EMERGENCIES IN GENERAL PRACTICE

COMA IN HYPOPITUITARISM

BY

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Chronic hypopituitarism is due to the destruction of the anterior lobe of the pituitary. The most frequent cause of this destruction is an ischaemic necrosis of the anterior lobe which occurs in women at delivery as a result of very severe obstetric haemorrhage or shock, such as from a retained placenta. (Peculiarly enough, severe haemorrhage in men does not lead to necrosis of the pituitary.) In other cases the gland may be destroyed by an adenoma or a cyst, or less often by an inflammatory condition such as sarcoidosis, gumma, etc. These tumours and granulomas can occur in either men or women, and they give rise to all the standard signs of hypopituitarism, but usually with additional symptoms due to local pressure in the region of the chiasma and hypothalamus. The post-partum type, being free from this complication and being the most common form of severe hypopituitarism, is taken as the example for the present account, but the description of the clinical aspects and of the coma is applicable *mutatis mutandis* to other varieties of hypopituitarism in men and women.

From the time of the delivery the patient is in permanent ill-health, and does not menstruate again. After some years she is liable to have an episode of coma. Sometimes the coma leads to death in a few hours or in a day or two. Sometimes the patient improves for a time but relapses and dies a few days later. In other cases she recovers gradually in two or three days, but even then the prospect is not good, because for the rest of her life she is liable to further episodes of coma at intervals varying from a few weeks to a few years. Nearly all the patients die in coma; some in the first attack, some after five or ten recurrences.

Preliminary Examination

It is convenient for purposes of description to follow the usual course of investigation of any comatose patient.

The doctor, on arriving at the house, makes a few preliminary inquiries. He is told that the patient has been a chronic invalid for several years but has not bothered to see a doctor recently. For two or three days she has been unusually drowsy or may have been vomiting, and within the last few hours she has lapsed gradually into coma.

In many cases the patient is lying curled up on her side like a foetus in the uterus; her arms and legs and neck are held firmly flexed. Less commonly all the muscles are flaccid and she lies on her back. The coma may be very deep, but there is often some response to painful stimuli: she may grunt or retract a limb. Examination of the nervous system gives variable results; the essential point that emerges is that there is no hemiplegia.

A more discerning inspection of the patient shows certain features of importance. The skin has a soft texture and is not scaly: it is usually dry, but there is heavy sweating in some cases. The face is peculiarly white, though the mucosae are not correspondingly pale. The eyebrows are thin, particularly in their outer halves, and there may be some puffiness around the eyes and across the bridge of the nose. The head hair is of normal amount and colour and is soft.

The pulse is usually weak; it may be fast, normal, or slow. The blood pressure is subnormal in most cases. The respirations tend to be shallow. The temperature may be raised, normal, or low. The other routine examinations usually give negative results.

At this stage the aetiology of the coma may seem quite obscure. However, if the doctor is aware of the possibility of hypopituitarism as a cause of coma, his suspicions will have been aroused by the appearance of the patient. There are then four easy investigations which will give an almost immediate presumptive diagnosis.

Diagnosis

The most important and most conclusive investigation is simply to look at the vulva. In hypopituitarism severe enough to produce coma there is no hair on the mons and only a few short hairs on the labia majora. If the patient has no pubic hair, confirmation of the diagnosis of hypopituitarism can be obtained from two sources. Firstly, the thyroid is too small to palpate; a palpable gland almost negatives the diagnosis. Secondly, there is atrophy of the genital tract. The vulva and vagina are atrophic, the cervix is very small and may be little more than a dimple, and the uterus is correspondingly small; these findings are very significant if the patient is under 45, though they are obviously of much less importance in a woman of 60. When the existence of hypopituitarism has been reasonably clearly established from the physical examination, the last step is to question the relatives about the details of the clinical history, because this will usually clinch the diagnosis.

For the benefit of those who may only have studied the rather misleading accounts of hypopituitarism which were current in medical textbooks a few years ago, three points must be made clear. Firstly, the patient's nutrition is usually quite satisfactory. A significant degree of emaciation throws serious doubts on the diagnosis of hypopituitarism, though it does not necessarily disprove it. Secondly, though no woman looks her best when she is in coma, these patients do not show premature senility. Thirdly, the state of the teeth is quite irrelevant.

When it has been established that the patient has a severe hypopituitarism, it may be accepted as reasonably certain that a coma of the type described here is due to the endocrine disturbance. Nevertheless, the other cause of coma should, of course, be excluded so far as is possible. In addition, if pathological facilities are available, a sample of blood should be collected for estimation of the blood sugar and any other examinations which may appear advisable.

If the existence of the hypopituitarism is not recognized, the coma may be incorrectly attributed to other conditions: (a) cerebral thrombosis, because of the gradual onset; (b) epilepsy, because of the convulsions which sometimes precede the coma; (c) meningitis, because of the rigidity of the neck; (d) uraemia, because of the white and sometimes puffy face and perhaps because of pyuria which may be mistaken for albuminuria; however, the blood pressure is not raised; (e) myxoedema, because of the appearance of the face, the dry skin, and the history of mental dullness and physical weakness; or (f) narcotic poisoning.

Types of Coma

In most cases hypopituitary coma seems at first sight to be of a rather uniform pattern. However, there are in fact

several different clinical and biochemical varieties. These variations are as yet not clearly understood, but certain broad clinical types can be recognized.

(1) *Pyrexial*.—The temperature is high (about 102 to 105° F.—38.9 to 40.6° C.), but the pulse rate is not correspondingly fast. The blood pressure is low (systolic pressure about 80). The coma is usually of gradual onset and tends to be of spastic type.

(2) *Hypothermic*.—In this group the coma is also of gradual onset in most cases but is commonly of flaccid type. There is no radial pulse and the heart is beating very feebly at a rate of about 30 to 40 a minute. The respirations are also very shallow and slow. The patient feels very cold to the touch. The temperature is usually recorded as 96 to 97° F. (35.6 to 36.1° C.), but this simply means that the clinical thermometer has failed to register. An ordinary chemical thermometer must be used to measure the true temperature. If the bulb is passed up the vagina to near the cervix, the stem protrudes far enough to allow a reading to be made without removing the thermometer. With this method it is found that the temperature is actually in the eighties or even in upper seventies (26–30° C.).

(3) *Hypoglycaemic*.—This is a general clinical group which includes cases which have a blood sugar of 15 to 30 mg. per 100 ml., and also a number of less typical cases with blood sugars as high as 50 mg. The temperature and pulse are about normal; the systolic blood pressure is about 100. In these cases the coma tends to develop rapidly, sometimes early in the morning. One variety is characterized by heavy sweating which often precedes the coma; these patients may recover consciousness quite suddenly and without treatment after a few hours of coma.

(4) *Other Types*.—The blood sugar is at a relatively normal level. The temperature and pulse are normal and the blood pressure is rather subnormal. The coma is commonly preceded by a few days of vomiting.

Treatment

There is as yet no specific treatment of the coma. Many of the patients recover spontaneously, and it is thus difficult to assess the value of any particular line of therapy. Nevertheless in practice certain methods are undoubtedly useful.

Intravenous Glucose.—If the blood sugar is very low, and the coma has not lasted too long, the intravenous administration of glucose usually has a dramatic effect. There are other cases in which the blood sugar is not extremely low but in which intravenous glucose produces a rapid though sometimes only partial improvement. In other cases, particularly the pyrexial and the hypothermic types, this treatment seems to be useless. In practice, it is only rarely that the results of blood-sugar estimations are to hand before treatment has to be begun. Nevertheless it is worth while to give glucose as a "blind" routine treatment to all the patients, or at any rate to those whose temperatures are normal. A significant proportion of the cases are hypoglycaemic and will be cured by glucose, and the others will be made no worse. One precaution must, however, be observed. Within a couple of hours after giving a large dose of intravenous glucose to a patient with hypopituitary coma the blood sugar may fall again to levels of 30 mg. or less. It is therefore important that, when the glucose has been begun, it should be continued for many hours, and that a careful watch on the blood sugar should be maintained afterwards.

The best method of administration is by intravenous drip of 20% glucose solution. The first half-litre may be given quickly, but thereafter the solution should be given at a rate of 1 litre every 8 or 12 hours (about 20 or 30 drops a minute). If the emergency appears serious and no continuous drip apparatus is at hand at the time, the glucose solution may be injected intravenously with a syringe in a dose of 100 ml. every hour until the apparatus can be obtained. In such a case it is wisest to cut down on a vein

at the ankle and insert a fine "polythene" tube which can be left in place for a day; it is essential not to ruin all the available subcutaneous veins, because these will probably be required on many occasions later.

Treatment of Hypothermia.—The second line of treatment is that of patients in severe hypothermia. In these cases it is very difficult to raise the body temperature with hot-water bottles, and it is correspondingly easy to burn the skin. The most satisfactory method of warming the patient is to put her into a tepid bath (about 95° F.—35° C.) and gradually add hot water to it until a pleasant hot-bath temperature (about 102° F.—38.9° C.) is reached. After the patient has been in the hot bath for about half an hour, her heart rate increases gradually, the pulse returns at the wrist, and the temperature in the mouth begins to rise. It takes about two hours to bring the heart rate and temperature to normal levels. At this stage the patient usually shows signs of returning consciousness. She is lifted out of the bath, dried quickly, and placed in a warm bed. If the treatment is successful, she recovers full consciousness in the course of the next day.

Antibiotics.—Patients with pyrexial coma are usually given antibiotics, and sometimes recover from the coma after the temperature has settled. In other cases without pyrexia, the same therapy may be given with the object of preventing the subsequent development of a pneumonia, just as in any other comatose patient. The treatment is non-specific, so the choice of antibiotic is a matter only of personal preference, with the proviso that the administration must be either intramuscular or intravenous.

Hormones.—Finally, consideration must be given to the use of various hormones in the treatment of the coma. The patient is suffering not only from a total insufficiency of the anterior pituitary, but also from an extremely severe insufficiency of the adrenal cortex and of the thyroid. There is thus a very strong theoretical argument for giving adrenocortical and thyroid hormones. In practice, however, these treatments are disappointing. Cortisone, "eucortone," deoxycortone and salt, and testosterone have usually been given. Some of the patients have recovered gradually in the course of a day or two; others have died. There is no convincing evidence that these treatments changed the course of the coma from what it would have been if no treatment had been given. On the other hand, there is no evidence that cortisone is harmful in these cases, and thus there is no particular reason for withholding it if the doctor believes that it may do good. The usual dose is about 100 mg. intramuscularly each day; successes and failures have been claimed with doses ranging from 25 to 700 mg.

General Prophylaxis

After the patient has recovered from the coma it is as well to refer her to hospital for a full endocrinological study, which may take a few weeks. She will probably return home on a maintenance dose of 12.5 mg. of cortisone daily, usually with small amounts of thyroid and testosterone in addition. It is essential to continue this cortisone therapy permanently, not only because of its effect on the general health of the patient but also for two other reasons. Firstly, there is increasing evidence which suggests that continued treatment with cortisone prevents recurrences of coma. Secondly, it is possible that the sudden withdrawal of treatment may lead to an attack of coma a few weeks later.

Apart from this mainstay of treatment, care must be taken to avoid the following factors, which are known to precipitate coma in these patients.

1. General anaesthetics, even for minor operations. If anaesthesia is essential a preliminary boosting dose of 50 to 100 mg. of cortisone is usually advised on theoretical grounds, though, in the nature of things, it is difficult to get any real proof that this treatment is of practical value.

2. Morphine, barbiturates, and many of the other sedatives. The usual reason for giving these drugs is as premedication before operations under general or local

anaesthesia, or to control a patient during one of the attacks of mental disturbance which may occur in hypopituitarism. Drugs of this type are best avoided.

3. Insulin is very dangerous to these patients and should never be given to them except for certain special laboratory tests.

4. If the patient does not have adequate nourishment for a day or two she may become comatose. Feeding should be continued throughout any illnesses.

5. Even apparently minor illnesses may lead to coma and should be treated at their onset. Attacks of diarrhoea and vomiting are dangerous. Many lung conditions such as pneumonia, gangrene, or tuberculosis can be astonishingly symptomless in the patient with hypopituitarism, and their only obvious clinical effect may be to produce coma.

6. It is stated in many textbooks that the administration of thyroid is very apt to produce coma in patients with hypopituitarism. There is no real evidence to support this idea, and in fact a dose of 2 gr. (0.13 g.) of thyroid daily is usually quite harmless. However, some patients do appear unduly sensitive, and others who have been misdiagnosed as myxoedema are treated with steadily increasing dosage of thyroid until vomiting and diarrhoea are produced. Such alimentary tract disturbances are of course serious.

7. These patients are unable to produce a diuresis, and excessive fluid intake may thus lead to water retention though with no overt oedema. Recent observations suggest that this sometimes gives rise to coma.

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CONTRIVANCE OF COLLEGIATION HARVEIAN ORATION

The 236th Harveian Oration before the Royal College of Physicians of London was delivered on October 18 by Sir JOHN CHARLES, Chief Medical Officer of the Ministry of Health.

In his introduction the Orator described briefly what was known of Harvey and his work and his services to the College. Much of his material had been culled from Harvey's *Praelectiones*, which he regarded as having been too little studied. It illuminated Harvey's rich fund of general knowledge and the philosophic bent of his mind. Of the ancient authorities on medicine Aristotle was to Harvey the prince of philosophers, and, like Harvey, Aristotle was a member of the household of a king. The father of Aristotle, Nicomachus, was court physician and friend of Amyntas II, father of Philip of Macedon and grandfather of Alexander the Great, and his son Aristotle was thought to have followed for a time his father's calling of physician. Later Aristotle became the tutor of the young Alexander, instructing him, among other accomplishments, in the use of drugs.

The Orator passed in review other court physicians: Grimbald, the physician of Henry I, whose claim to immortality was that he occasionally witnessed official papers, and

John Francis of St. Albans, the surgeon of Edward I, who appeared in the Treasury accounts as something of an over-prescriber of drugs. But it was not until Thomas Linacre came on the scene that a court physician was found who was able to influence the royal mind for the benefit of the profession in general. “It is difficult,” said the Orator, “to escape from the conclusion that this was the influence which determined the first Medical Act of 1511 which separated out the ‘cunning’ physician from the ‘uncunning’ practitioner of sorcery and witchcraft and recognized his status.” Moreover, it was due to Linacre's genius that the Royal College of Physicians was founded, thereby bringing the “contrivance of collegiation” into play for the protection and furtherance of the interests of the profession as a whole.

Though Harvey was in attendance at the courts of James I and Charles I and was indeed a trusted servant of the latter, he was employed less as a physician than as an emissary, and even as an emissary his influence on royal policy was negligible. Of even less political influence was his colleague Turquet de Mayerne, chief physician to James I, who became a Fellow of the College by invitation in 1616, and, while never actively participating in its work, was always willing to use his good offices in its service. Mayerne was a man of great medical reputation and considerable financial ability. He had intimate contact with the courts of France and England; yet, like Harvey, his influence on the policy of the rulers he so assiduously courted was quite negligible, and there was no record that he inspired any Government action even when it concerned the health of the nation.

Growing Prestige of the College

In marked contrast to the ineffectiveness of these medical intimates of rulers throughout the ages was the history of the College in the evolution of its functions, the assumption of responsibilities, and the acquisition of prestige. The Orator went on to describe how the College concerned itself primarily with the qualifications of those who were seeking its licence to practise, often in defiance of influential persons whose recommendations had been given to the unworthy; how it evolved the vestiges of a medical curriculum in the advice given to unsuccessful candidates that they should take a four-year course of Galen, with the set books all carefully listed; how it examined and adjudicated on the standards of practice of Fellows on the receipt of complaints; and how it became responsible for the inspection of grocers and apothecaries, who were enjoined to display their ingredients “in the windows of their shops, so that physicians passing by might judge of their goodness.” Among other acts of general application the College compiled the first pharmacopoeia in this country—the *Pharmacopoeia Londinensis*.

Spirituos Liquors

The Orator went on to give examples illustrating the virtues of the contrivance of collegiation and of the strength which close and friendly collaboration could confer on professional men who, individually, even in what might be regarded as most favourable circumstances, could exercise little effect on conditions affecting their own profession and the welfare of the people committed to their charge.

The enormous and devastating growth of the consumption of spirituous liquors, especially gin, in the early eighteenth century became a national scandal. In 1725–6 the College took the initiative by offering to the House of Commons in January certain representations against the pernicious use of such liquors. In these representations it was stated that it was the duty of the College to take care of the health of His Majesty's subjects in London and within a seven-mile circuit, and that it had for some years observed with concern the fatal effects of the consumption of several sorts of distilled spirits upon great numbers of both sexes. Despite the fact that it took thirty more years of hard campaigning by humanitarian persons to goad the