HYPOPITUITARISM WITH PITUITARY TUMOURS

CORTISONE IN THE TREATMENT OF STUPOR ASSOCIATED WITH HYPOPITUITARISM

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The incidence of hypopituitarism associated with tumours in and around the pituitary fossa is difficult to assess on account of changing criteria of diagnosis. With the development of tests, such as the insulin sensitivity, the estimation of the urinary 17-ketosteroids and 11-oxysteroids, tests of radioactive iodine uptake, and Thorn's test of the eosinophil response to the injection of 25 mg. of A.C.T.H., it is now possible to make a more accurate appraisal of the endocrine state of these patients and to predict the likely response to stress. In Grant's (1948) series of 71 patients with intrasellar tumours, in the pre-operative period, 65 (91%) had evidence of hypopituitarism, whereas Davidoff and Feiring (1948) found amenorrhoea or failure of potentia in only 50 out of 93 cases (57%).

From a study of the post-operative mortality in pituitary tumours some writers suggest that one of the chief causes of death may be an endocrine failure. In Grant's series of 71 cases with 85 operations, 8 deaths occurred (11.2%). Six of these "had burned out chromophobe adenomata with polyglandular function which was at a very low ebb." In three of them Grant records that following a relatively simple operation the patients became stuporous and semicomatose and died on the fifth, ninth, or twelfth post-operative day. Necropsy done on two of these patients showed atrophy of the adrenals, thyroids, and gonads. He comments that "a simple evacuation of the tumour was enough to abolish completely what little pituitary function remained." He believes the operative mortality in these cases of generalized glandular insufficiency is high, and surgical attack should be undertaken cautiously. He writes: "A satisfactory test for adrenal insufficiency would be of value so that surgical measures could be avoided in cases with severe adrenal cortical damage."

Roche, Thorn, and Hills (1950) utilized the eosinophil levels during and after surgery, and their response to A.C.T.H., as a method of assessing the adrenocortical function. They concluded that the measurement of the fall in eosinophils after the injection of 25 mg. of A.C.T.H. prior to surgery was a good index of the capacity of the adrenal cortex to secrete 11-oxysteroids and furnishes a means of pre-operative prognosis.

The object of this communication is to place on record details of four patients with pituitary tumours with varying degrees of hypopituitarism, and to comment on their endocrine state and on their reaction to the stress

of operation. In assessing the endocrine state of these patients we have relied on the history, the clinical state, the insulin sensitivity test, and the estimation of the urinary 17-ketosteroids as used by Fraser and Smith (1941). These authors found that patients with marked hypopituitarism have very low urinary 17-ketosteroids, and insulin-sensitivity curves which show a prompt fall of blood sugar and thereafter manifest hypoglycaemic unresponsiveness.

Case 1

A case of craniopharyngioma, with bitemporal hemianopia and marked hypopituitarism. After operation the patient passed into a drowsy semicomatose state, from which he slowly recovered without substitution therapy six weeks later, and in three months was discharged.

A single labourer aged 44 had noticed an increasing lethargy for five years, and for two months was unable to see objects on his left side. For a month he had complained of occipital headaches. His growth of hair on the face had always been sparse, and he had never shaved more than every other day. He had recently noticed failure of potentia and loss of libido.

On physical examination he was seen to be a well-nourished man with soft sallow skin having a tendency to dryness. His head hair was natural and his facial and body hair sparse. The axillary hair was scanty, and the pubic hair lacked curl and was of a female type of distribution. The optic disks were pale, and there was bitemporal hemianopia. His visual acuity was: left eye J 8, right eye J 6. A radiograph of the skull showed an enlarged sella turcica with erosion of the clinoid processes. An encephalogram revealed a rounded tumour arising from the enlarged sella turcica and indenting the third ventricle. A blood count showed: red cells, 4,130,000; haemoglobin, 11.46 g.; white cells, 6,650. The cerebrospinal fluid was under normal pressure and the contents were normal. The glucose-tolerance test gave 80, 110, 100, 100, 90 mg. per 100 ml. His blood pressure was 116/70.

On April 13, 1951, one of us (A.J.) did a right frontal craniotomy and an intracapsular removal of a craniopharyngioma. There was no intracapsular haemorrhage. On the day after operation he was restless and confused. His temperature and pulse were normal. There was no polyuria. He remained in a drowsy stuporous state, moving about in bed and replying indistinctly to questions. He was able to obey simple commands. His blood pressure was 100/60. His spinal-fluid pressure was 100 mm.; the fluid was xanthochromic; and the protein 160 mg. per 100 ml. Intravenous and intragastric glucose-saline was given, but he failed to rouse. On April 18 it was decided to explore the operation site again to exclude an extradural or subdural clot.

Operation revealed a small firm blood clot between the bone and the dura, and there was a minimal amount of clot beneath the frontal lobe. Following operation there was little improvement, and 36 hours later he was still in the same drowsy stuporous state and was more difficult to rouse. He was doubly incontinent. He made some response on painful stimulation. The spinal-fluid pressure was 100 mm. On April 21 exploration was again made. The frontal lobe appeared to be shrunken, but no blood clot was evident. He failed to rouse after the exploration, and six days later was still semicomatose and difficult to rouse. The total non-protein nitrogen was 24 mg. per 100 ml., serum sodium 342 mg. per 100 ml., serum potassium 16 mg. per 100 ml. The electrocardiogram was within normal limits. He remained in this drowsy semicomatose state for five weeks; then he began to rouse and gradually improved, regained sphincteric control, and a week later was able to get up in a chair. He improved steadily, and on July 11 was discharged. His visual acuity was: right eye

J 1, left eye J 2; and to confrontation there was a left upper quadrant defect. He had a complete amnesia for a period of five weeks after the initial exploration.

Case 2

A case of chromophobe adenoma causing visual-field defects and marked hypopituitarism. Following operation he passed into a stuporous state and actively refused food and fluids. Substitution therapy with testosterone, D.C.A., thyroid, and salt was started. A week later he was much improved. Discharged well.

A bus contractor aged 47 was admitted to the Dunedin Hospital on account of failing vision. Fifteen years previously he had had a severe bout of headache which settled in a week or two. He remained well until eight months before admission, when he noticed his vision was defective. He had never had a normal amount of hair on his chest and his facial hair was sparse at the sides. All axillary hair had fallen out over the past year and his pubic hair was very scanty. For a year there had been loss of libido and failure of potentia.

On examination he was seen to be a sallow-complexioned, well-developed, well-nourished man with a full head of fine hair, sparse hair on the sides of his face, sparse hair on the limbs, and none on the chest. There was complete lack of axillary hair, and his pubic hair lacked curl and was sparse and of a female type of distribution. The gonads were small and soft, the prostate small. His hands and feet were large. His visual acuity was J 2 in each eye. Both optic disks were white, with clearly defined edges. To small objects he had a complete bitemporal hemianopia with sparing of fixation-point. The rest of the central nervous system and other systems were normal. The blood pressure was 110/70. A radiograph of the skull showed a greatly enlarged pituitary fossa. An encephalogram showed the third ventricle and basal cistern to be filled and the tumour outlined. It appeared to be larger on the left side. A blood count showed: haemoglobin, 13.6 g.%; packed cell volume, 41%; white cells, 7,100 (eosinophils 125 per c.mm.). The blood and spinal fluid Wassermann reactions were negative. The spinal fluid was under normal pressure; there was a moderate increase of globulin; total protein, 70 mg. per 100 ml. The glucose-tolerance curve was flattened—70, 80, 90, 90, 100 mg. per 100 ml. The insulin-sensitivity curve (0.1 unit of insulin per kg.) was 70, 30, 25, 30, 40, 55 mg. per 100 ml. and showed marked hypoglycaemic unresponsiveness. The serum cholesterol was 295 mg. per 100 ml., and the urinary 17-ketosteroids 0.5 mg.

One of us (A.J.) did a left frontal craniotomy and removed a chromophobe adenoma. The patient failed to rouse in a normal fashion and remained drowsy and stuporous but could be got to answer questions. On the third post-operative day he was very restive and forcibly refused any fluid or food intake. This active refusal necessitated feeding by tube. He was incontinent of urine and faeces and continued in a stuporous state with a negativistic attitude, making nursing care difficult. His blood pressure was 104/64. The blood sugar was 115 mg. per 100 ml., and there was no sweating, tachycardia, or vomiting. The serum sodium was 230 mg. per 100 ml., and serum potassium 16 mg. per 100 ml. Two weeks after operation he was in much the same state and the double incontinence persisted. He was then given an implant of testosterone, 200 mg., and 100 mg. of D.C.A. Sodium chloride, 2 g., and thyroid siccum, 1½ gr. (0.1 g.), were given daily. His blood count was: red cells, 4,000,000; Hb, 11.9 g.%. Six days after the implants he was much improved, and was continent and co-operative and eating food normally. His temperature was normal and there was no excessive thirst. He was still drowsy and had a partial amnesia for two weeks in the post-operative period. His skin was dry and showed a branny desquamation on the face and limbs. He was discharged 40 days after the operation feeling well and more energetic than before operation. His visual acuity was: right eye J 2, left eye J 1. There was still an upper quadrant defect in both temporal fields.

Case 3

Chromophobe adenoma of the pituitary gland with bitemporal hemianopia and hypopituitarism. Patient failed to rouse after operation. Possible response to cortisone and "neosynephrine," with complete recovery.

A builder aged 46 was admitted on September 14, 1951, complaining of failing vision. Four years previously he had noticed difficulty in seeing objects on the left side, and thereafter the vision in the left temporal field gradually deteriorated. Three years previously he developed left frontal headaches, which were worse in the morning and throbbing in character. These cleared after several weeks. His skin had always been soft and his body hair scanty. He shaved daily, but his facial hair was sparse. His potentia and libido had never been notably good, and recently had failed completely.

On examination he was seen to be a well-developed and well-nourished man with sallow skin which was puffy about the face and wrinkled round the mouth. His head hair was fine and facial hair sparse. There was complete loss of axillary hair, and his pubic hair was scanty and of female distribution. There was very scanty hair on the limbs and chest. The eyebrows were normal. The gonads were small and soft on palpation. The visual acuity was: left eye 6/12, right eye 6/6. To confrontation tests there was a complete left temporal hemianopia and a partial right hemianopia. The disks were pale on the temporal halves. The rest of the central nervous system was normal. The heart was enlarged. The aortic second sound was accentuated, and the blood pressure was 190/120. The spinal-fluid pressure was 140 mm.; and there was no increase of cells; protein, 60 mg. per 100 ml. The Wassermann reaction was negative in the blood and spinal fluid. A radiograph of the skull revealed a considerable enlargement of the sella turcica and a few small flakes of calcium above and in front of it. The serum cholesterol was 305 mg. per 100 ml.; haemoglobin, 11.6 g.%; P.C.V., 36%; white cells, 6,000 (eosinophils 225 per c.mm.); glucose-tolerance test, 80, 110, 90, 90 mg. per 100 ml.; the insulin-tolerance curve (0.1 unit of insulin per kg.) was 75 mg. resting, 35, 35, 30, 30, 50, 65 mg. per 100 ml. Hypoglycaemic symptoms developed 20 minutes after the injection of insulin. The urinary 17-ketosteroids were 0.3 mg.

On September 24, 1951, one of us (A.J.) did a right frontal craniotomy and partially removed a chromophobe adenoma. The patient failed to rouse completely, and 36 hours later was confused, disorientated, and incontinent. He became increasingly drowsy, but could be roused by shouting, and he answered questions. Pulse and respirations were normal, temperature 103° F. (39.4° C.). It was possible that his state was due to a crisis of hypopituitarism, but post-operative haemorrhage could not be excluded and the right frontal flap was again turned down. A small amount of clot was removed from the vicinity of the pituitary fossa. In the second post-operative period he failed to rouse, and again the frontal flap was turned down and a small clot removed. On September 27 the serum sodium was 294 mg. per 100 ml., serum potassium 21 mg. per 100 ml., and blood sugar 120 mg. per 100 ml. The electrocardiogram did not reveal evidence of abnormal potassium level. His pulse was 158, blood pressure 100/70, and respirations 80. Cortisone therapy was started on September 27 with 100 mg. intramuscularly, and 0.5 ml. of neosynephrine was given and repeated two-hourly. Thereafter 50 mg. of cortisone was given six-hourly.

Forty-eight hours after cortisone and neosynephrine were begun there was a notable improvement in his condition. The temperature settled and he became more alert and noticed things around him. The blood pressure rose to 160/90. On September 30 the cortisone was reduced to 10 mg. six-hourly and 10 units of A.C.T.H. was given twice daily. On October 2 the cortisone and A.C.T.H. were discontinued. Next day his wound flap was found to be

infected with a coagulase-positive *Staphylococcus aureus*, but his general condition was very satisfactory. He had an amnesia for the duration of the crisis. On October 13 he was given two pints (1.14 litres) of blood, implants of 200 mg. of testosterone and 100 mg. of D.C.A. were made, and thyroid siccum, 1½ gr. (0.1 g.) daily, and sodium chloride, 2 g., were started. On October 21 he was feeling well but still had a freely discharging sinus in the scalp wound. The heart was probably enlarged. The blood pressure was 180/100 and the blood sugar 255 mg. per 100 ml. On November 30 his general condition was very good, and the right visual field was normal. The left temporal hemianopia still persisted. Osteomyelitis developed in the bone, which was excised, and complete healing followed.

Case 4

A case of acromegaly and chromophobe adenoma. After operation the patient failed to rouse. Re-exploration done, without improvement. Cortisone therapy started, with marked improvement in 28 hours.

A clerical worker aged 39 was admitted to the Dunedin Hospital on November 2, 1951. In 1939 he was often prostrated with severe bitemporal headaches; he had to consult a dentist on account of difficulty with his bite, and he had some trouble with his vision. Eight years ago he noticed difficulty of vision on the left side. This was first apparent when playing cricket, and he was forced to alter his stance as he was unable to see balls coming on the leg side. Although he noticed no change in his appearance, his family state that on his return from the second world war he was hardly recognizable on account of the gross changes in his face. His mother stated that at this time he was always tired and limp and ready to sleep. There had been relative loss of potentia and libido for a year or more. He shaved daily.

On examination he had all the classical features of a gross acromegaly with advanced changes in the face and upper and lower extremities. There was a kyphosis in the upper thoracic region, and he had almost complete bitemporal hemianopia with macular sparing. His visual acuity was 6/6 in each eye. There was pallor of both disks. The secondary sex characteristics were normal. Growth of facial and body hair was normal. The spinal-fluid pressure was 120 mm.; protein 60 mg. per 100 ml. An x-ray film of the skull revealed a very large sella turcica. Other skeletal changes were characteristic of acromegaly. An encephalogram showed evidence of extension of the tumour upwards and backwards. The Kepler test was normal. Factor A, 77. Serum sodium, 330 mg. per 100 ml.; serum potassium, 18.3 mg. per 100 ml. The glucose-tolerance curve was flattened—90, 110, 90, 70 mg. per 100 ml. The insulin-sensitivity curve, 90 mg. resting, 75, 70, 75, 80, 85 mg. per 100 ml., showed some insensitivity. P.C.V. 39%; haemoglobin 11.6 g.%. The electrocardiogram was within normal limits. The blood pressure was 128/74. The urinary 17-ketosteroids were 5 mg.

The pre-operative diagnosis was acromegaly and eosinophilic adenoma of the pituitary gland, which shows some evidence of being "burnt out," as the biochemical findings suggested some hypopituitarism. On November 19 one of us (A.J.) carried out a right frontal craniotomy and aspirated mucoid material from a large pituitary tumour. The patient regained consciousness half an hour after the operation was completed, but the following day was drowsy and difficult to rouse and had a tendency to vomit. He became increasingly drowsy, but could be roused if spoken to loudly and would obey commands. As the drowsiness was increasing it was decided to re-explore the operation site. An unimportant quantity of subdural clot was removed and the tumour capsule was full of blood clot but was not under tension. After operation he failed to rouse. There was no sweating or vomiting; the pulse was 100. The blood sugar was 115 mg. per 100 ml., the total N.P.N. 34 mg. per 100 ml., the serum sodium, 297 mg. per 100 ml.,

and the serum potassium 16.5 mg. per 100 ml. The blood pressure was 100/60.

Cortisone therapy was started, 50 mg. intramuscularly six-hourly. Twenty-four hours later his condition had deteriorated further and he could not be roused. Cortisone, 100 mg., was then given, and two hours later he roused and asked for a drink; thereafter he made steady improvement. He had an amnesia for the period of the crisis. Cortisone, 40 mg., was given six-hourly for four more days. On November 29, implants of testosterone, 200 mg., and D.C.A., 100 mg., were made, and thyroid, 1½ gr. (0.1 g.) daily, and sodium chloride, 2 g., were started. He made steady progress until the date of his discharge. The visual-field defect was improved.

Discussion

Each of these patients had a pituitary tumour—three a chromophobe adenoma and one a craniopharyngioma. Three showed clinical and biochemical evidence of advanced hypopituitarism, and the patient with acromegaly had clinical and biochemical evidence of partial hypopituitarism.

Assessment of the Degree of Hypopituitarism

Clinical.—In three of the patients the history was suggestive of a degree of hypopituitarism for years before the local signs of an intracranial tumour developed, as evidenced by scanty growth of body and facial hair, fine head hair, and lowered potentia and libido. In these three there had been recent falling of axillary and pubic hair, a reduced tolerance to cold, and a failure of potentia and loss of libido. On examination all were well developed and well nourished, with fine head hair in three and normal hair in the patient with acromegaly. The hair on the side of the face was sparse, body hair was sparse with complete loss of axillary hair, and the pubic hair was of a female type of distribution in Cases 1, 2, and 3. In Case 4 the body and facial hair was normal. In Cases 1, 2, and 3 the skin appeared slightly oedematous and sallow, and was wrinkled about the mouth. The testicles were small and soft in Cases 1, 2, and 3.

Laboratory Assessment.—In this our chief guides were the insulin-sensitivity test and the estimation of the urinary 17-ketosteroids. The insulin-sensitivity curves in Cases 2 and 3 were typical of hypopituitarism. In Case 4 the curve suggested a residual insulin resistance (see Table). In Cases 2, 3, and 4 the urinary 17-ketosteroids were 0.5 mg., 0.3 mg., and 5 mg. respectively.

Insulin Sensitivity (mg. per 100 ml.)

Case	Resting Blood Sugar	20 min.	30 min.	60 min.	90 min.	120 min.
2	70	30	25	30	40	55
3	75	35	35	30	30	65
4	90	75	70	75	80	85

It is apparent that Cases 1, 2, and 3 were in a state of advanced hypopituitarism before operation and that Case 4 was less so. In Case 1 the evidence of advanced hypopituitarism was apparent from the history and from the clinical examination. In Cases 2 and 3 the history, clinical examination, and laboratory tests all indicated that these men were in a state of advanced hypopituitarism. In Case 4 it was evident from the acromegaly that there had been overactivity of the eosinophil cells, but the low excretion of 17-ketosteroids strongly suggested that the patient had passed to a state of hypopituitarism, although the insulin-sensitivity curve still showed some evidence of insulin resistance.

These patients suffered from a form of stupor with altered consciousness and disorder of behaviour of varying duration following pituitary operations. In this state of stupor the patients lay quietly, the pulse was normal, the blood pressure was low, and the temperature was elevated in one and normal in three. The corneal reflexes and all superficial

and deep reflexes were present and natural. All could be roused by shouting or by painful stimulation, and at times they obeyed simple commands. There was marked confusion and disorientation, and one actively refused food and fluids. Incontinence of urine and faeces was common to all, but no grasping, groping, or other primitive reflexes were observed. After recovery there remained a period of amnesia for the duration of the stupor.

Treatment and Complication

Allott and Simmons (1951) reported the effect of cortisone in a crisis in one patient with Simmonds's disease. In their record the patient had passed into the state of crisis spontaneously. A state of hypoglycaemia was present, but in spite of intravenous glucose-saline the patient failed to rouse until cortisone was given: thereafter improvement was apparent in 24 hours, and after four days she had emerged from the crisis.

In our first patient no substitution therapy was attempted and the state of stupor persisted for 35 days. Thereafter there was steady improvement. In Case 2 substitution with testosterone, D.C.A., and thyroid was begun on the sixteenth day of the stupor and six days later he recovered consciousness. In Case 3 the crisis was resolved with a short course of cortisone (720 mg.) and A.C.T.H. (60 units intravenously) beginning on the third day of cortisone therapy, and improvement was marked in 48 hours, with a fall of temperature, return of orientation, and recovery of the sphincter control. In Case 4, cortisone therapy was begun on the third day, and 26 hours later he roused and thereafter made steady progress. In this case the total cortisone administered was 1.04 g. in six days. Subsequently, Cases 3 and 4 had implants of testosterone and D.C.A., and thyroid was started.

Complications of cortisone therapy have been reported by several authors. Summers and Sheehan (1951) have reported some cerebrovascular accidents during cortisone therapy. In our third patient osteomyelitis developed in the bone flap, and it is possible that he was predisposed to this infection by the cortisone therapy, as has been shown by other authors. For these and other reasons we believe that the administration of cortisone should be reserved for a short course of therapy in this state of stupor associated with hypopituitarism, and that for more prolonged substitution, testosterone, D.C.A., and thyroid are adequate.

In an attempt to explain the mechanism of the state of stupor we have described, several possible mechanisms have to be considered. The condition presents with an acute psychopathology, an altered state of consciousness, and some behaviour disorder. It may be due to a localized cerebral lesion situated in the frontal lobes or in the hypothalamus, or it might be an expression of a generalized cerebral defect due to hypoglycaemia, hypokalaemia, or to an endocrine failure, either local or generalized.

The handling of the frontal lobe during operation might be a cause of altered consciousness with incontinence. It is to be noted, however, that no primitive reflexes were elicited in these patients as might be expected if the lesions were in the frontal lobes.

Damage to the hypothalamus in the experimental animal and to the intramedullary or extramedullary lesions in man will give changes in sleep, consciousness, and behaviour. Some recorded cases have not been associated with endocrine dysfunction and have been reversed by operation (Cox, 1948). In addition Riddoch *et al.* (1938) have stated that "it is often impossible to assess the origin of certain symptoms which are common to lesions of both hypophysis and hypothalamus."

More recent observations by Williams and Parsons-Smith (1951) suggested that in stupor the inactivity results from disturbances in the ascending reticular system, which is concerned with the activation of afferent impulses. A degree of operative trauma in this region during operation is no doubt sustained, and this system might well have been damaged.

If we accept Selye's doctrine of the adaptation syndrome, then it is clear these patients with failure of the pituitary and secondary failure of the adrenal and other end-organ function are deprived of their protective mechanisms and are in no condition to respond to the stress of an intracranial operation. The state of stupor then may be the outcome of this general endocrine failure. The endocrinological and nervous functions are to some extent dependent on each other, and we believe the somewhat dramatic response to cortisone and other substitution therapy lends support to the theory of general endocrine failure.

In view of the secondary failure of the adrenal glands it would not be surprising to discover a state of crisis which resembles the crisis of Addison's disease. It is noted that moderate hypertension was common to all cases, and also that the serum sodium levels were just below normal in three of the patients. In none, however, was there vomiting, sweating, or a state comparable with the crisis of Addison's disease.

Patients with hypopituitarism are prone to attacks of hypoglycaemia on account of their increased sensitivity to insulin, defective gluconeogenesis, and their resultant hypoglycaemic unresponsiveness. In none of our patients did the state of crisis resemble that of hypoglycaemia. In Allott and Simmons's patient, quoted above, a state of hypoglycaemia was present in the crisis. In our cases there was no sweating, tremor, or tachycardia, and the blood-sugar levels in three were normal.

Allott (1939) and Cooper and MacCarty (1951) describe cases that developed raised serum sodium and blood chlorides and low urinary chlorides following intracerebral operations. In two of the latter's cases the electrolytic abnormalities followed surgical removal of pituitary tumours. No detailed account is given of the endocrine state of these two cases before the operation, but the clinical description of the condition of the two patients in the post-operative phase was comparable to that seen in our four patients. In our patients, however, the serum sodium levels were lowered in three and normal in one.

The evidence obtained from these cases is not complete enough to establish with any certainty whether one or several factors were operating. From the therapeutic response to substitution, a further means of investigation is available, and the results suggest that endocrine dysfunction may predispose to a state of stupor and possibly death. If this is established in future cases prophylaxis against this state of crisis may be possible by substitution therapy in the pre- and post-operative periods.

Summary

Four patients with hypopituitarism associated with pituitary tumours are described.

The assessment of hypopituitarism by clinical and biochemical methods is discussed.

Following operation the four patients passed into a state of stupor. The nature of this stupor is discussed.

In two patients the stupor was effectively treated with cortisone and subsequent substitution with testosterone, D.C.A., and thyroid.

In one patient the stupor appeared to be relieved by substitution with testosterone, D.C.A., and thyroid.

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