that the effectiveness of chlorpromazine was due to a two-fold action—a depression of shivering combined with a peripheral vasodilatation. Decourt *et al.* (1953) believe that its hypothermic properties depend almost entirely on its cellular hypometabolic action rather than on the autonomic nervous system. Ratschow (1953) found a 20% reduction in basal metabolism following chlorpromazine administration, and Bobbio *et al.* (1952) described a patient undergoing splenectomy who had a basal metabolic rate of +48% before operation, but during hibernation a fall occurred to +10%, which was maintained for about 48 hours. These workers showed also that the combination of surface cooling and hibernating agents had a depressing action on the thyroid as shown by a fall in the radio-iodine uptake of the thyroid glands of experimental animals.

There have been reports of liver damage following the use of chlorpromazine, and the risk involved in its administration during thyrotoxic crisis is that the anoxic injury to the liver may be accentuated. The liver-function tests in Case 2 showed a slight rise in the serum bilirubin concentration on the third day of the crisis, but further tests at later dates were normal.

Conclusion

Thus it seems that thyroid crisis can be explained as the result of prolonged hypermetabolism in uncontrolled thyrotoxicosis, and it should be regarded as an imminent risk in severe and inadequately controlled thyrotoxic patients.

Lahey repeatedly called attention to the importance of this condition and the necessity for adequate treatment: "Just as there is an emergency treatment for impending diabetic coma, there should be, and is, an emergency treatment for the impending thyroid crisis."

Summary

Two cases of thyrotoxic coma are described and the incidence of this complication in thyrotoxic subjects is discussed.

A survey is made of the literature dealing with the pathogenesis of thyrotoxic coma and its relationship to thyroid crisis. Uncontrolled hyperpyrexia and anoxia of the internal organs were considered to be important in the development of this complication.

Hitherto the recommended treatment has been that of fluid and electrolyte replacement with oxygen administration. It is suggested that adrenocortical extracts and chlorpromazine are useful adjuncts to this therapy.

ADDENDUM.—Since this paper was submitted for publication there has been reported the successful treatment of a case of thyroid crisis in which chlorpromazine was used as an aid to cooling (Hunter, 1955).

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DIABETES INSIPIDUS IN ASSOCIATION WITH POST-PARTUM HYPOPITUITARISM

BY

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The great majority of cases of hypopituitarism in women are now believed to be due to post-partum necrosis of the pituitary anterior lobe. Sheehan (1939), in an important paper on the subject, has fully established post-partum hypopituitarism as a clinical entity and has fully described the rather variable clinical picture. Since then an extensive literature on the subject has accumulated. Sheehan and Summers (1949) note that serious haemorrhage or collapse at the time of delivery is nearly always the determining factor in its occurrence.

The extent of the necrosis is, in general, roughly proportional to the patient's condition at delivery. It is probable that at least 80% of the anterior lobe must be destroyed before severe symptoms are produced.

The occurrence of symptoms of diabetes insipidus in association with post-partum necrosis and anterior pituitary insufficiency is exceedingly rare and is a striking phenomenon. It was first seen by Suchier (1927). Spain and Geoghegan (1946), at necropsy, found necrosis in both the anterior and the posterior lobes of the pituitary body. Other similar cases have been reported (Nassar *et al.*, 1950; Storti and Pederzini, 1952; Bracali, 1953; Engstrom and Liebman, 1953; Destro, 1953; Bottura *et al.*, 1954; MacGillivray and Adams, 1954) in which there was disagreement with the experimental data concerning the relationship between the anterior and the posterior lobe of the hypophysis. A further case is added to the few already reported.

Case Report

A woman aged 33 who married in 1947 was in apparently good health until the birth of her child in April, 1948. She was delivered by caesarean section in the eighth month because of the occurrence of eclampsia. She had considerable post-partum haemorrhage. During the puerperium there was a complete absence of breast activity, her mammary glands became soft and involuted, and there was no secretion of colostrum or milk. Within a few days, while still in hospital, the pubic and axillary hair disappeared and the hair of her head and eyebrows became thin. Later the restoration of rhythmic ovarian function failed; menstruation did not return.

About four weeks after delivery she developed polyuria and a proportional polydipsia. The diuresis ranged between

10 and 15 litres daily; the urine was of low specific gravity, and free of sugar and other abnormal constituents. This typical diabetes insipidus was transient, and lasted about three years, until 1951. At the same time (May, 1948) she complained of weakness, absence of sweating, sensitivity to cold, and loss of interest in her children, home, and friends. She was dull and apathetic, and her speech was thick. Six months later she developed generalized oedema and had a frankly myxoedematous appearance, with coarse features, dry skin, etc. The basal metabolic rate was -25% . At this time the diagnosis of primary myxoedema was made. For five years she was treated for irregular periods with different thyroid gland products, without any beneficial result. On the contrary, her general condition progressively deteriorated.

We first saw the patient on July 7, 1953. She had a frankly myxoedematous appearance, was very pale, dull, and apathetic, her speech was hoarse, slow, and slurred, and her skin was dry and rough. Sweating was absent, with loss of skin pigment and of capillary flush. Since 1948 she had had complete amenorrhoea, no libido, and no pubic and axillary hair. There was severe atrophy of the vulva, vagina, and uterus. The thyroid gland was not palpable. The temperature and pulse were normal, the blood pressure was 95/70 mm. Hg, and the electrocardiogram was typical of myxoedema.

Laboratory Investigations.—Urine, nothing abnormal. Blood urea, 20 mg. per 100 ml. Blood cholesterol, 346 mg. per 100 ml. Serum potassium, 15.8 mg. per 100 ml. Serum calcium, 585 mg. per 100 ml. Fasting blood sugar, 88 mg. per 100 ml. (not as low as would be expected, as for some days previous to the test the patient was under treatment with "thyranon"). Wassermann reaction and Kahn test were negative. Blood count: red cells, 3,250,000 per c.mm.; haemoglobin, 60% (9.6 g.); haematocrit, 32%; white cells, 5,400 per c.mm. (segmented neutrophils 62%, eosinophils 6%, lymphocytes 27%, monocytes 5%). X-ray examination of the skull showed a small sella turcica. The basal metabolic rate was -20% (not as low as would be expected, owing to the treatment with thyranon). Gastric function: there was a histamine-fast achylia. The Kepler-Power-Robinson test was positive (Factor A=10). Glucose-tolerance test: the blood-sugar levels at 0, 30, 60, 90, 120, 150, and 180 minutes were 106, 124, 106, 105, 106, 104, and 106 mg. per 100 ml. respectively. Insulin-tolerance test (0.1 unit of insulin per kg.): the blood-sugar levels at 0, 20, 30, 45, 60, 90, and 120 minutes were 106, 65, 50, 55, 65, 70, and 70 mg. per 100 ml. respectively. Eosinophil cell response to adrenaline, 135 before and 130 after; to corticotrophin, 150 before and 120 after; and to insulin, 140 before and 120 after. 17-ketosteroids before corticotrophin, 2 mg. a day; after corticotrophin, 8 mg. a day.

From the above we think that the diagnosis was probably that of post-partum hypopituitarism with secondary myxoedema, and transient diabetes insipidus, which began four weeks after delivery and lasted about three years.

The patient showed an excellent response to replacement therapy with D.C.A., thyranon, testosterone propionate, and oestradiol. After about six weeks on this treatment she had a very good diuresis, the oedema decreased, and her body weight fell by 10 kg. (22 lb.). The basal metabolic rate increased to $+7\%$, the red cells went up to 4,300,000, the skin lost its myxoedematous character and sweating reappeared. The patient became mentally alert and took a normal interest in her surroundings.

Cortisone (Sheehan and Summers, 1954) was not used, because of difficulties of supply.

Discussion

The problem in this case is the association of diabetes insipidus with hypopituitarism, because we know from animal experiments that removal of the posterior lobe alone produces diabetes insipidus, and that this disappears if the anterior lobe is removed. We know also that thyroidectomy prevents experimental diabetes insipidus. Therefore one

would expect that a necrosis of the anterior lobe and the subsequent atrophy of the thyroid would prevent diabetes insipidus in human beings. We know also that diabetes insipidus can be connected with lesions of the posterior lobe and of the adjacent hypothalamus, and that the polyuria resulting from ablation of the posterior lobe of the pituitary is less enduring than that which follows interference with the hypothalamus. Camus and Roussy (1920) state that the latter type cannot be controlled by injection of posterior lobe extracts. Complete ablation of the whole pituitary gland usually results in only transient polyuria, and the persistent polyuria produced experimentally can be relieved by ablation of the anterior lobe of the pituitary. Thus some hormone of the anterior pituitary must be functioning normally for true diabetes insipidus to be developed.

However, the facts do not support this theory. There are three groups of cases to consider (Sheehan and Summers, 1949). (1) Patients who develop a gumma of the pituitary commonly have diabetes insipidus for some weeks or months. It is possible that this is purely due to the pressure on the hypothalamus, and that the recovery is due either to shrinkage of the gumma or to the gradual destruction of the anterior lobe. (2) Giant-cell granuloma of the hypothalamus and pituitary together usually gives rise to a period of diabetes insipidus, which is presumably caused by the damage to supraoptic tracts. The recovery may be due to the gradual destruction of the anterior lobe or to the subsequent gradual atrophy of thyroid and adrenal. (3) There are occasional cases of post-partum necrosis of the anterior lobe in which diabetes insipidus begins two to three weeks after delivery and lasts for a month or so (Spain and Geoghegan, 1946; Sheehan and Summers, 1949; Nassar *et al.*, 1950; Storti and Pederzini, 1952; Bracali, 1953; Engstrom and Liebman, 1953; Destro, 1953. In Sheehan and Summers's case it lasted for many months.

In our case the diabetes insipidus began four weeks after delivery and lasted about three years. How can we explain this delayed onset and the spontaneous recovery after a variable period? We do not know. One can speculate about a localized inflammatory reaction above the necrosed pituitary, with a later spread to involve the adjacent hypothalamus. However, we know of no evidence that secondary inflammation does occur in the hypothalamus in patients who have had a post-partum necrosis of the anterior lobe. An alternative theory is that the post-partum necrosis may also involve part of the posterior lobe, as in the cases reported by Merkel (1914) and by Spain and Geoghegan (1946). Against this is the fact that removal of both the anterior and posterior lobes in animals does not produce diabetes insipidus.

Necrosis in the posterior lobe would not account for the delayed onset of the diabetes insipidus. Consequently we do not know the cause of diabetes insipidus in the cases of post-partum hypopituitarism. But there can be no doubt at all that it does occur occasionally.

Silvette and Britton (1938a, 1938b, 1938c), Ingram and Winter (1938), Corey and Britton (1941), Nagareda and Gaunt (1951), Storti and Pederzini (1952), and Mirski *et al.* (1954) express the view, based on experimental and clinical data, that there is an antagonistic action between the neurohypophysis and the suprarenal glands, and that the spontaneous recovery of the diabetes insipidus may be due to the insufficiency of the adrenal glands and the absence of its diuretic hormone, which has an antagonistic action to that of the antidiuretic hormone of the neurohypophysis.

This view we cannot confirm in our patient, because we did not see her early enough to be able to determine whether the beginning of her adrenal insufficiency coincided with the recovery of the diabetes insipidus.

Summary

A case of post-partum hypopituitarism with diabetes insipidus is described. This condition is extremely rare and only a few other cases have been reported in the

literature. The clinical and experimental data concerning the anterior and posterior lobes of the hypophysis are briefly discussed.

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TEST[†] FOR THE POWER OF FLEXOR DIGITORUM SUBLIMIS

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As a result of poliomyelitis the opponens pollicis is sometimes paralysed, severely disabling the hand. The function of the hand can be greatly improved if the flexor digitorum sublimis to the middle or ring finger is disinserted, wound round the tendon of flexor carpi ulnaris, threaded subcutaneously across the wrist, and attached to the distal end of the first metacarpal. This valuable operation should not, however, be carried out unless the finger selected as a donor has (1) a flexor digitorum sublimis muscle powerful enough to perform its new function, and (2) a flexor digitorum profundus capable, even without the sublimis, of flexing the finger strongly. It is easy to estimate power in the profundus, but to estimate the power of the sublimis is much harder, and the following test has proved useful.

FIG. 1.—Patient is unable to oppose the right thumb, the opponens pollicis having been paralysed by poliomyelitis.

Method

The patient's hand is placed palm upwards on a table. The finger to be tested is left free, while the surgeon—with his own hand—anchors the patient's remaining fingers to the table, keeping them fixed and straight. The patient is now asked to flex the free finger. If he has a strong sublimis

FIG. 2.—The proposed donor (ring) finger is being tested: the terminal joint is nearly straight, and it also feels flail.

FIG. 3.—Flexor digitorum sublimis has been transplanted from the ring finger to the thumb; it can be seen standing out under the skin and opposing the thumb.

FIG. 4.—Test is being repeated on the finger from which the sublimis is known to have been removed; the terminal joint is flexed and is also rigid. It is this combination of flexion and rigidity which shows that the sublimis is either absent or paralysed.