for the haemolysis. It is suggested that the haemolysis may be related to the reticulo-endothelial hyperplasia which occurs in typhoid.

The administration of A.C.T.H. in two cases controlled the haemolytic phenomena and produced prompt improvement in the typhoid state.

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MYXOEDEMA COMA

BY

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In the report of a committee of the Clinical Society of London (1888) on myxoedema it was stated that "intense anaemia, and a variety of nervous symptoms, such as maniacal excitement, coma, etc., precede the fatal event." Scant reference to coma as a terminal event in the natural history of myxoedema is made in modern textbooks or in recent accounts of the disease. The modern tendency is to look upon myxoedema as a readily curable disease and, indeed, hardly to consider it as a cause of death. Le Marquand *et al.* (1953) call attention to the scarcity of recent references to myxoedema as a cause of death and report two fatal cases. The purpose of this paper is to call attention to a terminal coma which is often the manner of death in myxoedema.

The following account is based on five examples of coma seen in four cases of myxoedema during the past few years; in all the cases the diagnosis was subsequently confirmed at necropsy. In one case two episodes of coma occurred.

Case 1

A man aged 59 was admitted to hospital in January, 1950, with a history of watery eyes for 10 weeks and of puffiness of the face for three weeks. There was little of significance in his past history, and apart from malaria during the 1914-18 war he had enjoyed good health. For many years he had complained of "rheumatism" in his right knee. A few days before admission he burned his right leg whilst sitting close to the fire. His face was puffy, especially round the eyes, the lips were thick, and the skin was pale. Axillary hair was absent and the pubic hair scanty. Cerebration was slow, but it was possible to obtain a reasonable history from him. His condition on admission did not give rise to any anxiety, and a series of investigations were planned to assess his endocrine state.

Within 72 hours of admission his condition greatly deteriorated; he became very confused mentally and had delusions of a persecutory nature. Next day he became very drowsy and it was extremely difficult to rouse him; 12 hours later he was stuporous and the plantar responses became extensor. His rectal temperature was 83° F. (28.3° C.). Thyroid extract, 1 gr. (65 mg.) thrice daily, was given as soon as the change in his state was observed, and when he became too drowsy to take oral therapy thyroxine sodium, 1 mg., was given subcutaneously every six hours. This treatment had no effect whatsoever and he died about 96 hours after the first change in his condition was noticed.

Post-mortem examination confirmed the clinical diagnosis of myxoedema. Sections from both lobes of the thyroid showed marked fibrosis. The adrenal glands were of normal size and showed no histological change. The pituitary was normal.

Case 2

A woman aged 65 was admitted to hospital in March, 1951; she had been in hospital on four occasions, and in 1946 a diagnosis of myxoedema was considered. At the time of her admission in 1951 she presented a typical myxoedematous appearance, with a puffy sallow face, sparse head hair, and thin eyebrows. Her voice was croaking. The mental state was one of stupor which gradually, within 48 hours, progressed into deep coma. The vaginal temperature on admission was 75° F. (23.9° C.) and the systolic blood pressure was 70 mm. Hg. The pulse was thin and the rate 60 a minute. The skin was pale and cold; the limbs were flaccid; the deep reflexes could not be elicited, and the plantar responses were extensor.

Thyroxine sodium, 2 mg., was given subcutaneously every six hours from the time of admission. In view of the pronounced hypothermia, and of previous successful experience in hypopituitary coma of raising the temperature by means of immersion in a hot bath, it was decided to attempt this method of treatment. The temperature was raised from 75 to 98.6° F. (23.9 to 37° C.) by immersion in a bath of water, the temperature of which was gradually raised (to avoid burning) to 98.6° F. (37° C.). This procedure had no effect on the coma, and, although the vaginal temperature remained at 98.6° F. (37° C.), the patient died on the following day.

Post-mortem examination showed an extremely small thyroid; in the right lobe was a nodule the size of a cherry stone and in the left a nodule the size of a small bean. Histologically the gland tissue was completely replaced by fibrous tissue in which there were a few groups of shrunken acini. The pituitary and adrenal glands were normal.

Case 3

A man aged 63 was admitted to hospital in February, 1952. Myxoedema had begun about four years previously, and he had taken thyroid intermittently until about a year before his final admission. Clinically he presented gross myxoedematous features, with a flabby yellow face, oedematous infra-orbital tissues, dry swollen hands, thin eyebrows, and sparse head hair. Axillary hair was completely absent and the pubic hair scanty. The voice was croaking and deafness was severe. The blood pressure was 155/100 and the pulse 66. He was mentally clear but sluggish. The rectal temperature was 91.4° F. (33° C.). An electrocardiogram showed slow voltage complexes with flat T waves in all leads. The haemoglobin was 11 g. per 100 ml. and the red-cell count 3,700,000 per c.mm.

Within 48 hours of admission the patient became drowsy, and, with the experience of the previous two cases as a guide, treatment was begun immediately. Thyroid siccum, 1 gr. (65 mg.) thrice daily, was given by mouth, and cortisone, 100 mg., and deoxycortone acetate, 10 mg., were given via an intravenous saline drip. There was no change in his condition during the next 24 hours, but on the following day he was stuporous. The rectal temperature was now only 87.5° F. (30.8° C.), and it was decided to substitute thyroxine

sodium, 2 mg. every six hours, for the thyroid extract, to continue with cortisone, and to attempt to raise the falling body temperature by immersion in a hot bath. This method was followed, and the final rectal temperature was 98.6° F. (37° C.). His condition steadily worsened, and a further 200 mg. of cortisone acetate was given. No improvement was effected and death occurred on the next day.

Post-mortem examination showed an extremely small thyroid in which histologically there was almost complete replacement of glandular elements by fibrous tissue. The pituitary and adrenal glands were normal.

Case 4

A man aged 59 was admitted to hospital in July, 1951. About a year before admission he had noticed that his skin was becoming dry and scaly and that he felt the cold. His hearing was impaired and his memory was failing. At the time of admission his eyes were puffy, the skin was dry, and the voice was croaking, but there was fairly abundant head hair, although the eyebrows were sparse. No thyroid tissue was palpable. The blood pressure was 130/75 and the pulse rate 64. The temperature ranged from 96 to 98° F. (35.6 to 36.7° C.). An electrocardiogram showed low-voltage complexes and negative T waves in all leads. An electroencephalogram showed, with maximum amplification, irregular 8-9 per second rhythm, with the greatest amplitude in the parietal region and also a certain amount of more rapid low amplitude activity in the parietal region. The B.M.R. was -30%, and the 17-ketosteroid excretion ranged between 0.6 and 0.75 mg. a day.

Cerebration at the time of admission was extremely slow and became progressively more sluggish, until on the fourth day after admission the patient was semi-stuporous. Thyroxine sodium, 1 mg., was administered six-hourly. Improvement was observed within 24 hours, and there was a gradual return to a normal conscious level during the next few days. Treatment was continued with thyroid extract.

This patient was readmitted to hospital in November, 1951, and at this time he was very drowsy when first seen. The rectal temperature was 83.5° F. (28.6° C.), the pulse rate 75. Treatment was begun with thyroxine sodium, 1 mg. every six hours, and cortisone acetate, 100 mg. every six hours. Despite treatment he lapsed into unconsciousness and died 48 hours after admission.

Post-mortem examination showed gross thyroid atrophy with replacement of glandular tissue by fibrous tissue. The adrenal glands were normal histologically, but the pituitary showed an excess of basophil cells.

Comment

In these cases it was not possible to carry out all the blood and urine analyses which are normally performed in endocrine investigations. Biochemical investigations were carried out as fully as possible during the terminal stage of the illness, and the results are shown in the Table.

Results of Biochemical Investigations (All Amounts are Given in mg. per 100 ml.)

Case	Sodium	Potassium	Phosphorus	Chlorides	Urea	Glucose	Cholesterol
1	323	22	4.2	—	40	110	180
2	280	22.5	3.9	500	31	140	160
3	276	24	4.0	515	53	94	280
4	304	22	4.1	568	48	—	310

The onset of coma in each case was gradual and progressed from drowsiness to deep, fatal coma within a few days. Le Marquand *et al.* (1953) report a case, however, in which the onset of coma seems to have been more rapid. Case 4 above appears to have had a pre-coma state, and this was prevented from progressing to full coma by prompt treatment.

All the patients were severely myxoedematous at the time of their admission to hospital. The coma in each case was

deep: the limbs were extended and flaccid, and the extremities were cold. The skin was pale, dry, scaly, and cold. The pulse was thready but the rate ranged from 60 to 75 a minute. The systolic blood pressure ranged from 70 to 130 mm. Hg. The tendon reflexes could not usually be elicited, and the plantar responses were sometimes extensor. In view of the occurrence of very low body temperature in hypopituitary coma (Sheehan and Summers, 1952), special note was made of this in these cases. Vaginal or rectal temperatures during coma ranged from 75 to 91.4° F. (23.9 to 33° C.), and was lower than the temperature recorded in some of the patients when not in coma. An incubator thermometer was used to record temperatures below the usual range of a clinical thermometer. Once coma develops it seems to be irreversible, and none of the methods of treatment used were successful.

Diagnosis should not present any difficulty; very gross myxoedematous changes were present in all the cases, and the history, when obtainable, was typical. Hypopituitary coma, particularly when myxoedema features are prominent, may present difficulty. In the common post-partum type of hypopituitarism the history will often make the diagnosis clear.

Discussion

The occurrence of coma as a terminal event in myxoedema is of interest, first, as a problem in the disordered physiology which results from loss of the thyroid secretion, and, secondly, because a very similar type of coma occurs in hypopituitarism (Sheehan and Summers, 1952).

All the cases in the present series had hypothermia, and a similar condition was observed in hypopituitary coma. Le Marquand *et al.* (1953, Case 1) also report hypothermia, and note that their patient was admitted to hospital during the middle of the winter, when they suggest that the risk of hypothermia is greatest. My experience of the present cases supports this observation, all the patients being admitted during the winter months. Although the body temperature was successfully raised to normal in two cases, no improvement was produced and the coma persisted. The temperature regulatory mechanism in severe myxoedema would seem to be influenced by low external temperatures in much the same manner as the temperature of cold-blooded animals. The changes produced by extremely low body temperature in these severely myxoedematous patients are apparently irreversible and elevation of the temperature to normal does not lead to recovery. It becomes a matter of great importance therefore to protect patients with gross myxoedema from severe external cold.

It is tempting to suggest that hypothermia is the cause of coma in these cases, and that these low temperatures are due to the depression of metabolism which results from loss of thyroid secretion. In only one case, in which the development of coma was presumed likely, was it possible to restore the patient with thyroid extract or thyroxine sodium. Once coma had developed administration of thyroxine was without effect, even when used in conjunction with hydrotherapy. Either lack of thyroid is not entirely responsible for the development of hypothermia or the body reaches a state in which it can no longer respond to the stimulus of thyroxine.

Consideration of the first of these possibilities—namely, that lack of thyroid is only part of the story—leads to a study of the recent work on the failure of adrenal cortical function which occurs in myxoedema (Statland and Lerman, 1950) in order to find an explanation of the occurrence of coma. In one of the present cases the 17-ketosteroid excretion was in the range of 0.6 to 0.75 mg. daily, an excretion rate similar to that found in hypopituitarism, and in two cases low levels of serum sodium and chloride were found. The administration of cortisone acetate in one case, and of deoxycortone acetate, saline, and cortisone in another, failed to revive the patients.

Further study of the coma in myxoedema is required to elucidate the pathology of this condition, and it is hoped that further cases of this interesting but rare complication of myxoedema will be reported.

Summary

Four cases of terminal coma occurring in myxoedema are reported. Extremely low body temperatures were recorded in all cases. No treatment so far tried has reversed the coma once it has developed.

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TURNER'S SYNDROME IN THE FEMALE CONGENITAL AGONADISM COMBINED WITH DEVELOPMENTAL ABNORMALITIES

BY

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Hypogonadism, manifesting itself as primary amenorrhoea and lack of development of uterus, vagina, and breasts, without any evident disease of or operative interference with ovaries, thyroid, or intracranial structures, is usually attributed to pituitary insufficiency. The tiny, frail, delicate, fair-skinned dwarf demonstrating the Lorain-Lévi syndrome is the prototype of primary hypopituitarism. One should not, however, label as examples of pituitary deficiency all other hypogonadic individuals with no resemblance whatever to the Lorain type. One such group has now been conclusively proved to be due to primary lack of development of ovaries.

Historical Background

This is recent. In 1938 Turner described seven cases with webbing of the skin of the neck, cubitus valgus, and infantilism. He noted that the short webbed necks of his cases were not due to any vertebral abnormalities, and bore no relation, therefore, to the Klippel-Feil group of conditions. He thought the syndrome might be of pituitary origin.

In 1942 Varney, Kenyon, and Koch reported the cases of four short, sexually retarded females who showed an increase of pituitary gonadotropins in their urine. Laparotomy demonstrated ovarian aplasia, which could not have been pituitary in origin in view of the urinary findings. The same year Albright, Smith, and Fraser (1942) independently demonstrated the primary origin of the syndrome and discussed in detail its differentiation from hypopituitarism on the basis of 11 cases of their own.

In 1944 Wilkins and Fleischmann published an interesting and thoughtful analysis of this syndrome of ovarian agenesis. They again showed a primary lack of development of the ovaries, which were "developed but little, if at all, beyond the stage of the primitive genital ridge." They point out that affected persons, though sexually underdeveloped, are obviously female in appearance, habitus, organs, and inclinations, so that female differentiation itself must be entirely independent of the embryonic gonad. They divide the syndrome into three constituents—first, the gonadal agenesis and its conse-

quences; secondly, the skeletal abnormalities, which cannot be directly occasioned by the ovarian agenesis but must be associated congenital developmental anomalies; and thirdly, other congenital dysgeneses, particularly involving the eye, ear, and aorta. They could find no evidence that the condition is hereditary.

Lisser and his co-workers (1947) were able to report on 25 cases which they had personally observed. They remark upon their extraordinary uniformity in appearance and build, and use the term "shield-like chest" to describe their patients' frontal aspect.

Salient Features of the Syndrome

1. *Gonadal*.—*Primary*.—Lack of development of ovaries—surgical exploration of some cases (Wilkins and Fleischmann) has revealed "ovaries" consisting of a primitive genital ridge composed only of stroma-like cells. Epithelial or primordial germ-cell proliferation is absent. *Secondary*.—Primary amenorrhoea—this is invariable, and the usual presenting complaint. The vagina and uterus are infantile in size and in mucosal differentiation. The breasts are non-existent, the nipples pin-point. The pubic hair is usually present but scanty; sometimes absent. Bone age is normal, or only slightly backward. Generalized osteoporosis of varying degree is present. Urinary gonadotropins are increased, the number of mouse units (depending on the method used) usually considerably exceeding 50 in 24 hours (Wilkins and Fleischmann, 1944; Sohval, 1951). Urinary 17-ketosteroids are diminished but not absent, typical values being around 2–5 mg. in 24 hours. Insulin tolerance is normal, with normal hypoglycaemic responsiveness. The appearance is female. Libido is usually present, often strong, and normally heterosexual. Oestrogen therapy leads to development of secondary sexual characters.

2. *Skeletal*.—Stature is short—around 53 in. (135 cm.)—not really dwarfed; rarely tall (Sohval). The build is stocky, thick-set, with wide "shield-like" chest. The span is often wide, some inches greater than the height; otherwise the proportions are normal. Minor vertebral chondrodystrophy is common; the cervical spine, although occasionally bifid, or fused as in Klippel-Feil's disease, is usually normal. Webbed neck is usually but not invariably present. It is remarkable that this odd deformity is so commonly associated with ovarian agenesis and occurs only very rarely in other circumstances. Cubitus valgus—a decreased "carrying angle" was part of the original syndrome described by Turner, but is not invariable. This obtuse angle between the humerus and radius is normally slightly smaller in females than in males, averaging 167 degrees (Gray's Anatomy, 1944). Pes cavus, talipes, syndactyly, and various minor vertebral anomalies also occur.

3. *Associated Anomalies*.—Ocular defects are curiously frequent, squint, ptosis, and cataract being the most common. Coarctation of the aorta has been found several times, and hypertension of independent occurrence is mentioned by Wilkins and Fleischmann. Mental defect and deaf-mutism are reported by those authors.

Diagnosis

Originally the diagnosis of primary ovarian agenesis was established by two special procedures—the direct examination of what genital tissue there was, usually by laparotomy, and the demonstration of increased urinary pituitary gonadotropins, which exculpated the pituitary gland. It was gradually realized, however, that the clinical syndrome as outlined above was so characteristic that it could be diagnosed without such elaborate enterprises; in fact, it has become one of the select group of disorders that can be diagnosed on sight (Case 2). The complaint of primary amenorrhoea, the stocky, thick-set, broad-chested, short individual, with webbed or at least short-looking neck, the lack of breast tissue, pin-point nipples, and minute pale-pink areolae make an unmistakable picture. Cases have