HYPOTHERMIC COMA IN MYXOEDEMA

BY

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The first mention of death in hypothermic coma due to myxoedema appeared in 1879 in *St. Thomas's Hospital Reports*. The patient was under the care of Dr. William Ord, who in 1877 had coined the term "myxoedema." In 1888 the Report on Myxoedema of the Clinical Society of London drew attention to the subnormal temperatures found in myxoedematous subjects and the importance of the environmental warmth for their welfare. G. R. Murray (1899), describing in the Goulstonian Lectures the treatment of myxoedema by extract of dried thyroid, stated: "One of the earliest signs of improvement is in the return of the temperature to the normal level." This rise in temperature could first be observed during the second week of treatment. Since then relatively little attention has been paid to the severe hypothermia in myxoedematous subjects until the papers of Le Marquand *et al.* (1953) and Summers (1953) appeared describing hypothyroid patients who had low temperatures before death. The fact that Summers could quote five instances in the space of two years suggests that the condition is not too uncommon.

This communication reports three further cases of hypothermic coma in myxoedema.

Case 1

A housewife aged 60 was admitted to the Derbyshire Royal Infirmary on January 22, 1953, under the care of Dr. D. V. Hubble. It was impossible to obtain a history from the patient because of her poor cerebration. Her relatives stated that in 1943 she suffered from an illness in which her eyes became prominent. After a while her eyes returned to normal and she started to gain weight. About 1949 she became forgetful, stubborn, and lethargic, and complained bitterly of always feeling cold. A year before admission, she was confused and drowsy for a period of time, but had eventually reverted to her previous state. For a few weeks before admission she complained of breathlessness. For six days she had been confused and disorientated.

On admission, though she was conscious and could respond to simple questions and requests, her cerebration, speech, and movements were slow. Her voice was deep and croaking. There was a reddish-blue discoloration of her cheeks on a background of pallor. The outer parts of the eyebrows were lost, the scalp hair was sparse and coarse, and the axillary and pubic hair were scanty. The tongue was enlarged and protruded. Supraclavicular pads of fat were present, together with myxoedematous deposits in the skin, which was dry, cold, and finely scaling. The coldness of the skin of the trunk, even after some time in a warm hospital bed, was a striking feature. The pulse rate was 54 and the blood pressure 130/90. The heart sounds were difficult to hear and there was no congestion of the jugular veins, but marked pitting oedema of the legs and sacral region was present. The chest was resonant and there were rhonchi and rales at both bases. All tendon reflexes were diminished and plantar responses were equivocal.

Investigations on Admission.—Haemoglobin, 112%; R.B.C., 4,720,000; W.B.C., 4,100; E.S.R., 1 mm.; haematocrit, 53%; alkali reserve, 71 ml. CO_2 per 100 ml. plasma; eosinophils less than 50 per c.mm. Urine, *p*H 6.2; fair amount of albumin; culture, no growth. For biochemical findings see Table.

At first the patient was conscious and not distressed, took food and fluids, and was reasonably co-operative. Twenty hours after admission she had an epileptiform convulsion, after which she was confused, restless, and after four hours comatose. She became cyanosed; her respirations were 10 a minute, though her pulse rate and blood pressure did not change. Because of the clinical impression of respiratory failure the air passages were aspirated and artificial respiration was given. In spite of some improvement her condition remained precarious and she died some 34 hours after the onset of coma.

Treatment consisted in administration of glucose-saline, dried thyroid tablets—a total of 2½ gr. (160 mg.) was given—and analeptics as necessary.

Her temperature was measured with a clinical thermometer only. On admission it was noted as 97.2° F. (36.2° C.), but for the 24 hours before death it was 95.2° F. (35.1° C.), this being the lowest point on the particular chart used. It is possible that had a special thermometer been used lower temperatures would have been recorded. This view is further supported by the fact that even the well-covered parts of the patient's body felt very cold to the touch, a condition observed in Case 2, in which much lower temperatures were recorded.

Post-mortem Examination.—There was mucinous infiltration of the media of the arteries, of the skin, and between the cardiac muscle fibres. The thyroid was small; it showed a late stage of Riedel's "woody thyroiditis." The pituitary and suprarenal glands were normal.

Case 2

A housewife aged 64 was admitted on February 18, 1954, to Ancoats Hospital, Manchester, under the care of Dr. H. T. Howat. It was impossible to obtain a history from the patient. Her husband stated that he returned home after seven months at sea, four days before the patient's admission. He found no striking difference in his wife's appearance or behaviour. She had been sensitive to cold for many years, but only recently had he thought she felt cold to the touch. For two days after his arrival she did all her household work as usual. On the morning of the third day she was difficult to rouse and seemed confused. As she did not improve she was admitted the following evening. Her previous health had been good apart from epilepsy, which disappeared after the menopause, at the age of 52.

On admission the patient was conscious. She answered simple questions and obeyed simple commands. There was a striking resemblance to Case 1, not only in facial appearance but also in all the external characteristics of severe myxoedema. The peculiar dry coldness of the skin over the whole body was again noted. The pulse rate was 40 a minute and blood pressure 140/100. The heart sounds were hardly audible but were normal. There was raised cervical venous pressure and oedema over the sacrum and of the legs up to the knees. Respirations were 14 a minute and there was dullness to percussion at both bases, with rales. No ankle- or knee-jerks could be obtained. Plantar reflexes were flexor.

Investigations.—R.B.C., 4,130,000 per c.mm.; W.B.C., 3,950 per c.mm.; haemoglobin, 78%; E.S.R., 25 mm. in one hour; serum proteins, 6.6 g.% (albumin 3.8 g., globulin 2.8 g.). E.C.G.: low-voltage complexes with flat T waves. The record was characteristic of myxoedema. For other investigations see Table.

The patient's condition remained unchanged for 24 hours. Then she gradually became drowsy, but at times was restless and noisy. About 36 hours after admission she became comatose. At the time her rectal temperature was 78° F. (25.5° C.), respirations 8 a minute, pulse 38, and blood pressure 108/80. Warmth was applied by means of a heat cradle, and although her temperature was slowly raised to 93.2° F. (34° C.) little change in her condition was noticed. She gradually deteriorated, and the clinical picture of respiratory failure ensued. She died some 20 hours after the onset of the coma.

In addition to application of warmth, she was treated with thyroid siccum, ¼ gr. (16 mg.) twice daily; deoxycortone

Details of Recent Cases

Author	Case	Age and Sex	Date of Occurrence	Temperature F.	Temperature (C.)	Oedema	Serum Na (mEq/l)	Serum K (mEq/l)	Serum Cl (mEq/l)	Urea (mg./100 ml.)	Gluc. (mg./100 ml.)	Cholest. (mg./100 ml.)
Le Marquand *et al.* (1953) ..	1	61 F	Jan., 1951	95°	(35°)	+	150	4·72	102	50	57	390
	2	50 F	,, 1952	95°	(35°)	+++	128	—	73	25	—	495
Summers (1953)	3	59 M	,, 1952	83°	(28·3°)		140	5·65	—	40	110	180
	4	65 F	March, 1951	75°	(23·9°)		122	5·77	86	31	140	160
	5	63 M	Feb., 1952	87·5°	(30·8°)		120	6·15	88	53	94	280
	6	59 M	Nov., 1952	83·5°	(28·6°)		132	5·65	97	48	—	310
Present cases	7	60 F	Jan., 1953	95·2°	(35·1°)	+++	112	3·2	62	36	—	242
	8	64 F	Feb., 1954	78°	(25·5°)	+++	134	4·23	94	14	75	388
	9	62 F	Dec., 1954	Less than 95°	(35°)	+	Normal	5·77	100	60	93	538

acetate by intramuscular injection (10 mg. in all), and adrenocortical extract in dextrose infusion and intramuscularly (30 ml. in all). She was also given analeptics.

Post-mortem Examination.—The thyroid gland was very small, and microscopically showed features of late Hashimoto's disease. The pituitary and suprarenal glands were normal.

Case 3

A spinster aged 62 was admitted to Crumpsall Hospital, Manchester, on December 9, 1954, under the care of Dr. S. Oleesky. Her brother stated that she had been quite well until about a year before admission. Since then she had gradually become lethargic, listless, and sensitive to cold. In the last two months her behaviour became irrational and at times she had persecutory delusions. Eight hours before admission she became unconscious. Her previous health had been good, and the menses regular till the menopause, at the age of 53.

On admission the patient was comatose. Her face was puffy, and there was loss of the outer parts of the eyebrows and of axillary hair. Pubic hair was sparse. The skin was dry and scaling. The whole of her body felt cold to the touch. The respirations were slow, the pulse was 40 a minute, and the blood pressure was unrecordable. There was oedema of the ankles but no congestion of the jugular veins. The pupils were dilated and reacted to light sluggishly. The limbs were rigid, the reflexes depressed, and plantar responses flexor. The rectal temperature could not be recorded on a clinical thermometer.

Investigations.—Haemoglobin, 13.5 g. Lumbar puncture: pressure, 120 mm.; clear colourless fluid; proteins, 160 mg. per 100 ml. with slight excess of globulin. E.C.G. showed sinus rhythm, rate 40, flat T waves, and low-voltage complexes. Radiographs showed no evidence of intracranial tumour, a normal pituitary fossa, and normal heart and lungs. For other findings see Table.

Electric blankets were used to warm the patient. On the night of admission she was given an intravenous infusion of 500 ml. of 5% dextrose with 10 mg. of corticotrophin, and 0.025 mg. of thyroxine sodium. For the next 20 days she was treated with intramuscular injections of corticotrophin gel, starting with 25 mg. twice daily, and gradually decreasing to 12.5 mg. daily. Simultaneously, she was given thyroxine sodium, 0.3 mg. daily, later increased to 0.6 mg. daily. Dried thyroid in doses varying from 1 gr. (65 mg.) daily to 1 gr. (65 mg.) thrice daily has since been used for maintenance treatment.

For the first two days the patient's rectal temperatures were not recordable by clinical thermometer. During the next seven days temperatures around 96° F. (35.6° C.) were maintained for as long as electric blankets were used. If these were removed, the temperature gradually fell until in about four hours it became unrecordable. From the tenth day temperatures ranging about 98.4° F. (36.9° C.) were maintained without external warming. The patient was comatose for the first two days, and only a little better for the next ten. She then gradually became fully conscious, though suspicious and at times deluded. Four weeks after admission her mental state approached normality.

At the end of January, 1955, she was still slow in speech and cerebration. Her blood pressure was 140/80 and pulse 76. The reflexes on the left side were brisker than on the right, but both plantar reflexes were flexor. The blood cholesterol was 164 mg. per 100 ml., C.S.F. proteins 44 mg. per 100 ml., and the electrocardiogram showed sinus rhythm of 72 with increase in voltage and return of upright T waves. The 17-ketosteroid excretion was 5.56 mg. in 24 hours (patient receiving corticotrophin gel 25 mg. daily and thyroxine 0.2 mg. thrice daily). The water diuresis test showed maximal flow of 6.3 ml./min. with load of one litre (over one month after conclusion of corticotrophin therapy). The patient was discharged from hospital in February, 1955, in satisfactory condition on thyroid tablets, 1 gr. (65 mg.) three times a day.

Discussion

The clinical recognition of severe hypothermia depends on the appreciation of the extreme dry coldness of the skin, and can be confirmed by measuring the body temperature with a low-reading thermometer. The skin of even the chest and abdominal areas, usually well covered and therefore warm, feels characteristically dry and cold, and remains so in a warm hospital bed. The sensation obtained on examination is very striking, and can be compared to that experienced when touching a cadaver. In none of three severely myxoedematous patients without significant hypothermia—98° F. (36.7° C.), 96.8° F. (36° C.), 97.6° F. (36.4° C.)—examined in an out-patients clinic was this sensation obtained. In severely shocked patients the skin may feel cold, but it is usually moist and clammy. Hypothermia may not only indicate the need for urgent treatment but may suggest a diagnosis of myxoedema or hypopituitarism where not suspected previously.

Not enough information was obtained to ascertain the cause of hypothermia in myxoedema coma or to assess the endocrine and metabolic state of patients suffering from it. Some of the facts are summarized in the Table. The following points emerge from it: (1) striking seasonal occurrence during winter months; (2) hypothermia, sometimes very severe, was present at the onset in all cases; (3) blood-sugar estimations were within normal range; and (4) in four out of nine cases serum sodium and chlorides were low (Cases 2, 4, 5, and 7). In two of these (Cases 4 and 5) serum potassium was high—which presents a combination of changes met with in adrenocortical failure. In Case 7 the serum potassium was low, which, together with low serum sodium and normal blood urea, suggests water retention. It is not clear by what mechanism these changes were produced, but they preceded the onset of coma.

It is also interesting to note that at no stage did shivering occur in the cases here recorded. The absence of shivering, and the ease with which the body temperature could be altered by the application of heat, point to complete failure of the thermo-regulatory centre.

Coma in myxoedema presents a clinical picture similar in many respects to coma in hypopituitarism (Sheehan and Summers, 1952; Whittaker and Whitehead, 1954). Caughey and Garrod (1954) discussed the factors concerned in causation of coma in hypopituitarism. It is possible that similar

considerations may also apply to coma in myxoedema, especially as there is evidence that adrenocortical failure may occur in myxoedema (Statland and Lerman, 1950; Hill *et al.*, 1950; Hubble, 1955), and there is a possibility of pituitary hypofunction too (Statland and Lerman, 1950; Hubble, 1955).

The treatment successfully employed in Case 3 relied on the early administration of thyroxine and corticotrophin together with the application of warmth. Alternatively a regime of management described by Caughey and Garrod (1954) for treatment of hypopituitary coma could on empirical grounds be suggested for treatment of coma in myxoedema. Early recognition of hypothyroidism with adequate and continuous therapy should prevent the occurrence of coma.

Summary

Three cases of coma with hypothermia in myxoedema are described. Hypothermia can be recognized clinically by appreciation of the extreme dry coldness of the skin and can be confirmed by measuring the temperature with a low-reading thermometer. Factors connected with the causation of hypothermic coma in myxoedema are discussed and the similarity to coma in hypopituitarism is considered.

ADDENDUM.—Since this paper was submitted for publication an additional case has come to my attention. A woman of 67 was admitted to the Royal Hospital, Sheffield, in February, 1955. The clinical features were similar to those in the above cases. There was no pitting oedema. The rectal temperature was 80° F. (26.1° C.). By application of electric blankets it was raised to 92° F. (33.3° C.). The patient did not shiver. Serum electrolyte concentrations were: Sodium, 118 mEq/l.; potassium, 3.5 mEq/l.; chloride, 76 mEq/l. Blood urea was 30 mg., and blood sugar 102 mg. per 100 ml. She was diagnosed as a case of Simmonds's disease, but at necropsy the pituitary and adrenal glands were normal. The thyroid gland showed advanced atrophy.

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The *St. Raphael Quarterly*, the journal of the Guild of St. Raphael (the Anglican guild for the promotion of the Ministry of Healing), has been issued under a new format, with Mr. P. Shuffrey as editor. Obtainable from the Guild of St. Raphael, 33, Wilton Place, S.W.1, the subscription is 3s. 6d. While the Church has come again to regard healing as part of her function, "her understanding of the matter has been mostly concerned with the results, a little with the how, but hardly at all with the why of it. The purpose of this journal . . . is to try to fill that gap." It is hoped that doctors, psychiatrists, priests, and theologians will contribute. In the autumn issue, 1955, three doctors and three priests write a joint article stressing that, while "a distinction must be drawn between the cure of a specific malady and the larger concept of healing," both doctor and priest are concerned with the issue of total health. The authors believe that the concept of psychogenic origins of illnesses has made a *rapprochement* between Church and Medicine easier.

MYXOEDEMA COMA IN A PATIENT WITH HASHIMOTO'S STRUMA

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Coma as a complication of thyroid myxoedema is not a frequent occurrence and is not often mentioned as a terminal event in the natural history of the disease. Summers (1953) described four cases of coma leading to death in patients with thyroid myxoedema. He suggested that hypothermia might be the cause of death and pointed out that treatment was ineffective once coma had developed.

We wish to report a case of coma, without discernible precipitating factor, occurring in a patient with myxoedema who died despite hormonal treatment and in whom the diagnosis was confirmed by radioactive tracer studies and post-mortem examination, including examination of the pituitary body.

Case Report

A 63-year-old white woman was admitted to the Institut Jules Bordet on March 14, 1954, with the chief complaint of constipation and asthenia. The onset of the disease dated back about six months before admission, when she experienced constipation alternating with periods of diarrhoea. She had several fainting spells during the week preceding admission. A detailed history was difficult to obtain because of her profound asthenia and lack of attention and interest. However, she did not complain of pain, and a review of the various systems was negative except for moderate ankle oedema at night and mild dyspnoea on exertion. She had always been sensitive to cold. The family history failed to reveal any significant fact: the patient was married and had two healthy children. Her past history was negative except for a strangulated hernia which was operated upon in 1940.

Physical examination showed a well-developed woman in a satisfactory state of nutrition. She was lying in bed quietly, paying little attention to her surroundings, fully conscious, but slow in answering questions, which she did in a monotonous and deep voice. The blood pressure was 160/100; temperature 99° F. (37.2° C.); pulse 68, regular. The skin and hair were dry and the patient looked anaemic. There was a puffiness around the eyes, and the face appeared somewhat swollen and was inexpressive. Examination of the head, neck, and chest showed nothing else of significance. The thyroid gland was not felt and there was no tenderness. The extremities were normal. Axillary hair was lacking, but pubic hair had a normal distribution. Neurological examination was negative. The patient was able to walk, but did not volunteer to leave her bed.

X-ray examination revealed the presence of residual fluid in the stomach with no other abnormality, a normal intestinal tract, and a moderate enlargement of the heart.

The urine was free of sugar and albumin, but contained a few white blood cells. The blood showed: haemoglobin, 13.6 g. per 100 ml.; white cells, 8,200 per c.mm., with a normal differential count; urea nitrogen, 34 mg. per 100 ml.; total cholesterol level, 336 mg. per 100 ml. of serum. The cephalin flocculation test was negative after 48 hours and thymol turbidity was 0.5 Maclagan unit. The complement-fixation test for syphilis was negative.

A diagnosis of myxoedema was made on admission. The basal metabolic rate was minus 8%. Examination by radio-