Myocardial infarction and peripheral gangrene also occurred. The disturbance of consciousness is related to the degree of hypothermia.

At temperatures between 90 and 95° F. (32.2 and 35° C.), if death occurred, the cause appeared to be the primary disease and not the hypothermia. The prognosis at temperatures below 90° F. (32.2° C.) was poor, and out of the 32 patients only four recovered completely. Four others, after an initial recovery, died later. High doses of intravenous hydrocortisone are recommended, particularly when consciousness is impaired.

In 11 of the patients *in vitro* tests of thyroid function were carried out. The red-cell uptake of $^{131}I$ triiodothyronine was in the hyperthyroid range in nine cases, but the serum P.B.I. was abnormally low in three of them. It is suggested that high results in the red-cell-uptake test may occur in accidental hypothermia because of the associated respiratory acidosis or metabolic acidosis. Antibiotics may also interfere with the tests. Several tests of thyroid function should be employed because various factors in hypothermia may interfere with individual tests.

We are grateful to our colleagues who referred to us some of the cases in this series, and we wish to thank Miss M. F. Crowley, of the Group Pathological Laboratory, for carrying out the biochemical investigations, and Miss H. Farran and Mrs. D. Richardson, of New End Hospital, for the tests of thyroid function.

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# Accidental Hypothermia

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The very cold weather of early 1963 caused 15 patients to be admitted to the Central Middlesex Hospital with accidental hypothermia. This paper describes the clinical and laboratory findings. We made a special study of the respiratory function and acid–base balance.

## Cases

### Clinical Aspects

The main clinical features are shown in Table I. The ages of the patients ranged from 55 to 90 years. Most of them lived alone in unheated rooms, but some appeared to have adequate heating. The history was almost always one of progressive confusion; slurring of speech, ataxia, and involuntary movements were common. These were followed by drowsiness and unconsciousness. The history was usually short, the patient passing into coma within three days, but in a few there had been progressive deterioration over a period longer than a week.

The clinical picture was constant and diagnostic. Shivering had stopped, the skin was icy cold to touch, and there was generalized muscular stiffness. The pulse rate was slow, and the blood-pressure tended to be low. Reflexes were depressed.

The diagnosis was easily confirmed with a low-reading thermometer and no special investigations were required. Difficulty arose only when an ordinary clinical thermometer was used. On clinical grounds it was not difficult to exclude the obvious causes of hypothermia, such as endocrine disease or overwhelming infection, but investigations did show several of its recognized complications: pancreatitis in Case 6 (Read

* From the Central Middlesex Hospital, Park Royal, London.

TABLE I

| Case No. | Age | Sex | History of Illness | Temperature °C. | Temperature °F. | Pulse | B.P. | Treatment | Result | Post-mortem Examination |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 87 | M | Found unconscious | 28 | 82 | 52 | 110/80 | Warming, penicillin | Recovery | — |
| 2 | 68 | F | Progressive confusion, 3 days | 25 | 77 | 28 | 0 | Warming, penicillin, hydrocortisone | Oliguria. Died after 2 days | Bronchopneumonia |
| 3 | 78 | M | Oedema, slurred speech, coma—10 days | 28 | 82 | 60 | 90/0 | Warming | Died after 2 hours | Myocardial fibrosis, coronary atheroma, acute bronchitis |
| 4 | 73 | M | Progressive confusion | 28 | 82 | 40 | 100/60 | Temperature remained at 28° C. Hydrocortisone | Blood urea 48. Died after 20 hours | Bronchopneumonia |
| 5 | 81 | F | Drowsy for 3 weeks. Not speaking, confused, 3 days | 28 | 82 | 40 | 70/50 | Warming, hydrocortisone, "aramine," penicillin | Blood urea 90. Died after 4 days | Bronchopneumonia, aortic aneurysm |
| 6 | 80 | M | Involuntary movement for 2 days. Unable to walk | 26 | 79 | 48 | 110/70 | Warming, hydrocortisone, aramine, penicillin | Blood urea 75. Died after 24 hours | Patchy consolidation |
| 7 | 55 | F | Dizzy and confused for a few days | 28 | 82 | 60 | 110/80 | Warming, hydrocortisone, aramine | Oliguria. Died after 12 days from uraemia | Bronchopneumonia, acute pancreatitis, chronic pyelonephritis |
| 8 | 69 | F | Found unconscious | 29 | 84 | 70 | 130/80 | Warming | Blood urea 100. Died after 9 hours | Bronchopneumonia |
| 9 | 79 | F | Progressive stupor 2 days | 29 | 84 | 40 | 150/90 | Warming, penicillin | Oliguria. Died after 4 days | ,, |
| 10 | 87 | F | Confusion 3 days | 29 | 84 | 58 | 190/80 | ,, ,, | Died after 12 hours | Bronchopneumonia, pericarditis |
| 11 | 90 | M | Shortness of breath 3 weeks | 32 | 89 | 80 | 90/50 | Warming, penicillin, prednisolone | Partial recovery; died after 15 days | Acute bronchitis, myocardial infarction |
| 12 | 63 | F | Progressive confusion | 32 | 89 | 80 | 180/110 | Warming, penicillin | Recovery | — |
| 13 | 86 | M | Pain in chest 2 days | 31 | 88 | 46 | 200/100 | ,, ,, | Blood urea 75. Recovery | — |
| 14 | 85 | M | Unable to speak 1 day | 28 | 82 | 60 | 80/60 | Warming | Died after 12 hours | Bronchopneumonia |
| 15 | 67 | F | Progressive stupor 5 days | 30 | 86 | 60 | — | Burr-holes | Died after 4 hours | Left ventricular failure |

*et al.*, 1961); renal failure in Case 7 (Prescott *et al.*, 1962); J waves on the electrocardiogram in Case 6 (Emslie-Smith, 1958).

## Treatment

The patients were put to bed in the ward, covered lightly, and allowed to reach normal temperature slowly without any active warming. The temperature usually rose steadily; if it did not the prognosis was very bad. Parenteral penicillin was given in an attempt to prevent secondary infection. Secretions were drained from the respiratory tract by posture, and, if possible, by encouraging coughing. If the systolic blood-pressure fell below 90 mm. Hg hydrocortisone and pressor amines were given; no immediate difficulty was experienced in restoring the blood-pressure to normal levels. In Case 15 it was thought that a subdural haematoma might be present, and exploratory burr-holes were therefore made.

The mortality was very high. Of the 15 patients only three survived, and one of the survivors died a week after discharge from hospital. "Bronchopneumonia" was an invariable finding at necropsy.

## Comment

Accidental hypothermia is probably not a new disease, but only in recent years have its clinical features been widely recognized (Duguid *et al.*, 1961). Provided that hypothermia is thought of, the diagnosis is not difficult to make, for the clinical picture is striking. The ordinary clinical thermometer is a dangerous instrument as it cannot read below 95° F. (35° C.) and so makes it impossible to diagnose hypothermia.

As the present series shows, treatment is unsatisfactory, and most of the patients die. Circulatory impairment and its complications are probably important. Impaired renal function, presumably secondary to impaired renal circulation, was common; urine output of less than 500 ml./24 hours was recorded in three patients, and when measured the blood urea was always found to be raised. However, even in Case 7, where the patient died of progressive renal failure, it is not possible to show clearly that circulatory impairment was responsible for death.

It has been known for some time that induced hypothermia is complicated by respiratory depression and metabolic acidosis (Brewin *et al.*, 1955). Nordqvist *et al.* (1960) reported respiratory depression in hypothyroid coma, though in their cases lowering of temperature was slight. The results of our studies, presented in the following section, seem to confirm the importance of respiratory changes.

## Respiratory Function and Acid-base Balance

### Methods

Arterial blood was obtained by percutaneous puncture of the brachial or femoral arteries in eight patients; all samples were analysed within five minutes. Oxygen saturation was determined with a Brinkman haemoreflector, *p*H with an Astrup micro-electrode, and $P_{CO_2}$ with a Severinghaus $CO_2$ electrode. *p*H and $P_{CO_2}$ were measured at an electrode temperature of 38° C. under strict anaerobic conditions. Table II shows the results. Correction for the effects of lowered body temperature is necessary for both *p*H and $P_{CO_2}$. The factor of Rosenthal (1948) was used for *p*H, and that of Bradley *et al.* (1956) for $P_{CO_2}$. The plasma total carbon-dioxide content was calculated from the measured values of *p*H and $P_{CO_2}$ by use of the Henderson-Hasselbach equation. Oxygen saturations were converted into oxygen partial pressures, taking into account both temperature and *p*H by use of the factors described by Severinghaus (1958). These calculated and corrected values are shown in Table III. The variations in temperature were great, but the corrected values can be regarded as good approximations.

TABLE II.—*Arterial Blood—Measured Values at 38° C.*

| Case No. | Temperature (°C.) | Saturation ($O_2$%) | *p*H | $P_{CO_2}$ (mm. Hg) |
|---|---|---|---|---|
| 2 | 25 | 94 | 7·35 | 43 |
| 4 | 29 | 96 | 7·35 | 47 |
| 5 | 28 | 92 | 7·29 | 59 |
| | 37 | 94 | 7·39 | 37 |
| 8 | 29 | 20 | 7·25 | 98 |
| 10 | 29 | 39 | 7·23 | 78 |
| 13 | 31 | 91 | 7·36 | 42 |
| 14 | 30 | 65 | 7·19 | 55 |
| 15 | 30 | 67 | 7·33 | 49 |

TABLE III.—*Arterial Blood—Values Corrected to Patient's Temperature*

| Case No. | Temperature (°C.) | Saturation ($O_2$ %) | $P_{O_2}$ (mm. Hg) | *p*H | $P_{CO_2}$ (mm. Hg) | $T_{CO_2}$ (mEq/l.) |
|---|---|---|---|---|---|---|
| 2 | 25 | 94 | 38 | 7·54 | 26 | 24 |
| 4 | 29 | 96 | 53 | 7·50 | 33 | 27 |
| 5 | 28 | 92 | 45 | 7·43 | 41 | 29 |
| | 37 | 94 | 74 | 7·39 | 37 | 23 |
| 8 | 29 | 20 | 9 | 7·39 | 70 | 45 |
| 10 | 29 | 39 | 16 | 7·37 | 57 | 34 |
| 13 | 31 | 91 | 46 | 7·46 | 33 | 26 |
| 14 | 30 | 65 | 28 | 7·31 | 41 | 22 |
| 15 | 30 | 67 | 25 | 7·45 | 35 | 27 |

## Results

### Oxygen

Oxygen saturations showed a wide variation from the normal to the grossly desaturated. In all of the patients, even when the saturation was normal, the *arterial* oxygen tensions were low. With fall in temperature the dissociation curve of haemoglobin is shifted to the left, so that the same percentage saturation is associated with a lower oxygen tension—for example, Case 2—saturation 94%, $P_{O_2}$ 38 mm. Hg. Information on the "normal" arterial oxygen tension during spontaneous hypothermia is not available, but it is possible to say with confidence that these results are abnormal, for in all of these patients there is a very large gradient between the arterial oxygen tension and the *alveolar* oxygen tension (Table IV). In Cases 2, 4, 13, and 15 the alveolar oxygen tension was normal (above 100 mm. Hg) and in Cases 5 and 14 it was between 90 and 100 mm. Hg. Lowering of the alveolar oxygen tension as a result of underventilation from respiratory depression played some part in lowering the arterial oxygen tension in Cases 8 and 10 (alveolar oxygen tensions 55 and 73 mm. Hg respectively). The increase in alveolar-arterial oxygen tension gradient was presumably the result of imbalance between ventilation and blood flow produced by the "bronchopneumonia" which was always found. The very high incidence of "bronchopneumonia" in hypothermic coma raises the possibility that there may have been cold injury to the lungs; if this were associated with damage to the alveolar membrane and hindrance to diffusion of oxygen, another explanation for the large alveolar-arterial oxygen tension gradient might be present; our figures are inadequate to confirm this speculation.

TABLE IV.—*Calculated Alveolar Oxygen Tension and Alveolar-Arterial Oxygen Tension Gradient*

| Case No. | $PAo_2$* (mm. Hg) | $Pao_2$ (mm. Hg) | A-a Gradient |
|---|---|---|---|
| 2 | 113 | 38 | 75 |
| 4 | 105 | 53 | 52 |
| 5 | 94 | 45 | 49 |
| | (99 | 74 | 25)—at 37° C. |
| 8 | 55 | 9 | 46 |
| 10 | 73 | 16 | 57 |
| 13 | 105 | 46 | 59 |
| 14 | 94 | 28 | 66 |
| 15 | 102 | 25 | 77 |

*Calculated from the alveolar-air equation

$$PAo_2 = PIo_2 - Paco_2\,(0{\cdot}2093 + \frac{0{\cdot}7907}{R}),$$

assuming R = 0·7
(except in Case 2, where it was known—0·675)

TABLE V.—*Naturally Occurring Hypothermia*

| Animal | Temperature (°C.) | *p*H | $P_{CO_2}$ (mm. Hg) | $H_{CO_3}$ (mEq/l.) |
|---|---|---|---|---|
| Turtle* | 37 | 7·44 | 56 | 36 |
| | 24 | 7·63 | 28 | 34 |
| Hamster† | 37 | 7·39 | 60 | 36 |
| | 5 | 7·44 | 32 | 40 |
| Squirrel† | 37 | — | 56 | — |
| | 5 | — | 40 | — |

* Robin‖(1962). † Lyman and Hastings (1951).

The anoxia is probably very important, even though the values for arterial oxygen tension may not seem low when compared with those seen in the respiratory failure of chronic chest disease. Lowered cardiac output, circulatory impairment, and increased blood viscosity make the hypothermic patient very vulnerable to anoxia. Even though lowered tissue demand may in part compensate for the reduction in available oxygen, it is likely that these patients suffer from severe tissue anoxia. The metabolic acidosis and rise in levels of blood lactic acid reported in induced hypothermia by Brewin *et al.* (1955) may be the result of this anoxia. The liability of these patients to sudden and unexpected death is striking, and this may also be due to tissue anoxia. Any treatment which warms the patient and increases tissue-oxygen demand without providing better blood-and-tissue oxygenation is likely to give poor results.

## Carbon Dioxide

The corrected figures for $P_{CO_2}$ appear to show little abnormality, except in two cases where the $P_{CO_2}$ is above the normal range at 37° C. (Case 8, 70 mm. Hg ; Case 10, 57 mm. Hg). The problem of defining the normal condition during hypothermia must be taken into account ; though there are no "normal values" some experimental guidance is available. $P_{CO_2}$ is determined by the ratio of $CO_2$ production to alveolar ventilation. At subnormal temperatures $CO_2$ production is depressed, and if alveolar ventilation remains constant $P_{CO_2}$ will fall.

In acute induced hypothermia in dogs Brewin *et al.* (1955) found respiratory depression with a rise in $P_{CO_2}$, but this may not be a good model for the "normal" in accidental hypothermia, which may be more closely related to the hypothermia occurring in poikilothermic or hibernating animals. The turtle, the hamster, and the squirrel all show a fall in $P_{CO_2}$ with fall in temperature (Table V), suggesting that a fall in $P_{CO_2}$ is the "normal" for hypothermia. Respiratory depression and carbon-dioxide retention therefore were probably more frequent in our patients than the figures at first suggest ; they were certainly important in Cases 8 and 10, and probably significant in Cases 5 and 14.

## Acid-base Balance

The effect of change of temperature on acid-base balance depends on changes in the ratio of bicarbonate to carbonic acid. As gas solubility increases at lower temperatures the carbonic acid concentration for a constant $P_{CO_2}$ will rise, and a fall in *p*H would be expected. This rise in $H_2CO_3$ is, however, offset in whole blood *in vitro* by an increase in bicarbonate concentration at lower temperature, and when $P_{CO_2}$ is constant whole blood *p*H is not changed by change of temperature (Brewin *et al.*, 1955). However, in the patient not only the blood but also the extracellular and intracellular fluid must be considered. The increase in bicarbonate with fall in temperature depends on decreased ionization of acid protein (in blood mainly haemoglobin) ; the extracellular fluid is low in protein and it is not known to what extent the intracellular protein undergoes this change in ionization. The overall effect of fall in temperature at constant $P_{CO_2}$ may, in fact, be that associated with increased solubility of $CO_2$—a lowering of *p*H—but in the intact animal a fall in temperature leads to a fall in $P_{CO_2}$ (see previous section), and this produces a rise in *p*H which dominates any other change.

In animals which are either poikilothermic or warm-blooded but hibernating, the turtle shows no change in bicarbonate concentration and the hamster a slight rise, but in both the *p*H rises as a result of a fall in $P_{CO_2}$ (Table V). The changes in the squirrel are documented with less certainty and are difficult to interpret. If these values in the turtle and hamster are the "normal" for hypothermia, all of our patients were acidotic. In Cases 8 and 10 the acidosis was clearly respiratory ; in the remainder it is less easy to be certain of the cause, but the respiratory component was probably the more important. It has been suggested that accumulation of lactic acid causes metabolic acidosis (Brewin *et al.*, 1955) ; in the one patient in this series in whom the arterial lactic acid level was measured (Case 8) it was, in fact, slightly elevated (11.4 mg./100 ml.). Though acidosis was common in our patients, it was not so severe as to suggest it was of great importance.

## Discussion

Our results show constant evidence of anoxia, together with some evidence of respiratory depression and acidosis. We feel that the anoxia is related to the high mortality, and that improvement in oxygenation might improve the results of treatment. The breathing of pure oxygen by the patient's unaided efforts will be of some help ; but the more severe case may need mechanical assistance to breathing, as respiratory depression is already present and may be made worse by oxygen-breathing. The advanced age and poor general condition of patients such as ours would make assisted respiration a formidable undertaking unless its duration was short. Good oxygenation by assisted respiration and rapid rewarming might improve the chances of survival if the problems of circulatory collapse could be solved.

## Summary

Fifteen cases of accidental hypothermia are described. Arterial-blood-gas studies constantly showed anoxia, and it is suggested that this is an important factor in the high mortality. Respiratory depression and carbon-dioxide retention also occurred.

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