# Acute Pancreatitis and Diabetic Ketoacidosis in Accidental Hypothermia and Hypothermic Myxoedema

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## Summary

**Serial serum amylase and blood glucose levels were measured in 68 hypothermic (rectal temperature 35°C or less) patients, including 15 who had hypothermic myxoedema (serum protein bound iodine 3·5 μg/100 ml or less). Raised amylase levels were found in 34 patients and probably reflected a mild acute pancreatitis. The high amylase levels correlated with low arterial $PO_2$ levels and significantly with high arterial $PCO_2$ levels and the base deficit but not with the severity or duration of the hypothermia. The acute pancreatitis does not explain why hypothermic patients with myxoedema have a poorer prognosis than those who are euthyroid. The pancreatitis occasionally contributed to the development, sometimes delayed, of diabetic ketoacidosis, blood glucose levels of over 120 mg/100 ml being found in 20 patients. There was a significant correlation between the raised serum amylase levels and the hyperglycaemia. Hypoglycaemia, sometimes profound, was found in 12 patients.**


## Introduction

Acute pancreatitis occurring after induced hypothermia in patients with cancer was first noted at necropsy (Sano and Smith, 1940; Smith, 1940). More than 80% of patients dying from accidental hypothermia may have gross pancreatic changes varying from the occasional focus of fat necrosis to frank haemorrhagic pancreatitis with fat necrosis of the immediately adjacent tissues. If there have been recurrent episodes of hypothermia chronic pancreatitis may also be found (Emslie-Smith, 1958; Duguid *et al.*, 1961; Read *et al.*, 1961; Prescott *et al.*, 1962; Murphy and Faul, 1963; Mant, 1969). The mechanism of production of these lesions is unclear (Holmes and Emslie-Smith, 1961; Read *et al.*, 1961) though intravascular sludging may play a part (Duguid *et al.*, 1961).

Raised serum amylase levels are commonly found in patients with accidental hypothermia (Duguid *et al.*, 1961; Holmes and Emslie-Smith, 1961; Read *et al.*, 1961; Prescott *et al.*, 1962; Murphy and Faul, 1963; Jones *et al.*, 1966; McKean *et al.*, 1970). Such high levels, usually reverting to normal in about a week (Holmes and Emslie-Smith, 1961; Murphy and Faul, 1963), may be found without the usual clinical manifestations of acute pancreatitis which occur in euthermic patients (Jones *et al.*, 1966).

Hyperglycaemia, too, is common but not invariable in patients with accidental hypothermia (Alexander, 1945; Fruehan, 1960; Duguid *et al.*, 1961; Prescott *et al.*, 1962; Murphy and Faul, 1963), and occasionally exceedingly high blood sugar levels are found (Laufman, 1951; Duguid *et al.*, 1961; Murphy and Faul, 1963). This hyperglycaemia has been attributed to an increased rate of hepatic glycogen breakdown during the initial stages of exposure followed by a decrease in the peripheral utilization of glucose as lower body temperatures are reached (Fruehan, 1960) and to profound stimulation of the suprarenal glands (Laufman, 1951).

Insulin release from the pancreas is inhibited by hypothermia itself (Curry and Curry, 1970; Baum and Porte, 1971) but it is not known whether the acute pancreatitis which is sometimes associated with accidental hypothermia and hypothermic myxoedema contributes further to the hyperglycaemia. None the less, even in uncomplicated diabetic ketoacidosis hypothermia is recognized as a cause of death (Soler *et al.*, 1973).

## Patients and Methods

Two groups of hypothermic (deep rectal temperature 35°C or less) patients were studied—53 euthyroid patients (table I) and 15 patients with serum protein bound iodine (P.B.I.) levels of 3·5 μg/100 ml or less (table II) who were considered to be cases of hypothermic myxoedema (Sprunt *et al.*, 1970). The associated disorders found in these patients and other clinical and biochemical data are shown in tables I, II, and III.

Many of the patients included here were mentioned in previous reports on the current accidental hypothermia study in the Dundee area (Maclean *et al.*, 1968, 1973; Sprunt *et al.*, 1970).

Regardless of the severity of their hypothermia or of their clinical symptoms all the patients were given intensive nursing care and their medical management was supervised by one of us (D.M.). The basic medical management of the hypothermia in both the euthyroid and hypothyroid groups was the same. All the patients were allowed to rewarm spontaneously through their own metabolic processes and without any additional active rewarming aids, each patient being placed in a room at 26·4-32·2°C and insulated against further heat loss by a covering of a sheet or one or two blankets. Oxygen therapy and artificial respiration were confined to a few patients and antibiotics were given only to those with clinical or radiological evidence of infection during or after recovery from their hypothermic episode. Intravenous fluids were not routinely used and the early correction of acid-base and ionic imbalances was undertaken in only a few instances. Steroids were not generally used (Sprunt *et al.*, 1970). Thyroid hormone was not used in the euthyroid patients, but in those with hypothermic myxoedema failure to rewarm at a satisfactory rate over 12 hours was considered a positive indication for its use. Other drugs were not used routinely or generally though intravenous frusemide with or without digoxin was used to treat pulmonary oedema when it was present. In general any treatment given was determined by clinical problems other than the hypothermia. Thus the respective numbers of euthyroid and hypothyroid patients so treated were as follows: no treatment 28, 5; antibiotics 13, 5; hydrocortisone 7, 2; digoxin 3, 1; frusemide 4, 2; potassium supplements 3, 2; artificial respiration 1, 0; oxygen 3, 0; and intravenous fluids, etc., not controlled by central venous pressure measurements—plasma 1, 0; packed cells 1, 0; saline 5, 1; dextrose 7, 1; bicarbonate or lactate 4, 3; and insulin 2, 1.

The biochemical estimations were performed serially in each patient. Serum P.B.I. and urea levels were estimated by standard autoanalyser techniques and the acid-base status was assessed using the Astrup technique. The serum amylase levels were determined by a method involving the degradation of the starch fraction amylose (Street and Close, 1956, 1958) and the values obtained multiplied by 3.1 to convert them to Somogyi units (King, 1965). Blood glucose was assayed by the Auto Analyzer N2B-II methodology.

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TABLE I—*Clinical and Biochemical Data on Hypothermic Euthyroid Patients*

| Case No. | Age & Sex | Rectal Temperature (°C) | Estimated Duration (Hr) | Serum Amylase (Somogyi Units/100 ml) | Blood Glucose (mg/100ml) | Serum P.B.I. (μg/100 ml) | Serum Urea (mg/100ml) | Arterial Blood Gases and Acid-base Status | | | | | Systolic B.P. (mm Hg) | R/D | Pancreatitis at Necropsy | Associated Disorders |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | pH | $P_{CO_2}$ (mm Hg) | $P_{O_2}$ (mm Hg) | $HCO_3$ (mmol/L) | Base Deficit (mmol/L) | | | | |
| 1 | 78 F. | 22·2 | 19 | <60 | 205 | 7·7 | 38 | — | — | — | 23 | — | 90 | D (1)* | — | Cerebral haemorrhage; K 2·8 mmol/l. |
| 2 | 62 M. | 23·0 | 48 | <60 | 93 | 5·3 | 34 | — | — | — | 20 | — | 60 | R | — | None |
| 3 | 81 F. | 25·2 | Unknown | 300 | 336 | 6·1 | 45 | 7·20 | 33 | 92 | 19 | 5 | 80 | D (1) | No | Cerebral haemorrhage |
| 4 | 79 M. | 25·6 | 8 | 450 | 84 | 4·4 | 88 | 7·30 | 42 | 77 | 19 | 6 | 80 | D (3) | — | Stroke |
| 5 | 94 F. | 27·0 | 6 | 277 | 92 | 6·7 | 48 | 7·30 | 60 | 44 | 23 | 1 | 160 | D (28) | — | Epilepsy; stroke (27)* |
| 6 | 84 F. | 27·2 | 24 | 720 | — | 5·7 | 130 | — | — | — | 31 | — | 100 | D (2) | — | Stroke |
| 7 | 88 F. | 27·8 | 24 | 900(4)* | 72 | 5·1 | 134 | 7·17 | 53 | — | 18 | 12 | 100 | D (4) | Yes | Bronchopneumonia |
| 8 | 89 F. | 27·8 | 24 | 415(3) | 140 | 4·7 | 115 | 7·26 | 29 | 95 | 14 | 13 | N.R. | D (2) | — | Bronchopneumonia; K 2·8 mmol/l. |
| 9 | 87 M. | 27·8 | 168 | 129 | 95 | 3·8 | 57 | 7·37 | 35 | 49 | 20 | 5 | 80 | R | — | Erythroderma; congestive cardiac failure |
| 10 | 83 M. | 28·0 | 24 | 165 | 40 | 6·0 | 160 | 7·27 | 35 | 58 | 16 | 12 | N.R. | D (1) | No | Perforated acute duodenal ulcer; K 6·7 mmol/l. |
| 11 | 92 F. | 28·2 | 48 | 525(2) | 118 | 4·5 | 103 | 7·25 | 48 | 94 | 20 | 4 | 130 | R | — | Transient stroke |
| 12 | 86 F. | 28·3 | 12 | 250 | 149 | 3·9 | 10 | — | — | — | 20 | — | 140 | R | — | Congestive cardiac failure; urinary tract infection; senile dementia |
| 13 | 69 M. | 28·3 | 14 | 800 | — | 3·6 | 72 | — | — | — | 14 | — | 130 | D (1) | No | Malnutrition; Hb 3·0 g/100 ml; bronchopneumonia; $H_2O$ depletion |
| 14 | 63 F. | 28·3 | 10 | 96 | — | 6·1 | 54 | — | — | — | 17 | — | 170 | D (1) | No | Cerebral haemorrhage; acute gastric erosions; inhalation pneumonia |
| 15 | 83 F. | 28·3 | 120 | 345(2) | 66 | 6·5 | 77 | 7·33 | 50 | 85 | 24 | 0 | 140 | R | — | Arteriosclerosis; Parkinsonism |
| 16 | 75 F. | 28·4 | 48 | 221(3) | 124 | 6·3 | 66 | 7·40 | 36 | 77 | 22 | 2 | 130 | R | — | Congestive cardiac failure |
| 17 | 80 M. | 28·9 | 48 | <60 | — | 4·0 | 87 | — | — | — | 20 | — | N.R. | D (1) | — | Stroke |
| 18 | 74 F. | 28·9 | Unknown | 173(2) | 78 | 6·3 | 87 | — | — | — | 33 | — | 120 | R | — | Congestive cardiac failure |
| 19 | 57 F. | 29·0 | 12 | 75 | 88 | 4·1 | 23 | 7·35 | 39 | 101 | 21 | 4 | 112 | R | — | Exposure outdoors; ? + ethanol |
| 20 | 81 F. | 29·4 | 168 | 160 | 86 | 7·0 | 96 | — | — | — | 20·5 | — | 90 | D (1) | No | Chronic pyelonephritis; bronchopneumonia; cardiomegaly; Hb 11·2 g/100 ml |
| 21 | 85 F. | 29·4 | 48 | >800 | 160 | 4·8 | 16 | — | — | — | 16 | — | 120 | D (1) | Yes | Bronchopneumonia; pulmonary infarction; cardiomegaly; old myocardial infarction |
| 22 | 71 F. | 29·4 | 192 | 491 | 87 | 5·6 | 27 | 7·36 | 49 | 55 | 31 | +1 | 140 | D (6) | — | Bronchopneumonia; Hb 9·4 g/100 ml |
| 23 | 55 F. | 29·4 | 336 | 1,200 | 600(4)* | 5·9 | 84 | — | — | — | 20 | — | 95 | D (28) | Yes | Chronic alcoholism; fatty liver; purulent bronchitis; cerebral softening; K 3·0 mmol/l. |
| 24 | 79 M. | 29·9 | 48 | 220 | — | 5·9 | 68 | — | — | — | 25 | — | 112 | R | — | Malnutrition; ischaemic heart disease |
| 25 | 73 M. | <30·0 | 24 | 484 | 265 | 3·6 | 144 | — | — | — | 11·5 | — | 90 | R | — | Ethanol intoxication |
| 26 | 91 F. | 30·0 | 24 | 215(4) | — | 10·9 | 101 | — | — | — | 27 | — | 140 | R | — | Bronchopneumonia; treated myxoedema |
| 27 | 75 M. | 30·3 | 72 | 246 | — | 5·6 | 69 | — | — | — | 20 | — | N.R. | R | — | Bronchopneumonia |
| 28 | 85 F. | 30·4 | 24 | 100 | 88 | 5·1 | 81 | 7·36 | 36 | 92 | 21 | 5 | 110 | R | — | Hb 10·2 g/100 ml |
| 29 | 24 M. | 30·6 | 2 | <60 | — | 5·7 | 32 | — | — | — | 21 | — | 110 | R | — | Immersion in cold water |
| 30 | 81 F. | 31·0 | 16 | 2,400 | 210 | 4·2 | 52 | 7·09 | 30 | 35 | 10 | 22 | 100 | R | — | Stroke; bronchopneumonia |
| 31 | 84 M. | 31·1 | 12 | 60 | 59 | 5·0 | 128 | — | — | — | 28 | — | 60 | D (1) | No | Bronchopneumonia; pulmonary oedema; pleural effusions |
| 32 | 72 F. | 31·1 | 14 | <60 | — | 10·4 | 34 | — | — | — | 22 | — | N.R. | D (1) | — | Congestive cardiac failure; stroke |
| 33 | 80 F. | 31·4 | 48 | <60 | <10 | 3·6 | 140 | 7·12 | 21 | 45 | 7 | >25 | 170 | R | — | Congestive cardiac failure; pernicious anaemia; jaundice |
| 34 | 60 F. | 31·7 | 8 | 64 | <10 | 6·8 | 64 | — | — | — | 8 | — | N.R. | D (1) | No | Melanocarcinomatosis; portal vein thrombosis; K 7·4 mmol/l. |
| 35 | 73 F. | 31·7 | 14 | 3,600 | 140 | 4·0 | 35 | — | — | — | 25 | — | 170 | D (3) | No | Cerebral haemorrhage and oedema; pulmonary oedema; K 3·0 mmol/l. |
| 36 | 42 F. | 31·7 | 8 | 69 | — | 5·7 | 19 | 7·06 | 95 | 102 | 27 | 10 | 98 | R | — | Nembutal and Stelazine overdose; K 2·3 mmol/l. |
| 37 | 70 F. | 31·9 | 7 | 136(2) | — | Euthyroid† | 46 | — | — | — | 24 | — | 80 | D (2) | — | Subdural haematoma; severe cerebral injury; Hb 11·9 g/100 ml; K 2·9 mmol/l. |
| 38 | 81 F. | 32·0 | 6 | 105 | 133 | 4·8 | 102 | 7·37 | 34 | 69 | 20 | 5 | 115 | D (6) | — | Congestive cardiac failure (ischaemia) |
| 39 | 75 F. | 32·0 | 24 | 156 | 202 | 7·9 | 47 | — | — | — | 19 | — | 180 | D (1) | — | Emaciation; cerebral haemorrhage |
| 40 | 84 F. | 32·0 | 4 | <60 | 140 | 7·5 | 55 | — | — | — | 27 | — | 100 | R | — | Arteriosclerotic dementia |
| 41 | 82 F. | 32·0 | 12 | 900 | 105 | 5·8 | 54 | 7·29 | 53 | 88 | 21 | 3 | 120 | R | — | None |
| 42 | 89 M. | 32·2 | 72 | 225 | 85 | 5·0 | 198 | 7·30 | 30 | 125 | 17 | 10 | 130 | R | — | None |
| 43 | 91 F. | 32·8 | Unknown | 82 | 118 | 4·2 | 116 | — | — | — | 17 | — | 100 | R | — | Hb 8·1 g/100 ml; Fe deficiency; treated pernicious anaemia |
| 44 | 23 M. | 32·8 | 8 | 148 | — | 5·4 | 23 | — | — | — | 19 | — | 125 | R | — | Chlorpromazine overdose |
| 45 | 83 M. | 33·0 | 12 | <60 | 40 | 5·0 | 124 | — | — | — | 16 | — | 130 | D (1) | No | Rectal carcinoma |
| 46 | 71 F. | 33·1 | 18 | 1,285 | 670 | 4·3 | 98 | — | — | — | 7 | — | 60 | R | — | Diabetes mellitus (on chlorpropamide); bronchopneumonia; dysproteinaemia |
| 47 | 97 F. | 33·3 | 240 | 305(2) | 171 | 6·2 | 217 | — | — | — | 22 | — | 85 | R | — | Malnutrition |
| 48 | 70 M. | 33·3 | 6 | 860 | 149 | >16·0‡ | 217 | 6·85 | 41 | 55 | <5 | >22 | 70 | D (1) | — | Urinary tract infection; pulmonary oedema |
| 49 | 76 F. | 33·3 | 24 | 113 | 112 | 8·3 | 52 | 7·35 | 43 | 78 | 22 | 3 | 125 | D (21) | — | Subarachnoid haemorrhage |
| 50 | 28 F. | 34·1 | 3 | 391(2) | 102 | 6·9 | 28 | 7·35 | 39 | 42 | 21 | 4 | 130 | R | — | Amitriptyline overdose; K 3 mmol/l. |
| 51 | 63 F. | 34·9 | 12 | >600 | — | 4·0 | 133 | 6·99 | 38 | 22 | 11 | 23 | N.R. | D (1) | No | Mitral valve disease; pulmonary oedema; small-bowel infarction (embolic); Hb 20·6 g/100 ml; W.B.C. 27,600/mm³ |
| 52 | 88 F. | 34·9 | 6 | 92 | 13 | 5·4 | 61 | — | — | — | 34 | — | 130 | R | — | Diabetes (excess insulin); Hb 11·5 g/100 ml; K 7·9 mmol/l. |
| 53 | 73 F. | 35·0 | Unknown | 287 | 172 | 6·3 | 34 | — | — | — | 17 | — | 95 | D (1) | — | Recent myocardial infarction |
| Mean ± 1 S.D. | M. + F. | 75 ± 16 | 44 ± 67 | 417 ± 611 | 143 ± 132 | 5·6 ± 1·6 | 80 ± 50 | 7·25 ± 0·14 | 42 ± 15 | 72 ± 26 | 20 ±6 | 9 ±8 | 98 ± 48 | — | — | |
| | M. | 71 ± 20 | 38 ± 43 | 268 ± 264 | 101 ± 70 | 4·9 ± 0·9 | 100 ± 60 | 7·22 ± 0·21 | 37 ± 5 | 73 ± 31 | 17 ±7 | 11 ±7 | 78 ± 48 | — | — | |
| | F. | 76 ± 14 | 47 ± 76 | 476 ± 697 | 155 ± 144 | 5·9 ± 1·7 | 72 ± 44 | 7·26 ± 0·12 | 44 ± 16 | 72 ± 26 | 21 ±7 | 8 ±8 | 106 ± 46 | — | — | |

* Figures in parentheses refer to days after admission or day of test.
† P.B.I. not estimated because of recent carotid angiogram.
‡ Falsely high P.B.I. (recent I.V.P. elsewhere), excluded from mean.
N.R. = Not recordable, taken as zero.
R/D = Recovered/died.

## Results

Of the 53 euthyroid hypothermic patients 28 had serum amylase levels above the normal range—that is, over 200 Somogyi units/100 ml—but in only 11 did the values exceed 550 Somogyi units/100 ml and suggest the diagnosis of acute pancreatitis (Wilkinson, 1962). Six patients with hypothermic myxoedema had raised amylase levels and two of these had levels compatible with acute pancreatitis. No patient with serum amylase values compatible with a diagnosis of acute pancreatitis had signs of an "acute abdomen." In each group the mean amylase level was higher for women than for men, but this difference was not significant. The mean amylase level in the euthyroid group was greater than that for the patients with hypothermic myxoedema, but this difference was not significant.

In all 68 patients the peak recorded serum amylase levels correlated with low $P_{O_2}$ ($P < 0{\cdot}10$) and high $P_{CO_2}$ ($P < 0{\cdot}001$) levels and with the base deficit in the arterial blood ($P < 0{\cdot}05$). No significant correlation emerged between the peak serum amylase levels and the patient's age or rectal temperature or the estimated duration of the hypothermia before the patient's admission to hospital. Similarly there was no significant correlation between the serum amylase levels and the serum P.B.I., serum urea, arterial blood pH or bicarbonate levels, or systolic blood pressure.

The mean amylase value (± 1 S.D.) in the patients dying

TABLE II—*Clinical and Biochemical Data on Hypothermic Hypothyroid Patients*

| Case No. | Age & Sex | Rectal Temperature (°C) | Estimated Duration (Hr) | Serum Amylase (Somogyi Units/100 ml) | Blood Glucose (mg/100ml) | Serum P.B.I. (μg/100 ml) | Serum Urea (mg/100ml) | Arterial Blood Gases and Acid-base Status | | | | | Systolic B.P. (mm Hg) | R/D | Pancreatitis at Necropsy | Associated Disorders |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | pH | $Pco_2$ (mm Hg) | $Po_2$ (mm Hg) | $HCO_3$ (mmol/l.) | Base Deficit (mmol/l.) | | | | |
| 54 | 71 F. | 26·7 | 8 | 261 | — | <2·0 | 278 | — | — | — | 5 | — | 150 | D (1)* | No | Chronic lymphatic leukaemia; hydronephrosis; bronchopneumonia; Hb 10·2 g/100 ml |
| 55 | 89 M. | 28·3 | 12 | 160 | 90 | 3·2 | 251 | — | — | — | 6 | — | 90 | D (1) | No | Malnutrition; Hb 6·3 g/100 ml; lobar pneumonia; chronic glomerulonephritis; $H_2O$ depletion |
| 56 | 89 M. | 28·9 | 16 | <60 | — | <2·0 | 56 | — | — | — | 32 | — | 85 | D (7) | — | Congestive cardiac failure; Hb 10·7 g/100 ml; pancytopenia |
| 57 | 87 F. | 29·4 | 12 | 1,100(2)* | — | 2·8 | 40 | — | — | — | 4 | — | N.R. | D (1) | — | Treated pernicious anaemia |
| 58 | 79 M. | 29·4 | Unknown | 450 | 880 | 2·6 | 134 | — | — | — | 10 | — | 70 | D (1) | No | Treated congestive cardiac failure; $H_2O$ depletion |
| 59 | 63 F. | <30·0 | 168 | 164 | 110 | 2·8 | 52 | — | — | — | 28 | — | 95 | D (7) | No | Myxoedema |
| 60 | 80 F. | 30·0 | 336 | 360(3) | 142 | 1·2 | 54 | — | — | — | 24 | — | 110 | R | — | Treated pernicious anaemia K 2·8 mmol/l. |
| 61 | 73 M. | 30·0 | Unknown | 100 | 118 | 2·8 | 283 | — | — | — | 7 | — | 120 | R | — | Congestive cardiac failure; Hb 11·8 g/100 ml; progressive renal failure; K 7·4 mmol/l. |
| 62 | 67 F. | 31·1 | Unknown | 180 | <20 | 2·7 | 96 | — | — | — | 19 | — | N.R. | D (1) | No | Carcinomatosis (renal primary); bronchopneumonia; K 6·5 mmol/l. |
| 63 | 69 M. | 31·1 | 24 | 75 | 134 | 3·5 | 61 | 7·15 | 46 | 103 | 14 | 17 | 110 | R | — | Cerebrovascular disease; ? + ethanol, ? + CO poisoning |
| 64 | 71 F. | 32·0 | 12 | 184 | 142 | 2·8 | 174 | 7·22 | 25 | 28 | 11 | 17 | 95 | D (1) | No | Recent myocardial infarction; pulmonary embolus + oedema; fatty kidneys; dementia; Hb 10·3 g/100 ml; K 8·0 mmol/l. |
| 65 | 72 M. | 32·2 | 72 | 600 | 75 | 3·5 | 120 | 7·22 | 20 | 80 | 12 | 19 | 100 | D (5) | — | Thrombocytopenia; progressive abdominal distension ? cause; K 2·7 mmol/l. |
| 66 | 80 M. | 33·0 | 18 | <60 | — | 2·7 | 305 | — | — | — | <5 | — | 100 | D (1) | No | Chronic alcoholism, cirrhosis; acute myocardial infarction + fibrosis; pulmonary oedema; pulmonary infarction; pleural effusions; cerebral softening; K 7·2 mmol/l. |
| 67 | 78 F. | 33·3 | 48 | 129(2) | 70 | <2·0 | 104 | 7·35 | 44 | 46 | 23 | 2 | 100 | D (7) | Yes | Acute parotitis; congestive cardiac failure; pulmonary oedema; bronchopneumonia; cerebral softening; bilateral adrenal medullary haemorrhages |
| 68 | 73 F. | 35·0 | 240 | 244(5) | 105 | <2·0 | 72 | — | — | — | 24 | — | 140 | R | — | Congestive cardiac failure; paranoid state; Hb 5·4 g/100 ml (? Fe deficiency) |
| Mean ± 1 S.D. M. + F. | | 76 ± 8 | 81 ± 109 | 275 ± 274 | 171 ± 238 | 2·6 ± 0·6 | 139 ± 95 | 7·24 ± 0·08 | 34 ± 13 | 64 ± 34 | 15 ± 9 | 14 ± 8 | 91 ± 42 | — | — | |
| M. | | 79 ± 8 | 28 ± 25 | 215 ± 219 | 259 ± 348 | 2·9 ± 0·5 | 173 ± 105 | 7·19 ± 0·05 | 33 ± 18 | 92 ± 16 | 12 ± 9 | 18 ± 1 | 96 ± 17 | — | — | |
| F. | | 74 ± 8 | 118 ± 132 | 328 ± 320 | 98 ± 47 | 2·3 ± 0·6 | 109 ± 81 | 7·29 ± 0·09 | 35 ± 13 | 37 ± 13 | 17 ± 9 | 10 ± 11 | 86 ± 57 | — | — | |

*Figures in parentheses refer to days after admission or day of test.
N.R. = Not recordable, taken as zero.
R/D = Recovered/died.

TABLE III—*Mean Clinical and Biochemical Values (±1SD) for whole Series*

| | Age | Rectal Temperature (°C) | Estimated Duration (Hr) | Serum Amylase (Somogyi Units/100 ml) | Blood Glucose (mg/100ml) | Serum P.B.I. (μg/100 ml) | Serum Urea (mg/100ml) | Arterial Blood Gases and Acid-base Status | | | | | Systolic B.P. (mm Hg) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | pH | $PCO_2$ (mm Hg) | $PO_2$ (mm Hg) | $HCO_3$ (mmol/l.) | Base Deficit (mmol/l.) | |
| M. + F. | 75 ± 15 | 30·3 ± 2·7 | 51 ± 77 | 386 ± 556 | 149 ± 158 | 4·9 ± 1·9 | 93 ± 67 | 7·25 ± 0·13 | 41 ± 15 | 71 ± 27 | 19 ± 7 | 9 ± 8 | 97 ± 47 |
| M. | 73 ± 18 | 29·9 ± 2·5 | 35 ± 39 | 252 ± 247 | 158 ± 215 | 4·2 ± 1·2 | 123 ± 82 | 7·21 ± 0·17 | 36 ± 9 | 78 ± 28 | 16 ± 7 | 13 ± 7 | 84 ± 41 |
| F. | 76 ± 13 | 30·5 ± 2·7 | 59 ± 90 | 450 ± 647 | 147 ± 134 | 5·3 ± 2·1 | 78 ± 53 | 7·26 ± 0·12 | 43 ± 16 | 68 ± 27 | 20 ± 7 | 8 ± 8 | 103 ± 48 |

within the first week of admission to hospital (422 ± 627) was greater than in those who survived this period (348 ± 477), but this difference was not significant.

The blood glucose level, determined in 51 patients, was raised (greater than 120 mg/100 ml) in 16 of the 40 patients who were euthyroid and 4 of the 11 with myxoedema. There was a significant correlation between the serum amylase and blood glucose levels ($P < 0.001$) but not between the blood glucose levels and the patients' temperatures. Low blood sugar levels (less than 80 mg/100 ml) were found in 12 patients, including three with myxoedema.

Only patients with blood glucose levels either in excess of 250 mg/100 ml or of 40 mg/100 ml or less were considered for treatment of this aspect of their illness. One patient (case 25; blood glucose 265 mg/100 ml) received intravenous saline but no insulin and recovered without further manifest glucose intolerance. In case 3 (blood glucose 336 mg/100 ml) the patient had sustained a massive intracerebral haemorrhage and so was not treated. In case 23 the patient was found to have a blood glucose of 600 mg/100 ml with ketoacidosis on the fourth day after admission to hospital and after becoming euthermic. She required insulin until her death four weeks later. A known diabetic previously treated with chlorpropamide (case 46) had a blood glucose level of 670 mg/100 ml and required 300 units of soluble insulin during the 24 hours before she became euthermic and her diabetic ketoacidosis was corrected; her insulin requirements remained high. She also received intravenous saline, potassium, and alkali while hypothermic. In case 58 the patient was given 100 units of soluble insulin and intragastric normal saline but died from acute severe pulmonary oedema before his diabetic ketoacidosis was corrected. Half of each dose of soluble insulin was always given intravenously and half by deep intramuscular injection.

Of the six patients with severe hypoglycaemia three (cases 34, 45, and 62) had malignant disease and so were not given glucose. One patient (case 52; blood glucose 13 mg/100 ml) was given 20 ml of 20% glucose solution intravenously and recovered. A further patient (case 10; blood glucose 40 mg/100 ml) died despite receiving the same treatment but at necropsy he was found to have peritonitis secondary to perforation of an acute duodenal ulcer. In case 33, despite a blood glucose level of less than 10 mg/100 ml, the patient was given 16 units of soluble insulin intravenously as part of her emergency treatment for hyperkalaemia, but she was simultaneously given 20 ml of 25% glucose solution intravenously and regular glucose drinks thereafter. She survived for almost a week.

## Discussion

In euthermic patients serum amylase levels greater than 550 Somogyi units/100 ml strongly support a diagnosis of acute pancreatitis, and levels of greater than 2,000 Somogyi units/100 ml are sometimes reached within 24 hours of its onset. In

most patients the level returns to normal within 48-72 hours but occasionally high values persist for a week. Serum amylase values of 800-2,000 Somogyi units/100 ml may also occur transiently when secondary pancreatic damage results from acute disturbances of adjacent organs, such as perforated gastric or duodenal ulcers, gastric operations, small-intestinal strangulation or obstruction, stones in the common bile duct or morphine-induced spasm of the sphincter of Oddi, empyema of the gall bladder, and dissection of the wall of the abdominal aorta (Wilkinson, 1962).

In the absence of pancreatic disease bacterial and mumps parotitis commonly lead to serum amylase values of up to 900 Somogyi units/100 ml but their clinical recognition is easy. Serum levels of up to 1,600 Somogyi units/100 ml have occasionally been associated with blood urea levels of 500-600 mg/100 ml, but one large study of uraemic patients failed to show any significantly raised serum amylase levels (Wilkinson, 1962). Part of the serum content of amylase is probably derived from tissues such as the liver, striated muscle, and the Fallopian tubes, since the experimental removal of the pancreas and salivary glands in animals fails to alter significantly the normal serum level of the enzyme (Wilkinson, 1962).

The raised serum amylase levels found in our patients with accidental hypothermia and hypothermic myxoedema probably mostly reflected a mild degree of acute pancreatitis, though clearly this may not have been the whole explanation. One patient, for example, had acute necrotizing parotitis, but this complication was probably one facet of her general debilitated state rather than a specific effect of hypothermia. A number of patients had other upper gastointestinal tract lesions capable of causing secondary acute pancreatitis. Our findings confirm that impaired renal function, which was common, plays no part in the raised serum amylase levels found. It is possible that other tissues such as striated muscle may release amylase into the serum during hypothermia, since earlier work has shown large increases in the serum levels of the muscle enzymes creatine kinase, "α-hydroxybutyrate dehydrogenase," and aspartate aminotransferase (Maclean *et al.*, 1968). The liver is unlikely to be a major source of the amylase since alanine aminotransferase levels are only minimally raised in patients with accidental hypothermia and hypothermic myxoedema (Maclean *et al.*, 1968).

The necropsy rate in this series was low and raised serum amylase levels were not always associated with the finding of acute pancreatitis at necropsy—for example, cases 13 and 58. This finding has been noted previously (Duguid *et al.*, 1961). When present at necropsy the pancreatitis ranged from being mild with focal areas of haemorrhagic destruction of the gland, with or without fat necrosis in the adjacent tissues, to widespread destruction of the gland with abscess formation, as in case 23.

The mechanism behind these findings is unknown and many factors may contribute to them. The pancreatic damage does not appear to represent a direct cold injury to the gland. When the series as a whole was divided into the three generally accepted levels of severity of hypothermia—32·2°C and above (16 patients), 32.1-26·7°C (48 patients), and 26·6°C and below (4 patients)—there appeared to be no correlation with the mean (± 1 S.D.) amylase levels—343 ± 341, 414 ± 630, and 218 ± 192 Somogyi units/100 ml respectively. This is confirmed by our finding no significant correlation between the amylase levels and either the patient's lowest recorded rectal temperature or the estimated duration of the hypothermia.

Arterial hypoxia, hypercapnia, and a base deficit do correlate with the raised amylase levels but the precise explanation is conjectural. One critical point at issue is whether or not during hypothermia the tissues receive enough oxygen to meet their demand (Cooper and Ross, 1960). In both animals and man, during cooling to 15°C the oxyhaemoglobin dissociation curve moves so far to the left that at normal arterial blood and tissue oxygen and carbon dioxide tensions haemoglobin binds its oxygen so tenaciously that this oxygen may be unable to meet tissue oxygen demands (Brown and Hill, 1923; Lange *et al.*, 1949; Penrod, 1951; Cooper and Ross, 1960; Callaghan *et al.*, 1961; Keatinge, 1969). Under these circumstances haemoglobin may give up its oxygen only when exposed to a $Po_2$ considerably less than normal (Cooper and Ross, 1960), and the oxygen in physical solution in the plasma may then become of increasing importance as a source of tissue oxygen (Callaghan *et al.*, 1961). Cooper and Ross (1960) believe that estimated tissue $Po_2$ levels during hypothermia are probably low enough to allow the tissues to extract sufficient oxygen from the oxyhaemoglobin despite the extreme shift to the left in the oxyhaemoglobin dissociation curve.

The dissociation of oxyhaemoglobin may be encouraged by a rise in arterial $Pco_2$ levels, since this shifts the oxyhaemoglobin dissociation curve to the right and also flattens its shape, thus opposing the effects of hypothermia (Lange *et al.*, 1949; Callaghan *et al.*, 1961). This makes less attractive the hypothesis that tissue hypoxia has an important role. Moreover, though there may be an initial rise during the early stages of hypothermia (Adolph, 1950) tissue oxygen consumption generally falls progressively and in proportion to the fall in body temperature (Fuhrman and Crismon, 1947; Adolph, 1950, 1956; Horvath *et al.*, 1953; Edwards *et al.*, 1954; Lougheed *et al.*, 1955; Stone *et al.*, 1956; Cooper and Ross, 1960) in all metabolizing cells except possibly the liver (Fuhrman and Crismon, 1947). In man, for example, oxygen consumption falls by about 26% over the temperature range 34-30°C (Michenfelder *et al.*, 1965). There is no evidence that essential oxidative enzyme processes, which are responsible for energy metabolism in the cells, are inactivated during hypothermia (Adolph, 1956; Cooper and Ross, 1960; Keatinge, 1969).

The raised arterial $Pco_2$ levels and the base deficits might contribute to pancreatic cell injury through the common mechanism of acidosis, but there was no significant correlation between the serum amylase and the arterial blood pH levels.

Duguid *et al.* (1961) suggested that intravascular sludging might play a part in the causation of the lesions found in hypothermic patients, but we found no correlation between high serum amylase levels and a low systolic blood pressure. Other work on this problem is currently being undertaken and the evidence so far suggests that intravascular sludging may not be a major contributory factor.

Several practical aspects deserve to be emphasized. Acute pancreatitis is common in patients with accidental hypothermia and hypothermic myxoedema. It is usually mild but even when severe it is not accompanied by signs of an acute intra-abdominal emergency and does not directly affect the patient's chances of survival. Those patients dying within one week of their admission to hospital had a mean amylase value (± 1 S.D.) of 422 ± 627 Somogyi units/100 ml, whereas those surviving beyond this time had a mean value of 348 ± 477 Somogyi units/100 ml; this difference is not significant. Likewise, those patients with hypothermic myxoedema did not have a more severe form of acute pancreatitis, so that the pancreatitis does not contribute to the poorer prognosis in these cases.

The significant correlation between the serum amylase and blood glucose levels was the most important finding, since four patients had diabetic ketoacidosis on admission and in another its recognition was delayed for several days after that of the raised amylase level. The pancreatic damage presumably augments further the drop in insulin production which occurs as a direct result of the hypothermia, and the cold also decreases its effectiveness (Cooper and Ross, 1960). At body temperatures of 31-21°C even very large doses of insulin may have little effect on reducing high blood glucose levels (Wynn, 1956; Cooper and Ross, 1960). When a hypothermic patient with hyperglycaemia suffers from diabetes mellitus, therefore, some workers consider it advisable to raise the body temperature rapidly to 31-32°C before giving insulin (Cooper, 1968). Where appropriate this complication merits treatment in its own right. In one of our patients, a chlorpropamide-controlled diabetic, high doses of

soluble insulin were required to control her diabetic ketoacidosis.

When the hypothermic patient with hyperglycaemia does not have diabetes mellitus insulin may not be required, as normoglycaemia is spontaneously restored during or soon after rewarming (Prescott *et al.*, 1962), as occurred in case 25. Our experience suggests that most euthyroid and some hypothyroid hypothermic patients rewarm spontaneously at satisfactory rates (Maclean *et al.*, 1973), so that when insulin is given to hypothermic patients the start of this therapy can be delayed until the body temperature is above 32°C. After this care should be taken not to give unnecessarily high doses, and the blood sugar should be monitored regularly to detect any tendency toward the development of hypoglycaemia during or soon after rewarming as the effectiveness of the administered insulin increases.

Though even grossly raised serum amylase levels may not in themselves be associated with increased mortality or morbidity (Knight *et al.*, 1973) all patients with accidental hypothermia and hypothermic myxoedema should have their serum amylase and blood glucose levels measured soon after admission to hospital. Not only will this indicate diabetic ketoacidosis when it is present but raised amylase levels will identify patients likely to develop diabetic ketoacidosis in the ensuing few days. Unsuspected hypoglycaemia, with its signs masked by the hypothermic state (Duckworth and Cooper, 1964; Hockaday and Fell, 1969), will also be detected. Its correction may contribute to the patient's recovery (Roe, 1963; Jones *et al.*, 1966) and sometimes leads to the immediate restoration of consciousness (Whittaker and Whitehead, 1954; Murphy and Faul, 1963; Duckworth and Cooper, 1964). Arterial blood gas estimations may further help to identify the hypothermic patient at risk of developing pancreatitis.

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