteomyelitis or cellulitis. Urinary tract infection was evident in 2 (11.1%) and a dental abscess in 1 patient (5.6%). There were 8 patients (26.7%) who either did not administer insulin prior to developing ketoacidosis or were new diabetics. Four patients (13.3%) did not exhibit an identifiable precipitating factor. No patients were suspected on clinical grounds, to have myocardial infarction.

DISCUSSION AND REVIEW OF THE LITERATURE

Small intramuscular dose of insulin given as hourly injections is effective in reducing mortality in the treatment of diabetic ketoacidosis in Kenyatta National Hospital as it is elsewhere. This regimen of insulin administration as an adjunct to vigorous fluid and electrolyte replacement coupled with appropriate antibiotic cover and supportive care appears to be simple and safe. No hypoglycaemia developed during treatment in any of the patients and mild hypokalaemia occurred in 20% of the patients. This contrasts sharply with the retrospective study of Thomas (21) where intratreatment blood sugar estimations of 0 mg per 100 mls and 8 mg per 100 mls were recorded. In the same study serum potassium levels of 1.9, 2.9, 2.8 and 2.9 mmol per litre were observed for different patients during treatment. In the pioneer work of Alberti (22) no cases of late hypoglycaemia was noted whilst using a small dose insulin regimen. And only one patient developed a hypokalaemia of 3.2 mmol per litre during treatment. Working in Addis Ababa, Abdulkadir, Mengishi, Daniel and Seboxa et al (23) reported only one death during the treatment of 14 ketoacidotic patients with small doses of insulin given hourly by the intramuscular route. In this Ethiopian experience the patients were monitored entirely by clinical parameters and the only biochemical aspect estimated was blood sugar (using 'Destrostix' - Ames). In a proper hospital set up, however,

appropriate laboratory investigations would add considerably to the successful outcome of therapy. Before a further discussion of the current status on insulin, fluid and electrolyte management in ketoacidosis is reviewed, ketoacidosis as seen at the Kenyatta National Hospital during this study is discussed.

Ketoacidosis at Kenyatta National Hospital

Of the total admissions of diabetic patients to the hospital, ketoacidosis forms a sizeable proportion (9.3%). Two retrospective studies on diabetic ketoacidosis have been done at the Kenyatta National hospital: Mngola et al (20) in 1975 and Thomas (21) in 1978-1980. In respect to the age range, and the mean age of the fatal cases, the patients seen by Thomas (21) and those in this study are comparable. It appears that the percentage of diabetics admitted in ketoacidosis in this particular study was smaller than in the previous studies. There is a general downward trend in the percentage of diabetics being admitted in ketoacidosis with time (26% in 1975; 22% in 1978-1980 and 9.3% in 1981-1982). This could probably be a reflection of the improving general awareness of patients of the tell-tale symptoms of decompensating diabetes mellitus. Also significant is the fact that 53.3% of the patients were new diabetics in this study while in 1975, new diabetics formed 32% of the ketoacidotic patients ($P = 0.15$, statistically not significant).

The new diabetics who were probably less aware of their condition would present in ketoacidosis whereas older diabetics would have sought medical help earlier. The age of the patients ranges from 12 to 70 years in both this study and that by Thomas (21). Alberti's (22) study of 14 patients gave a similar age range (14 years to 77 years). According to Bradley (1) diabetic coma may occur in patients of any age - from under one year to 80 years. The male to female ratio is 1:1, a ratio similar to that obtained by Alberti (22). However, among Joslin Clinic patients having diabetic coma, the ratio of females to males was 2:1 (1) a striking observation when one considers that diabetes is equally as common in males as in females in the younger age groups. According to Bradley (1), ketoacidosis is common during the developmental period when adolescent rebellion is frequent. Adolescent rebellion is more common in girls than in boys, hence partially explaining the increased proportion of females presenting in ketoacidosis. This is an American experience, what the Kenyan situation is, remains to be analysed.

The symptoms of diabetic ketoacidosis as seen at Kenyatta National Hospital are no different from those seen elsewhere. The cardinal complaints of polyuria, polydipsia and fatigue are uniformly obtained from decompensating patients. Vomiting is quite common while abdominal pain and diarrhoea occur occasionally.

The pathogenesis of these gastrointestinal symptoms is still unclear (24, 25).

Water and electrolyte loss is a common finding which, in severe cases, results in hypotension. As ketoacidosis worsens the rise in hydrogen ions have a negative inotropic effect on the heart and cause vasodilatation. This further worsens hypotension and also induces hypothermia (1,6). In fact despite 18 patients having infection only 5 (27.8%) were febrile. Mild hypothermia or inappropriate normothermia are quite common in ketoacidosis (6,26). The cause of this inadequate rise in temperature is probably the peripheral dilatation which occurs because of acidaemia. The importance of this is that a valuable sign of infection is lost. Only 3 patients (10%) presented in true coma. Alberti and Nattrass (6) in their review of severe diabetic ketoacidosis point out that only 10% of cases of ketoacidosis in contemporary series are in true coma. This is in contrast to cases 30 or 40 years ago when up to 50% of cases presented in coma (6).

In hospitals or clinics where laboratory facilities may be extremely limited, the great majority of patients in ketoacidosis can be successfully treated (1). Urine tests to determine glycosuria and ketonuria can be performed using glucose strips and acetest/ketostix respectively. Often a reading of 2+ (1 Gm per 100 mls) or above is obtained. However, as oliguria ensues the excretion of glucose may be reduced to less than 1 Gm per 100 mls of urine. Ketonuria is usually 4+ but the

same provision as for glycosuria may apply in severe ketoacidosis. Blood studies consistently reveal increased levels of sugar, urea, uric acid, ketones and organic acid. Blood sugar values of 11 mmol per litre to 44 mmol per litre or above are obtained. The value for blood sugar is however, extremely variable (1). Recent ingestion of food, long intervals following the last insulin dose and diminishing glycosuria as renal function fails contribute to extremely high blood glucose levels.

In diabetic ketoacidosis, blood ketones are in excess of 3 mmol per litre (normal being 0.15 mmol per litre (2,5). The biochemical basis for ketosis has been dealt with in the introduction (14). For clinical purposes it is usually sufficient to demonstrate by the use of ketostix that plasma ketones are positive at a dilution of more than 1:2. Body cells with the exception of those of the central nervous system which have little if any such capacity metabolize fatty acids and ketone bodies (1). Hepatic over production of B-hydroxybutyric and acetoacetic acid is primarily responsible for the acidosis. In diabetic ketoacidosis, the production of B-hydroxybutyric acid is quantitatively the greatest (27) and thus contributes the most to the excess hydrogen ion load. Qualitatively, however, acetoacetic acid may be more significant because of its greater effects in suppressing cerebral oxygenation (28).

B-hydroxybutyrate and acetoacetate are strong organic acids that completely dissociate at body pH (Pk - 3.8), providing one milliequivalent each of hydrogen ion and the ketoacid anion. Acidosis ensues when the buffer base is reduced and respiratory compensation is unable to maintain a normal pH (29). Ordinarily, ketone use by peripheral tissues regenerate bicarbonate, thus balancing or offsetting the loss of bicarbonate that occurs at the time that the acid is produced. There is now a large body of literature, in animals and man that indicates that the hyperketonaemia of starvation and diabetic ketoacidosis is due to a concomitant impairment in the use of ketones by peripheral tissues (30,31).

The severe osmotic diuresis that occurs is accompanied by loss of electrolytes that amounts to approximately 500 mmol of sodium, 350 mmol of chloride, 300 to 1000 mmol of potassium, 50 to 100 mmol of calcium and phosphate and 25 to 50 mmol of magnesium (6). In addition there is a theoretical deficit of 300 to 500 mmmol of base (6). Nonetheless the concentration of the above electrolytes in serum or plasma may be high, low or normal. Such was the case in this study (Table 5).

The only accurate guide to the administration of alkali is estimation of the pH. Kussmaul's respiration is usually evident at a pH of 7.2 but disappears at a pH of 6.8 when severe depression of the central nervous system occurs and the breathing becomes shallow.

It was found impossible to do pH estimations in every case as the only facilities available for doing it were in the Intensive Care Unit. In all, 3 patients had blood gas analysis done, one of whom had a pH of 6.9 (Patient No. 7), he was given sodium bicarbonate and eventually made a smooth recovery.

Myocardial infarction is uncommon in black Kenyans (32) and in other black East Africans (33). Electrocardiographic tracings would be invaluable for the detection of myocardial infarction and potassium derrangements. In view of the fact that myocardial infarction is uncommon at Kenyatta National Hospital it would probably be too costly to monitor every ketoacidotic patient electrographically. If it were not for the expenses that would be involved electrocardiographic monitoring would, however, be very useful for the detection of potassium changes. Although electrocardiographic evidence is lacking, save for two patients, none of the cases seen in this study were considered to have suffered a myocardial infarction.

Infection was the single most important precipitating factor of ketoacidosis in this study, being responsible for 60% of cases (Table 8). The second most important factor was errors in insulin administration in known diabetics or lack of insulin administration in new diabetics. 13.3% of the patients had no identifiable cause of ketoacidosis. As already mentioned myocardial infarction was not diagnosed in

any of the cases. The type of infection most prevalent was that of the respiratory tract. Thomas (21) found infection as the precipitating cause of ketoacidosis in 62% of her patients. In the series by Clarke, Campbell, Fraser et al (34) infection was the precipitating cause of ketoacidosis in 67% of patients. The marked increase in cortisol (35) and glucagon (36), in infection has been incriminated in the causation of ketoacidosis. Several other precipitating factors are known including cerebrovascular accidents, and trauma both of which are associated with increased circulating levels of glucagon and catecholamines. Additional factors include gall bladder disease,pancreatitis menstruation, pregnancy, acute hyperthyroidism (thyroid storm) (37), steroid therapy (38) and insulin resistance of the idiopathic type (39). Acromegaly, Cushing's syndrome and pheochromocytoma are rarer causes (1).

CURRENT TRENDS IN MANAGEMENT OF DIABETIC KETOACIDOSIS

Insulin:

Most of the recent controversies on the treatment of diabetic ketoacidosis have centred on the use of insulin, in particular the amount which should be given and the route by which it should be administered. Until 1972 it was traditional to use what would now be considered very large doses of insulin in the treatment of ketoacidosis. Average total doses used were about 200 units in the first 3 hours and 300 to 800 units in

the ensuing 24 hours. In this study the total dose of insulin used in the first 24 hours averaged 60.7± 1 unit (range 30 to 145 units).Root and Black in 1945 (40) and Malins in 1949 (41) showed that large doses of insulin were not only necessary but also saved lives in the treatment of diabetic ketoacidosis. As recently as 1976, Madison (42) drew a caution that on the bases of data available at the time, low dose insulin infusion should be considered a research tool. He further warned that this trend of using lower and lower doses of insulin must be stopped before it degenerates into a futile irrational and dangerous race to see who can treat this disorder with the lowest possible dosage of insulin. Froesch (43) repeated the same warning. However, from 1973 papers began to appear describing the therapeutic effectiveness of small doses of insulin in ketoacidosis, administered either by continuous intravenous infusion or intramuscularly (2,22,44,45,46,47,48,49). In four of the studies sited above the small doses of insulin were administered intramuscularly (45,46,48,49). In paediatric practice Morseley (50) has used the intramuscular insulin approach with resounding success. The glucose lowering effects of both the low dose intramuscular insulin regimen and the high dose conventional regime were showed to be similar by Katabachi, Ayayari, Guerra et al (46) in a randomized study. The advantages of low dose intramuscular insulin lie in the fact that hypokalaemia and hypoglycaemia are minimized, complications

which were commonly noted with the high dose regimens.

The studies with small dose insulin tends to dispel the original arguments that insulin resistance was of crucial importance in the treatment of keto-acidosis. The reasons originally given for this apparent resistance in ketoacidosis included acidaemia (51), antibodies and circulating antagonists, hypothermia (52), anti-insulin hormones and lipid metabolites (53). A review of the problem is given by Alberti (54). Despite the above considerations small dose insulin has been shown to effectively lower blood glucose and to correct the other derrange-ments that occur in ketoacidosis (2,44,45,22). Infection, however, has been shown to lessen response to low dose insulin in the early stages of treatment (22,55,56).

The route of insulin administration has been another point of controversy since the inception of low-dose insulin treatment. It is necessary first to establish the aims of insulin therapy. The successive aims are correction of hyperglycaemia, inhibition of lipolysis (and therefore ketogenesis) and gluconeo-genesis, improvement of peripheral ketone body utilization and ultimately increased peripheral metabo-lism (6). In normal man serum concentrations of insulin rarely exceed 50 uU per ml. Lipolysis, glycogenolysis and gluconeogenesis can be inhibited

by increments of 10 to 20 uU per ml (57,58,59). Larger amounts are necessary to achieve maximal rates of glucose uptake by peripheral tissues (60). The aim of therapy is therefore to achieve serum levels that are efficacious.

Insulin when given as a bolus intravenously has a half-life of only 4 to 5 minutes (61), so that even if a large dose is given there will be little or no insulin left in the circulation 30 to 40 minutes later. If insulin is to be given intravenously continuous infusion is therefore necessary. As mentioned earlier continuous intravenous low dose insulin has been shown by many workers to be safe and effective (2,44,45). Abdullah has used the method with success at a provincial hospital in Kenya (62). Many investigators have drawn attention to the fact that up to 75% of insulin may be adsorbed to glassware and plastic tubing (2). However, this can be adequately combated by the addition of albumin or a small volume of the patients own blood to the infusate. There is the risk of transmitting infection such as hepatitis by using albumin. Page (2) has demonstrated that adsorption becomes negligible when the insulin is present in relatively high concentration in the infusion syringe.

Intramuscular soluble insulin has a half life in muscle of approximately two hours (54). Using this route a serum insulin concentration of 60-70 uU per ml would be sustained by a 5 units intramuscular injection given hourly. To achieve this serum level expediently

a priming dose of 20 units of insulin is given at least in part intramuscularly (54).

Subcutaneous insulin has a half life of 4 hours. Its major drawback is that it takes too long to achieve effective serum concentrations and there is a possibility of a depot accumulation which poses the danger of late hypoglycaemia.

The conventional large insulin doses achieved serum insulin levels of 500 to 1,000 uU per ml (29), these are concentrations vastly in excess of physiological needs . It would not be too difficult to see how such doses predispose to late hypoglycaemia.

In conclusion, it would appear that small doses of insulin given intramuscularly as hourly doses after a priming dose of 20 units would be ideal for a medical set up of the type we have at the Kenyatta National Hospital. During the conduct of this study it became quite clear that the meticulous delivery of intravenous fluids required for the success of the continuous intravenous infusion - small dose-insulin regimen cannot be achieved on the general medical wards. Whereas intramuscular injections are easily given and instructions can be followed with ease. The expense of infusion pumps precludes their supply to the general medical wards. As already indicated the danger of late hypoglycaemia is minimal since only a small depot of insulin is available at any one time.

FLUID AND ELECTROLYTE

Fluid:

Large amounts of fluids are lost during the evolution of ketoacidosis. In this study a mean of about 5 litres of fluid was administered in the first 24 hours (range 2.5 to 8 litres). The fluid loss in ketoacidosis has variously been put at 5 to 8 litres, (5,22). The degree of dehydration will depend on the type of diabetes, the length of the prodromal phase and the amount of fluid intake and urine output. Fluid administration will therefore be guided by what is conceived to be the fluid deficit. The fluid regimen cited in Appendix I is recommended because it is easy to follow and ensures that all ketoacidotic patients receive adequate fluids initially. The eventual requirements of individual cases are of course quite variable. Although no patient in this study was fluid overloaded, where possible a central venous pressure line would be appropriate especially in the elderly and in those with cardiac disease. The initial fluid administered is isotonic saline solution (0.154 M). Most authorities agree that this is the best strength of saline to use although the calculated deficit is hypotonic solution (5,6). When a blood sugar level of about 14 mmol per litre is achieved a 5% dextrose in saline solution is substituted to prevent too rapid a fall in intracellular osmolality. This measure may serve to decrease

the likelihood of cerebral oedema (63).

Potassium:

Perhaps the most important electrolyte disturbance in diabetic ketoacidosis is the marked deficit that develops in total body potassium (64,65). On presentation hypokalaemia is uncommon in ketoacidosis. In fact in this study only 13.3% of the patients had hypokalaemia on initial serum potassium estimation. However, all required potassium supplementation, inspite of which 20% developed hypokalaemia during treatment. It is therefore important that potassium supplements should be started early (i.e. as soon as insulin treatment is commenced) and vigorously too. All patients should receive potassium supplements unless they are hyperkalaemic or have evidence of renal impairment. Although the total potassium deficit is 300 to 1,000 mmol, the aim of treatment in the acute stage is not to replace this amount, but to maintain a normal serum potassium level (5). The deficit is eventually corrected as the patient commences oral intake. 2 of the patients who died had hypokalaemia during treatment but in addition they had severe infections. None of the deaths was attributed to hyperkalaemia. It seems therefore reasonable to recommend a more aggressive approach towards potassium supplementation. The use of 20mmol per each half litre of saline as opposed to 13 mmol as given in this study would probably obviate

hypokalaemia altogether. Above all, however, one must point out that there is no other true guide to the administration of potassium supplements other than serum potassium estimation. It was found difficult to do meaningful electrocardiograms on the general medical wards during the acute phase of the illness.

Kreisberg (29) in a review discusses the recommendation that some of the potassium should be administered as potassium phosphate to take care of the phosphate deficiency as well. He, however, goes on to say that the advantages of phosphate supplements may be of theoretical benefit only. In a set up like the Kenyatta National Hospital it would be unwarranted to recommend phosphate supplements in the routine management of ketoacidosis. This might obscure the more important aspects of insulin, fluid and potassium administration and the search for precipitating factors.

Bicarbonate:

The controversy regarding the use of alkali in the treatment of ketoacidosis is still a major focus for disagreement. Matz (66) has pointed out that we still know little of the intracellular changes in pH that accompany the extracellular changes and even less of their effects on metabolism. Alkali therapy can cause hypokalaemia, a paradoxical fall in pH of the cerebrospinal fluid (67) and impaired oxyhaemoglobin dissociation (68). The use of alkali should be

reserved for those patients with a pH below 7.1 and as soon as this is reached further use of alkali should be discontinued (5,6). When alkali is needed additional potassium supplement is essential. In this study only one patient received alkali in the form of sodium bicarbonate on account of a severe acidosis of pH 6.8.

PRECIPITATING FACTORS

As stated elsewhere the single most important precipitating factor is infection. Hence it is very important that no efforts should be spared in trying to exclude an infection in all cases of ketoacidosis. The importance of infection has been widely acclaimed by investigators (50,64,69). At Kenyatta National Hospital it has not always been easy to perform routine blood, urine and stool cultures as emergency room procedures. It is however, desirable that whenever possible such studies should be undertaken to guide in the correct choice of antibiotics for the treatment of infections. In this study every case was given a broad spectrum antibiotic. Although this goes against the dictum of the microbiologist that antibiotics should be given for specific infections, it is probably best to err on the side of commission where investigation facilities are limited. Errors in insulin administration often in the form of omission, underdosage or the use of poorly stored insulin forms the next category of precipitating factors. A host of other factors can precipitate

ketoacidosis - this has been discussed elsewhere, but despite an assiduous search for a precipitating factor, a number of patients show none (64). As already discussed myocardial infarction is not prevalent in the black African population in Kenya, however, in centres where it is common, the prognosis of patients presenting with a combination of myocardial infarction and ketoacidosis is bad. Soler, Bennett, Fitzgerald et al (64) give a mortality of 50%.

Supportive Care

Patients in diabetic ketoacidosis are very ill. Those with an obtunded sensorium and vomiting are in danger of aspiration pneumonia. Timely aspiration of the stomach will obviate this danger. The use of oxygen in hypoxic ketoacidotic patients is as essential as in other medical conditions leading to poor oxygen delivery. The general principles of good nursing care are applicable to diabetic ketoacidosis. The eventual outcome of severely ill patients could well depend on this.

Mortality:

As pointed out in 1961 by Fitzgerald, O'Sullivan and Malins (70) comparison of the percentage mortality figures from different centres for diabetic ketosis is difficult. One important reason is the lack of uniformity in the definition of the problem. Of great relevance is the comparison of figures obtained in the same centre at various times. Even these, however,

must be considered against other innovations in medical care. The death of 5 out of 30 patients in this study still stands as a high mortality figure (16.7%). The impressive mortality rates of under 5% obtained in some units have yet to be attained (46). These excellent survival rates have been obtained in metabolic or research units where control of environmental factors and the intensity of physicians and nursing care are virtually beyond duplication. However, the experience of Abdulkadir et al (23) in far less stringent conditions lends support to the recommendation that small dose intramuscular insulin is effective, simple and safe in inadequately equipped centres. Of the 5 patients who died during treatment 2 were 60 years and 70 years, the rest were young; below 32 years of age. None of the patients showed hypoglycaemia during therapy and two of the fatal cases showed hypokalaemia of 3.0 mmol per litre and 3.2 mmol per litre. The mortality rate of 16.7% in this study when compared with the combined mortality rate of the 2 earlier retrospective studies on diabetic ketoacidosis at the Kenyatta National Hospital of 31% is statistically not significant ($P = 0.175$, i.e. probability of difference in mortality 31% versus 16.7%). There is however a drop in the mortality rate and a larger number of patients would need to be collected to achieve statistical significant.

Case No. 3

A 23 year old female presented with a large pituitary tumour giving rise to acromegaly and visual impairment. She had a craniotomy and lapsed into ketoacidosis post-operatively. She developed a dental abscess, but before this could be attended to she deteriorated rapidly and died inspite of adequate rehydration and control of ketoacidosis. At post-mortem massive pulmonary embolism was seen with thrombosis in the pelvic veins.

Case No. 10

A 70 year old new diabetic who had chest infection and had pre-renal azotaemia on admission. In spite of adequate rehydration, with return of adequate kidney function the patient died. Serum potassium and blood sugar were well maintained. The cause of death here would remain speculative as no post-mortem was performed.

Case No. 13

A 32 year old new diabetic, who had absconded from treatment of pulmonary tuberculosis. She presented with over-whelming chest infection. The serum potassium was 3.2 mmol per litre, 4 hours after commencement of treatment. No lower readings were obtained. The cause of death was probably severe chest infection.

Case No. 16

This was a young girl of 18 years who was controlled on lente insulin from 6 months earlier. She presented very severely dehydrated with a chest infection of seven days duration. Despite energetic antibiotic and fluid management she did very poorly and died 12 hours after admission. The cause of death here was probably severe broncho-pneumonia with septicaemia.

Case No. 22

A 60 year old female who was a known diabetic controlled on chlorpropamide for 7 years. She presented very severely dehydrated and hypokalaemic (serum potassium 3.1 mmol per litre). The serum potassium never rose beyond 3.1 mmol per litre, and only 3 estimations were possible. It appears hypo-kalaemia could have contributed to death in this patient since she was well hydrated by the time of her death and the infected gangrenous toe did not give rise to immediate anxiety.

Some of the deaths that occur in ketoacidosis are unavoidable; occurring in patients with lethal conditions in whom ketoacidosis is coincidental. In others however, deaths are avoidable and are due to clinical errors or biochemical disasters such as hypokalaemia, hypoglycaemia and cerebral oedema (71). The former two have been dealt with before but the latter merits some attention.

CEREBRAL OEDEMA:

Several reports appear in the literature of the fortunately infrequent but usually catastrophic occurrence of cerebral oedema and death in patients who otherwise appear to be recovering from ketoacidosis (72,73,74). Most cases of ketoacidosis who develop cerebral oedema die but at least one case of spontaneously reversing cerebral oedema has been reported (75). Several explanations for cerebral oedema in these patients have been advanced (76,77).

1. PARADOXICAL CENTRAL NERVOUS SYSTEM ACIDOSIS

The administration of bicarbonate with resultant correction of the systemic acidosis, will decrease peripheral chemoreceptor stimulation and would reduce the stimulus to hyperventilation from this site. Retention of carbon dioxide and its equilibration across the blood brain barrier, in the presence of fixed CSF bicarbonate concentration results in decreasing CSF pH at a time when systemic pH is improving (78). Against this theory is the fact that:

a) The CSF pH values of patients treated with bicarbonate are not appreciably different from those who do not receive bicarbonate (79).

b) Respiratory rate generally does not decrease acutely with correction of systemic acidosis (8).

c) CSF pH decreases from 7.35 to 7.27 whereas systemic pH increases from 7.09 to 7.26 (67). In patients studied CSF pH of less than 7.26 was recorded without any adverse effect on the mental status (67).

2. ALTERED CENTRAL NERVOUS SYSTEM OXYGENATION

In ketoacidaemia the oxygen haemoglobin dissociation curve is shifted to the right (i.e. increased oxygen unloading). The fall in 2,3-diphosphoglycerate which occurs in ketoacidosis shifts the curve to the left. The net result of the above two opposing effects results in no shift of the oxygen-haemoglobin dissociation curve. Rapid correction of systemic pH which occurs in energetic treatment shifts the curve to the left, hence decreasing oxygen unloading (81,82). It is believed that poor oxygenation of the central nervous system results in cerebral oedema. However, direct evidence of this theory is lacking.

3. UNFAVOURABLE OSMOTIC GRADIENTS.

In dogs, the sudden correction of sustained hyperglycaemia leads to increased CSF pressure and cerebral oedema (83). It has been postulated that "idiogenic osmoles" are formed in the brain, protecting it from excessive water loss in the presence of excessive hyperosmolality (71).

The identity of these osmotically active particles (originally thought to be sorbitol but subsequently proved not to be) is still unknown. Cerebral oedema occurs when the osmotic gradient between the brain and plasma is greater than 35 mOsm/kg water (84). This gradient would only occur when the blood glucose concentration was reduced to less than 14 mmol per litre within 4 hours (71). In view of its effects on electrolyte transport in other tissues (85,86), insulin may directly increase the electrolyte content of brain tissue and therefore be important in the pathogenesis of this problem.

CONCLUSIONS

1. Ketoacidosis is a common complication of diabetes mellitus at the Kenyatta National Hospital.
2. The signs and symptoms of diabetic keto-acidosis at Kenyatta National Hospital are similar to those seen elsewhere.
3. The diagnosis of diabetic ketoacidosis can be firmly made using a mimimum of laboratory investigations, namely blood sugar estimation and urine glucose and ketone quantification.
4. From this study it would appear that a small dose intramuscular insulin regimen as an adjunct to fluid, antibiotic and electrolyte supplement therapy is safe and simple in the treatment of diabetic ketoacidosis. The same regimen appears to lower the mortality rate of patients presenting in diabetic ketoacidosis (29% in 1975; 33% in 1978-80 and 16.7% in this study - although the probability of difference in mortality 31% (combined 1975 and 1978-80 average) versus 16.7% is not statistically significant $p = 0.175$.
5. Vigorous potassium supplementation is mandatory in the majority of ketoacidotic patients.

6. The use of alkali was found to be only occasionally necessary.

7. Infections especially respiratory infections form the commonest group of precipitating factors for diabetic ketoacidosis.

8. Myocardial infarction is uncommon as a precipitating factor of DKA in the K.N.H.

9. An efficient and reliable laboratory back-up service is absolutely essential if the morbidity and mortality rates are to be reduced to anything near those of well equipped areas.

APPENDIX I

WORK UP AND TREATMENT OF PATIENTS IN DIABETIC KETOACIDOSIS

A. 1. History, clinical examination.

2. Urinalysis (glucose, ketones, protein), blood glucose, white blood cell count (total and differential).

3. Urea and electrolytes, blood gas analysis, haemoglobin, white blood cell count (total and differential), blood culture, urine culture and throat swab.

B. 1. Fluids

a. Normal saline 1L in 30 min, 1L. in next 1 hr. 1L. in next 2 hrs, 1L in next 4 hrs then ½ L every 4 hourly (adjust according to degree of hydration).

b. When blood glucose is approximately 14 mmol/L change to 5% dextrose in normal saline ½ L every 4 hourly.

c. If Na^+ concentration is greater or equal to 155 mmol/L give ½ normal saline.

2. Insulin (Soluble)

a. Give as soon as blood glucose results available and after commencement of fluids. 20 units stat; if severely dehydrated, 10 units intravenously and 10 units intramuscularly otherwise 20 units intramuscularly.

b. 5 units one hourly intramuscularly.
If no response in 2 hours double the dose.

c. When blood sugar is approximately 14 mmol/L change to 5 units 2 hourly intramuscularly.

d. When severe symptoms and blood sugar controlled and oral feeding commenced by 24 - 48 hours, change to 10 units t.d.s. and use urine sugar and blood sugar to monitor treatment.

3. Potassium chloride (KCl)

a. Start KCl with insulin, 5 mls of 20% KCl (13 mmol) in each unit of intravenous solution after the lst 3 to 4 units of fluid. Monitor serum potassium level closely.

b. If no urinary flow or inadequate flow by 3 - 4 hours give potassium supplements cautiously.

c. Supplementation may continue up to one week by the oral route.

4. Alkali (sodium bicarbonate) caution!

a. If pH over 7.1 no alkali. If less give 50-100 mmol over 30 minutes and repeat blood gas analysis.

b. Additional potassium supplements necessary with alkali.

5. Broad spectrum antibiotics to most cases.

6. Nasogastric tube to vomiting and comatose patients.

7. Oxygen as necessary.
8. Whole blood or plasma if systolic blood pressure consistently below 80 mm Hg.

C. MONITORING

1. Blood sugar one hourly for 2 hours then 2 hourly.
2. Serum sodium and potassium levels 2 hourly for 4 hours then 4 hourly.
3. Temperature, pulse, respiration and blood pressure ½ hourly when very ill then one hourly.
4. Urine output, if no urine in 3-4 hours catheterize.
5. Central venous pressure in intensive care unit.
6. Electrocardiographic monitoring in intensive care unit.

TABLE 1: STUDY OF 30 PATIENTS IN DIABETIC KETOACIDOSIS

GENERAL INFORMATION

PATIENT	AGE (YRS)	SEX	DURATION OF DIABETES	PREVIOUS TREATMENT	TRIBE
1	50	F	NEW	-	KIKUYU
2	50	M	11 YEARS	EUGLUCON 15mg O.D.	LUO
3	23	F	NEW	-	KIKUYU
4	45	F	NEW	-	KIKUYU
5	16	F	1 YEAR	LENTE INSULIN	KIPSIGIS
6	14	M	NEW	-	KIKUYU
7	29	M	NEW	-	KAMBA
8	45	F	NEW	-	KIKUYU
9	35	F	2 YEARS	DIABINESE 500mg O.D.	KIKUYU
10	70	M	NEW	-	KIKUYU
11	16	F	NEW	-	KIKUYU
12	17	F	2 YEARS	LENTE INSULIN 40u.OD	KAMBA
13	32	F	NEW	-	KIKUYU
14	37	F	1 YEAR	DIABINESE 125mg O.D.	LUO
15	37	M	NEW	-	KIKUYU
16	18	F	½ YEAR	LENTE INSULIN	LUO
17	21	M	NEW	-	SWAHILI
18	13	M	NEW	-	KAMBA
19	32	M	4 YEARS	LENTE INSULIN 30u.OD	KIKUYU
20	60	M	¼ YEAR	DIABINESE 500mg O.D.	UGANDAN
21	16	F	NEW	-	KIKUYU
22	60	F	7 YEARS	DIABINESE 500mg O.D.	KISII
23	40	F	NEW	-	KIKUYU
24	44	M	4 YEARS	LENTE INSULIN 40u.OD	KIKUYU
25	14	F	2 YEARS	LENTE INSULIN 30u. OD	KIKUYU
26	14	M	3 YEARS	LENTE INSULIN 30u.OD	KIKUYU
27	32	M	NEW	-	KIKUYU
28	17	M	2 YEARS	DIABINESE 500mg OD	KIKUYU
29	35	M	NEW	DIABINESE 500mg OD.	KIKUYU
30	40	M	NEW	-	KIKUYU

TABLE 2: TRIBAL DISTRIBUTION OF PATIENTS

ETHINIC GROUP	NUMBER	PERCENTAGE
KIKUYU	20	66.7
KAMBA	3	10.0
LUO	3	10.0
KISII	1	3.3
KIPSIGIS	1	3.3
SWAHILI	1	3.3
UGANDAN	1	3.3

STUDY OF 30 PATIENTS IN DIABETIC KETOACIDOSIS

TABLE 3: SYMPTOMS AND THEIR DURATION

PATIENT NO.	POLYURIA	POLYDIPSIA	FATIGUE	DURATION (DAYS)	VOMITING	ABDOMINAL PAIN	DIARRHOEA	COUGH	DYSURIA	OTHERS
1	X	X	X	1	X	0	0	X	0	-
2	X	X	X	2	X	0	0	X	0	-
3	X	X	X	1	0	0	0	0	0	DENTAL ABSESS
4	X	X	X	3	0	0	0	X	0	-
5	X	X	X	14	0	0	0	0	0	-
6	X	X	X	14	0	0	0	0	0	-
7	X	X	X	2	0	0	0	0	0	-
8	X	X	X	10	0	X	0	X	0	-
9	X	X	X	14	X	0	0	0	X	-
10	X	X	X	?	X	0	0	X	0	-
11	X	X	X	14	0	0	0	0	0	-
12	X	X	X	2	0	0	0	0	0	CELLULITIS OF RIGHT ARM
13	X	X	X	14	0	0	0	X	0	-
14	X	X	X	2	0	0	0	0	0	-
15	X	X	X	14	0	0	0	0	0	-
16	X	X	X	7	0	0	0	X	0	-
17	X	X	X	21	X	0	0	0	0	-
18	X	X	X	7	X	X	X	0	0	-
19	X	X	X	7	X	0	0	0	0	-
20	X	X	X	7	0	0	0	0	0	-
21	X	X	X	14	0	0	0	0	0	-
22	X	X	X	1	X	0	0	0	0	-
23	X	X	X	14	X	0	0	X	0	-
24	X	X	X	5	X	0	0	X	0	-
25	X	X	X	7	X	0	0	X	0	-
26	X	X	X	2	X	0	0	X	0	-
27	X	X	X	7	X	0	0	X	X	-
28	X	X	X	2	X	X	X	X	0	-
29	X	X	X	3	X	0	X	0	0	-
30	X	X	X	14	0	0	0	0	0	-

X - SYMPTOM PRESENT

0 - SYMPTOM ABSENT

TABLE 4: SIGNS IN 30 PATIENTS PRESENTING IN KETOACIDOSIS

PATIENT NO	DEHYDRATION	TEMPERATURE °C	KUSSMAULS RESP.	CHEST SIGNS	STATE OF CONSCIOUSNESS	FITS	BLOOD PRESSURE	PULSE /min	RESP. RATE /min	OTHERS
1	MILD	36	X	X	DROWSY	FOCAL	110/80	90	24	PULMONARY TUBERCULOSIS + PNEUMONIA
2	SEVERE	36^{7}	X	0	NORMAL	0	170/95	120	26	UPPER RESPIRATORY TRACT INFECTION
3	MILD	$*38_{6}$	X	0	DROWSY	0	130/70	120	40	DENTAL ABSESS
4	MILD	35^{6}	X	X	NORMAL	0	110/80	92	24	PNEUMONIA
5	SEVERE	36	X	0	COMA	0	100/70	80		URINARY TRACT INFECTION
6	MODERATE	36	X	X	PRECOMA	0	100/70	80	40	PNEUMONIA + OSTEOMYELITIS (R) SHOULDER
7	MILD	36^{5}	X	0	NORMAL	0	120/70	100	22	-
8	MODERATE	36_{5}^{2}	X	0	DROWSY	0	110/80	85	20	PULMONARY TUBERCULOSIS (PAST)
9	SEVERE	36_{5}^{2}	X	0	NORMAL	0	110/70	114	20	DYSURIA
10	SEVERE	$*37_{8}^{5}$	X	X	PRECOMA	0	140/90	120	26	BASAL CREPTS
11	MILD	36_{5}^{8}	0	0	NORMAL	0	110/70	88	20	-
12	MOD	36^{5}	X	0	COMA	0	110/60	92	20	CELLULITIS RIGHT HAND
13	SEVERE	*39	X	X	COMA	0	100/60	120	30	PULMONARY TUBERCULOSIS
14	MOD	37	X	0	NORMAL	0	130/90	70	20	TENDER HEPATOMEGALLY
15	SEVERE	37	X	0	CONFUSED	0	120/80	96	36	-
16	SEVERE	37	X	X	PRECOMA	0	150/80	128	44	BRONCHOPNEUMONIA
17	MILD	36_{5}	0	0	NORMAL	0	110/70	88	23	-
18	SEVERE	36^{5}	X	X	PRECOMA	0	120/60	120	40	CREPTS RIGHT LUNG
19	MOD	36	X	0	CONFUSED	0	130/80	100	24	-
20	SEVERE	36	X	0	DROWSY	0	140/100	80	18	-
21	MOD	36	X	0	NORMAL	0	100/60	72	26	-
22	SEVERE	35_{5}	X	0	PRECOMA	0	130/80	100	26	CELLULITIS RIGHT LEG
23	MOD	$*38^{5}$	X	X	DROWSY	0	110/70	120	36	PULMONARY TUBERCULOSIS
24	MOD	$*38_{2}$	0	0	NORMAL	0	130/80	92	22	CELLULITIS BOTH FEET
25	MOD	36^{2}	X	X	NORMAL	0	120/60	120	32	PNEUMONIA
26	MOD	36^{4}	X	X	PRECOMA	0	120/70	160	22	CREPTS AND UPPER RESPIRATORY TRACT INFECTION
27	SEVERE	36_{5}	0	0	NORMAL	0	90/20	80	24	DYSURIA
28	SEVERE	35_{5}	X	0	DROWSY	0	140/90	90	28	-
29	SEVERE	36^{5}	X	0	CONFUSED	0	140/80	120	22	-
30	MOD	36	X	0	DROWSY	0	120/80	180	18	-

KEY: X - SIGN PRESENT
0 - SIGN ABSENT

BLOOD PRESSURE IN mm of Hg.
*FEBRILE PATIENTS

STUDY OF 30 PATIENTS IN DIABETIC KETOACIDOSIS

TABLE 5: INITIAL LABORATORY INVESTIGATIONS

* KEY OVER LEAF

PATIENT NO.	URINE SUGAR	URINE KETONES	BLOOD SUGAR mmol/L	Na^+ mmol/L	K^+ mmol/L	BLOOD UREA NITROGEN mmol/L	pH	HAEMOGLOBIN G%	WHITE BLOOD CELL COUNT	%NEUTROPHILS	CHEST X-RAY	ELECTRO - CARDIOGRAM	EXPLAIN
1	2+	1+	20+	140	4.2	11.7	-	-	-	-	X	N	CHEST X-RAY-PNEUMONIA
2	2+	2+	14.1	136	4.6	8.3	-	16.2	$12x10^9$	47	-	-	-
3	3+	2+	20+	145	6.5	5	7.27	-	-	-	N	-	HCO_3 II mmol/L
4	2+	2+	20+	136	5.2	6.7	-	-	-	-	N	-	-
5	2+	1+	20+	150	3.0	16.7	-	11.3	-	-	-	-	URINE CULTURE-KLEBSIELLA
6	2+	1+	20+	138	5.4	10	-	16.5	$21x10^9$	*72	-	-	OSTEOMYELITIS RIGHT HUMERUS
7	2+	1+	15.5	130	5.6	4.2	6.9	-	-	-	N	-	HCO_3<3
8	4+	4+	20+	*165	3.2	5	-	-	-	-	N	-	-
9	2+	1+	20+	132	3.8	5.8	-	-	-	-	N	-	-
10	3+	1+	20+	144	4.2	25	-	-	-	-	X	-	CHEST X-RAY-PNEUMONIA
11	4+	2+	20+	145	5.2	5	-	-	-	-	-	-	-
12	2+	1+	20+	135	5.1	10	7.15	-	-	-	N	-	HCO_3 - 10.5 mmol/L
13	3+	1+	20+	140	5.2	3.3	-	10.5	$10.9x10^9$	*87	X	-	CHEST X-RAY-PULMONARY TUBER--CULOSIS
14	2+	2+	20+	130	4.8	5	-	-	-	-	-	-	-
15	4+	2+	20+	132	5.6	5	-	-	-	-	-	-	-
16	4+	3+	20+	130	6.2	6.7	-	15.1	$15x10^9$	*70	X	-	CHEST X-RAY-PNEUMONIA
17	4+	2+	20+	135	4.8	6.7	-	-	-	-	-	-	-
18	3+	2+	20+	130	5.4	13.3	-	17	$6.7x10^9$	-	-	-	-
19	2+	2+	20+	130	4.0	5.8	-	16.8	14.2x10	*88	N	-	-
20	2+	1+	20+	124	4.8	45.8	-	16.4	10x10	-	-	-	BENIGN PROSTATIC HYPERTROPHY
21	3+	3+	20+	132	5.8	5.8	-	-	-	-	-	-	-
22	2+	2+	20+	147	3.1	11.6	-	12.0	$24.7x10^9$	*96	-	-	-
23	2+	1+	18	150	5.2	4.2	-	12.0	-	-	X	-	CHEST X-RAY-PULMONARY TUBER-CULOSIS
24	4+	1+	20+	128	5.4	15	-	-	-	-	N	N	-
25	3+	2+	20+	135	4.4	5.8	-	-	-	-	X	-	CHEST X-RAY-PNEUMONIA
26	4+	3+	20+	140	3.0	6.7	-	15.1	$10.5x10^9$	-	-	-	-
27	2+	2+	20+	150	6.4	10.8	-	17.6	$17.5x10^9$	72	-	-	-
28	2+	1+	17	145	5.5	6	-	-	-	-	X	-	CHEST X-RAY-PNEUMONIA
29	3+	2+	20+	145	4.5	5.6	-	-	-	-	-	-	-
30	2+	2+	20+	132	6.0	7.8	-	-	-	-	-	-	-

INDEX TO TABLE 5

- URINE SUGAR AND KETONES EXPRESSED AS +'s ACCORDING TO 'URISTIX' COLOUR READING

- BLOOD SUGAR 20+ mmol/L: BLOOD SUGAR LEVEL ABOVE 20 mmol/L.

- Na^+: SERUM SODIUM LEVEL IN mmol/L

- K^+ : SERUM POTASSIUM LEVEL IN mmol/L

- CHEST X-RAY: X-DONE AND FOUND ABNORMAL
  : N-DONE AND FOUND NORMAL

STUDY OF 30 PATIENTS IN DIABETIC KETOACIDOSIS

TABLE 6: SOME INTRATREATMENT DATA

PATIENT	TIME FOR CONTROL (HOURS)	TOTAL SOLUBLE INSULIN ADMINISTERED IN 1ST 24 HRS (UNITS)	TOTAL FLUIDS REQUIRED (1ST 24 HRS) (mls)	LOWEST BLOOD SUGAR mmol/L	LOWEST SERUM POTASSIUM LEVEL RECORDED mmol/L	OUTCOME ALIVE (A) DEAD (D)
1	8	55	3,000	3	4.0	A
2	14	70	5,000	12	3.6	A
3	16	60	4,000	6.6	4.0	D
4	8	55	4,000	5.0	5.2	A
5	9	60	5,000	3.0	3.0	A
6.	12	65	4,200	3.0	3.9	A
7	12	50	4.500	9.0	5.0	A
8	5	40	6,000	11.5	3.2	A
9	5	40	4,800	3.0	3.0	A
10	18	75	6,500	3.5	4.2	D
11	6	40	5,250	5.6	4.2	A
12	24	85	6,000	5.2	3.8	A
13	6	50	5,200	10	3.2	D
14	13	60	4,200	5.6	4.0	A
15	11	45	5,100	4.3	4.8	A
16	12	40	4,050	11.4	4.7	D
17	13	75	5,500	5.6	4.8	A
18	10	38	3,000	15	5.0	A
19	10	60	5,400	8.8	4.0	A
20	8	60	4,290	7	4.8	A
21	10	55	5,150	12.5	4.2	A
22	24	77	4,500	7.0	3.0	D
23	5	40	4,700	6.0	4.0	A
24	26	145	4,000	6	4.2	A
25	4	30	2,500	4	4.2	A
26	8	55	5,750	7	3.0	A
27	12	130	8,000	9.2	5.4	A
28	5	50	7,000	11	3.7	A
29	8	60	5,200	8.8	3.9	A
30	9	55	5,850	7	4.1	A

STUDY OF DIABETIC KETOACIDOSIS AT KENYATTA NATIONAL HOSPITAL

DATA OF THE FIVE DECEASED PATIENTS

TABLE 7:

PATIENT	SEX	AGE (YRS)	DURATION OF DIABETES	TREATMENT BEFORE ADMISSION	DURATION OF SYMPTOMS DAYS	RESP. RATE /min	PULSE RATE /min	BLOOD PRESSURE mmHg	MENTAL STATE	BLOOD SUGAR mmol/L	Na^+ mmol/L	K^+ mmol/L	LOWEST BLOOD SUGAR	LOWEST K^+	PRECIPITATING FACTOR
1	F	23	NEW	-	1	40	120	130/70	DROWSY	20+	145	6.5	6.6	4.0	DENTAL ABSCESS
2	M	70	NEW	-	?	26	120	140/90	PRECOMA	20+	144	4.2	3.5	4.2	RENAL FAILURE AND CHEST INFECTION
3	F	32	NEW	-	14	30	120	100/60	COMA	20+	140	5.2	10	3.2	ACUTE CHEST INFECTION AND PULMONARY TUBERCULOSIS
4	F	18	½ YR	LENTE INSULIN 48 UNITS PER DAY	7	44	128	150/80	PRECOMA	20+	130	6.2	11.4	4.7	RESPIRATORY INFECTION
5	F	60	7 YRS	DIABINESE 500mg PER DAY	1	26	100	130/80	PRECOMA	20+	147	3.1	7	3.0	INFECTED AMPUTATION SITE (L) BIG TOE

KEY: Na^+ - SERUM SODIUM LEVEL
K^+ - SERUM POTASSIUM LEVEL
\+ - ABOVE 20 mmol/L
RESP. - RESPIRATORY
F - FEMALE
M - MALE

TABLE 8: STUDY OF 30 PATIENTS IN DIABETIC KETOACIDOSIS

PRECIPITATING FACTORS

	PRECIPITATING FACTOR	NO	PERCENTAGE
1	INFECTION	18	60
2	NO INSULIN OR ERRORS	8	26.7
3	MYOCARDIAL INFARCTION	0	0
4	UNKNOWN	4	13.3
TOTAL		30	100

TABLE 9: PATIENTS WITH INFECTION AS A PRECIPITATING FACTOR

TYPES OF INFECTION

	TYPE OF INFECTION	NO	PERCENTAGE
1	RESPIRATORY AND PULMONARY TUBERCULOSIS	12	66.70
2	URINARY	2	11.10
3	OSTEOMYELITIS AND CELLULITIS	3	16.70
4	DENTAL ABSCESS	1	5.60
TOTAL		18	100.0

TABLE 10: SYMPTOMS AT TIME OF PRESENTATION

SYMPTOM	NUMBER	PERCENTAGE OF TOTAL
POLYURIA	30	100%
POLYDIPSIA	30	100%
FATIGUE	30	100%
VOMITING	15	50%
ABDOMINAL PAIN	3	10%
DIARRHOEA	3	10%
COUGH	2	43.3%
DYSURIA	2	6.7%
OTHERS	2	6.7%

TABLE 11: THE STATE OF CONSCIOUSNESS OF THE 30 PATIENTS ON ADMISSION

STATE OF CONSCIOUSNESS	NUMBER	PERCENTAGE
NORMAL (ALERT)	11	36.7
DROWSY	7	23.3
CONFUSED	3	10.0
PRECOMA	6	20.0
COMA	3	10.0

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