is discounted, and the overalls absorb approximately their own weight of sweat. The very real protection which overalls provide against steam leaks, burns from very hot metal parts, dirt or oil, and flash burns in wartime cannot be denied; but they should be made of the lightest and most ventile and durable fabrics which will meet these other requirements.

Since Bedford (1946) proposed that the effective temperature scales should be used in the Navy for describing warm environments, no better alternative has appeared. The ventilated dry- and wet-bulb thermometers, of either the "sling" or Assmann design, still provide the medical observer with the most accurate and convenient method for measuring the air temperature and humidity. The silvered katathermometer has not been replaced by any more simple and equally accurate alternative for measuring turbulent air currents of low velocity. The globe thermometer has emerged successfully from a series of comparisons, with other available methods for determining the mean radiant temperature, made by Newling in a "radiant-heat tunnel" at Singapore. The "corrected effective temperature" also gained support from physiological investigations by Macpherson and others of the team in the same radiant-heat tunnel (Macpherson, 1952). But it is wise to remember that the effective temperature scales were constructed primarily to deal with the thermal environment to which persons engaged in light work are exposed indoors during the summer in homes and offices in North America. They are most useful when used for this type of environment, and are beset with pitfalls when used for situations which they were not designed to meet.

Conclusions

Apart from information about the various factors which limit work at high temperatures, probably the most useful facts which have been derived from these studies so far are, first, that the effects on men in the Tropics are very similar to the effects observed on men doing the same kind of work in temperate climates, provided the workers are trained to work in the heat and are able to recuperate between exposures in an atmosphere which is not so warm that it induces perceptible sweating; secondly, that the upper tolerable levels of warmth for men in a similar state of training for work in warm atmospheres are much the same whether they are living in the Tropics or in England; and, thirdly, that the variations between individuals, and even in the same individual from day to day, are very great at times. Observations made on small numbers, or on only a few occasions, may be misleading if they are used as a basis for general conclusions. Finally, with regard to men who are not specially trained to work at high temperatures, Weiner and Macpherson (1953) have produced evidence, from experiments carried out under otherwise identical conditions in Singapore and at Oxford, which indicates that untrained men in England are less heat-tolerant than untrained men in Singapore.

I have referred to only a few aspects of the many problems which arise from the impact of warm climates on man, and no attempt has been made to review contemporary opinion on these controversial topics. There is still much to be learnt. Special situations, such as those which result when men have to work hard and wear impermeable protective clothing in warm atmospheres, may need to be investigated as separate problems when they arise, and the effects of repeated and prolonged exposure to warm atmospheres require much more study. But, within the limitations of the techniques available at the present time, many of the principles which are relevant to the practical problem of maintaining the efficiency and health of men engaged in military or naval operations in warm humid climates

are now established as firmly as they are likely to be by a purely experimental approach, and should be tested thoroughly in practice. In this way the shortcomings of the results of research will be revealed and new problems will be uncovered.

This paper is published by permission of the Medical Director-General of the Navy, Surgeon Vice-Admiral Sir Alexander Ingleby-Mackenzie.

REFERENCES

- Bedford, T. (1946). *Med. Res. Coun. Lond. War Memo. No. 17.*
 Carthew, M. (1927). *J. trop. Med. Hyg.*, **30**, 113.
 Castellani, A. (1929). *Ibid.*, **32**, 173.
 Critchley, M. (1945). *British Medical Journal*, **2**, 145, 208.
 — (1947). *Brit. J. industr. Med.*, **4**, 164.
 Eijkman, C. (1924). *Lancet*, **1**, 887.
 Ellis, F. P. (1947). *Brit. med. Bull.*, **5**, 1015.
 — (1948). *British Medical Journal*, **1**, 587.
 — (1950). *Med. J. Malaya*, **4**, 175.
 — (1952a). *Lancet*, **2**, 527.
 — (1952b). *J. Hyg., Lond.*, **50**, 415.
 — (1953a). *Ann. roy. Coll. Surg. Engl.*, **13**, 369.
 — (1953b). *Symposium on Fatigue*. Ergonomics Research Society. Lewis, London.
 — (1953c). *J. Hyg., Lond.*, **51**, 386.
 Kenney, R. A. (1954). *Brit. J. industr. Med.*, **11**, 38.
 Ladell, W. S. S., Waterlow, J. C., and Hudson, M. F. (1944). *Lancet*, **2**, 491, 527.
 Lamprell, B. A. (1948). *Med. J. Malaya*, **3**, 34.
 Lee, D. H. K., and Macpherson, R. K. (1948). *J. appl. Physiol.*, **1**, 60.
 Lugg, J. W. H., and Ellis, F. P. (1954). *Brit. J. Nutr.*, **8**, 71.
 Mackworth, N. H. (1950). *Spec. Rep. Ser. med. Res. Coun. Lond.*, No. 268.
 Macpherson, R. K. (1949). *Pap. Dep. Physiol. Univ. Qd.*, **1**, No. 10.
 — (1952). *Abstr. XIX int. Physiol. Congr.*, p. 583.
 O'Brien, J. P. (1947). *Brit. J. Derm. Syph.*, **59**, 125.
 Royal Naval Tropical Research Unit. Unpublished reports to the Medical Research Council's Royal Naval Personnel Research Committee.
 Sanderson, P. H., and Sloper, J. C. (1953). *Brit. J. Derm.*, **65**, 252.
 Stannus, H. S. (1927). *Trans. roy. Soc. trop. Med. Hyg.*, **20**, 327.
 Stenning, J. C. (1945). *J. roy. nav. med. Serv.*, **31**, 129, 195.
 Thomson, M. L. (1946). *Rep. R.N.P. 46/345 Royal Naval Personnel Research Committee. Med. Res. Coun. Lond.*
 Weiner, J. S., and Macpherson, R. K. (1953). *Abstr. XIX int. Physiol. Congr.*, p. 874.
 Wolkin, J., Goodman, J. I., and Kelley, W. E. (1944). *J. Amer. med. Ass.*, **124**, 478.

COMA AND ALLIED DISTURBANCES OF CONSCIOUSNESS IN HYPOPITUITARISM

BY

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In an early account of hypopituitarism Simmonds (1914) described a woman who was subject to attacks of unconsciousness, one of which ended in death. Later it came to be recognized that these patients were prone to loss of consciousness and often died in coma, a phenomenon which was usually attributed to hypoglycaemia. Further experience has shown, however, that hypoglycaemia is only one of many factors which may affect their state of consciousness. Allott and Simmons (1951) and Summers and Sheehan (1951) have discussed "hypopituitary coma" in post-partum necrosis of the pituitary gland, while Caughey *et al.* (1952) and Ingraham *et al.* (1952) have reported on coma with tumours in and around the pituitary fossa. In other papers Caughey (1953, 1954) has described a variety of factors causing disturbances of consciousness in hypopituitarism. These changes of consciousness included hypersomnia, fainting, hypoglycaemic attacks, and "hypopituitary coma." From these and other reports it is clear that these patients are unduly vulnerable to factors affecting the level of consciousness, and that the diagnosis and

correction of the resulting coma require recognition as a medical emergency. Now that measures are at hand which will protect these patients against many of the effects of surgery, infection, and other stresses, and in the light of more recent experience, we feel justified in presenting a further report.

This report is based on 17 cases of hypopituitarism. All the patients showed disturbances of consciousness, which varied in severity from mild confusion, hypersomnia, and defective cerebation to stupor and profound coma. The immediate precipitating factors were numerous, and included operations in the vicinity of the pituitary fossa, pituitary apoplexy, infections, hypoglycaemia, drugs and anaesthetics, electrolyte disturbances, water intoxication, and cerebral anoxia. Ten of these cases have been fully described already (Caughey, 1954) and are not recapitulated here in any detail; the remainder are reported more fully. The endocrine findings in all these cases are summarized in the Table. As a result of further experience the material is presented in a different form from that used in the earlier report. Examples are given to illustrate coma arising from the various precipitating causes. Then the aetiological factors and, finally, diagnosis, prevention, and treatment of hypopituitary coma, are discussed.

Factors Which May Precipitate Changes in Consciousness

1. Surgery of the Pituitary Gland

After operations on pituitary tumours there is a risk of coma which may prove fatal. In Grant's (1948) series of 71 cases of pituitary adenomata, three patients died in post-operative coma which lasted from five to twelve days. Before operation their basal metabolic rates were less than -30%, and at necropsy there was atrophy of the gonads and of the adrenal and thyroid glands. Of Grant's 30 patients with craniopharyngioma, 10 died shortly after operation, several in coma and with manifest polyglandular hypoplasia. Grant believed that there was a higher operative mortality when endocrine function was defective, and advised caution before proceeding with surgical exploration.

We have seen prolonged coma follow intracranial operation in four patients with pituitary tumours (Cases J. P.,

S. M., J. H., and K. M.). All had hypogonadism, but in only two was there clear evidence of adrenal or thyroid failure. We have also seen a similar type of coma following operation on a pituitary eosinophil adenoma in a patient with acromegaly, but with minimal evidence of hypopituitarism (Caughey, 1954). After operation these patients failed to regain consciousness and remained stuporous, or comatose, for several days, one for as long as six weeks, before recovering. The clinical findings were remarkably uniform. The patients lay quiet and incontinent, but could just be roused by painful stimuli. Primitive reflexes, such as grasping and sucking, could not be elicited. They all recovered and showed complete amnesia for the period of coma. Pulse rate and blood pressure were normal or only slightly lowered. The temperature was raised in one, normal in three, and low in one. Blood-sugar levels were normal, and in only one was there a low plasma sodium concentration. The following is an illustrative case.

J. H., an architect builder aged 46, had developed a bitemporal hemianopia over the course of four years, and for three years had had left frontal headaches. His skin had always been soft and bodily and sexual hair growth scanty. On examination he was well nourished but sallow, with a wrinkled face. Facial and pubic hairs were scanty and axillary hair was absent. Both optic disks were pale and the pituitary fossa was enlarged. Adrenal function was found to be defective (see Table). After an intracapsular removal of a chromophobe adenoma, he became semi-comatose and was doubly incontinent. He was twice re-explored, confirming the absence of haemorrhage at the operative site. Three days after the second operation the blood pressure was 100/70 mm. Hg and the plasma sodium and potassium 129 and 5.5 mEq respectively per litre, and the blood sugar 120 mg. per 100 ml. Cortisone (intramuscular) and phenylephrine were given on the fourth post-operative day, and consciousness returned two days later, with amnesia for the period of stupor.

2. Pituitary Apoplexy

So-called pituitary apoplexy is a rare syndrome caused by haemorrhage into a pituitary adenoma. Aitken and Russell (1934) described such a case in a man aged 50 with hypopituitarism. A few hours after the onset of dizziness, weakness, and vomiting he became semiconscious and remained so for three days. On recovery he was found to have become blind in the left eye, and he remained lethargic until 41 weeks later, when he died in his sleep. At necropsy there was a chromophobe adenoma of the pituitary gland associated with an intrasellar haemorrhage, and the testes and adrenal and thyroid glands were found to be atrophied.

The following case also illustrates this further cause of coma.

Endocrine Function in 17 Cases of Hypopituitarism Subject to Coma or Allied Disturbances of Consciousness

Case	Age	Sex	Adrenal Function								Additional Features	
			Gonadal Function		Increased Insulin Sensitivity	Impaired Water Diuresis	Thyroid Function					
			Clinical Hypogonadism	17-Ketosteroid Excretion mg./24 Hrs.			E.C.G. Voltage	B.M.R. %	Plasma Cholesterol mg./100 ml.	¹³¹ I Uptake		Clinical Myxoedema
Post-partum pituitary necrosis*	G. . .	50	F	Yes	—	—	—	—	420	Normal	Yes	Diab. mellitus (modified)
	J. T. .	57	F	"	0.5	Yes	—	—	—	—	"	
	G. G. .	36	F	"	1.1	—	Yes	—	—	—	"	
	McK. ‡	53	F	"	0	Yes	—	—	220	—	"	
	McL. .	46	F	"	—	No	—	—	410	—	"	
	J. B. .	53	F	"	0.9	Yes	Yes	—	—	—	"	
	I. F. .	54	F	"	—	Yes	Yes	Low	—	Subnormal	"	
	E. K. .	52	F	"	0.6	"	"	"	—	—	"	
D. B. ‡	24	F	"	—	—	—	—	—	—	—	"	
Craniopharyngioma	H. B. .	74	M	"	3.1	Yes	—	—	—	260	—	Dwarfism
	J. D. .	52	M	"	9.5	"	—	—	—	—	—	
	J. P. ‡	44	M	"	—	—	—	—	—	—	—	
	I. K. .	63	M	"	5.0	Yes	Yes	Low	—	—	—	
Pituitary adenoma	S. M. ‡	47	M	"	0.5	"	—	—	—	295	—	Yes No
	J. H. ‡	46	M	"	0.3	"	—	—	—	304	—	
	K. M. ‡	36	F	"	4.3, 7.5	No	Slight	Normal	—	—	Normal	
	L. S. ‡	47	M	"	1.4, 1.9	Yes	Yes	Low	+3, +4	187	"	

* All gave a history of failure of lactation and amenorrhoea following severe post-partum haemorrhage or sepsis.

† Pituitary tumour verified at operation.

‡ Diagnosis verified at necropsy, which also revealed hypoplasia of the adrenal cortex.

FIG. 1.—Hypopituitary coma in relation to replacement therapy in Case I. F. The comatose attacks were not prevented by regular therapy with thyroid extract and testosterone implants. During two years of regular cortisone therapy there has been only one attack of hypopituitary coma, which occurred during influenza contracted 10 days after stopping cortisone. During episode 9 (mild hypersomnia during coryza) the daily dose of cortisone remained at 12.5 mg.

Factors associated with HYPOPITUITARY COMA.

FIG. 2.—Clinical and biochemical findings during attacks of hypopituitary coma in Case I. F. Five of the episodes tabulated in Fig. 1 are shown in greater detail. Of the clinical and biochemical findings, the only factor common to all the episodes was pyrexia.

L. S., a painter aged 47, was admitted to another hospital, unconscious, in May, 1954. In August, 1950, he was found to have hypopituitarism, due to a chromophobe adenoma of the pituitary gland. There was failure of gonadal and adrenal function, but thyroid function was normal. After a year of testosterone therapy he refused further treatment.

On the day of his final admission he was found semiconscious and incontinent of faeces, having been well the previous day. On examination he was stuporous and febrile—temperature 103° F. (39.4° C.)—with a blood pressure of 108/60. Neurological examination was then negative. The following day he became irritable and could not be roused; the plantar responses were now extensor, and the right pupil was small and reacted poorly to light. Lumbar puncture yielded a clear fluid with normal pressure. That evening he died. Necropsy (Dr. S. Robinson) showed an unruptured unilocular cyst, 3 cm. in diameter, full of blood-stained fluid, bulging from the pituitary fossa into the base of the brain, and arising from a chromophobe adenoma. The brain was oedematous, with flattened convolutions and ablation of the lateral ventricles. There was moderately severe adrenal and testicular atrophy, but the thyroid gland was essentially normal.

The coma in this case was probably due to acute haemorrhage into a cystic chromophobe adenoma in a patient with hypopituitarism.

3. Infections

Patients with hypopituitarism usually sleep well and for long periods. Infections often aggravate their hypersomnia and may cause mental confusion or coma (Wilson, 1953; Coughy, 1954; Peters *et al.*, 1954).

One of our patients stated that during influenza and other fevers she would sleep for 48 hours without waking to take food. Another (J. D.) slept for two days during an attack of influenza. Infections, such as colds, influenza, or gastro-enteritis, caused drowsiness, confusion, and eventually coma in eight of our patients, as illustrated by the following two cases:

I. F., a widow now aged 54, was first admitted to hospital in 1947 with severe hypopituitarism. In 1925 her fourth pregnancy had ended with a post-partum haemorrhage and puerperal fever, and was followed by scanty and infrequent menses. After a fifth pregnancy in 1927 there was loss of libido, and her menses ceased at the age of 36 (1936). Since 1940 she had gained weight, and since 1945 had noticed dryness and puffiness of her skin and thinning of her scalp and superciliary hair. She became constipated and intolerant of the cold and complained of being "muddle-headed" and always drowsy. On examination she looked myxoedematous. The axillary hair was absent and the pubic hair scanty. The blood pressure was 120/80 mm. Hg with a pulse rate of 56. Hypopituitarism was confirmed (see Table) and on admission haemoglobin was 65%, blood urea 38 mg. per 100 ml., and plasma chlorides 107 mEq per litre.

A week later she developed a pneumonic lesion and became febrile, and at times stuporous. Several features such as hypotension (90/65), haemoconcentration (haemoglobin rose to 90%; plasma chloride 117 mEq per litre), and azotaemia (blood urea 136 mg. per 100 ml.) were suggestive of an adrenal crisis. She responded incompletely to antibiotics and intravenous saline, and remained in a fluctuating state of hypotension (blood pressure 65–100/40–70), with nausea, vomiting, hypochloraemia (plasma chloride 90 mEq per litre) and acidosis (plasma CO₂, 17.8 mEq per litre) for three months. During this period the administration of thyroid, 3 gr. (0.2 g.), daily and "eucortone" (10 ml.) on alternate days made little difference to her clinical course. Subsequent Cutler tests aggravated her hypotension but caused little chloride depletion. Her progress in relation to therapy over the next seven years is summarized diagrammatically in Fig. 1. After a period of comparative well-being on thyroid extract alone, she suffered many attacks of stupor and coma, mostly precipitated by gastro-enteritis or acute infections of the upper respiratory tract, and all accompanied by fever. Continued thyroid extract, with the addition later of testosterone implants, did not lessen the frequency of the comatose attacks. The clinical and biochemical findings at the onset of coma were very variable (Fig. 2); hypoglycaemia was present only once. Since taking cortisone, 12.5 to 25 mg. a day, she has been free from coma for two years, despite repeated infections; the only exception being when she caught influenza after discontinuing therapy for 10 days.

The following case is of exceptional interest in that fatal coma during acute pyelonephritis occurred within three

months of a severe post-partum haemorrhage, pituitary necrosis being confirmed at necropsy.

D. B., a housewife aged 24, was admitted to hospital unconscious in April, 1949. During the week before admission she had complained of frequency of micturition and backache, and on the morning of admission she had become comatose and incontinent. Three months previously her fourth pregnancy had ended with a post-partum haemorrhage (systolic blood pressure 60 mm. Hg, haemoglobin 32%), treated some hours later by blood transfusion. Subsequently she had failed to lactate and had become languid, anorexic, and unable to perform her usual household duties. On examination she was deeply unconscious, with rigid limbs and extensor plantar responses. Her temperature was 101.4° F. (38.6° C.), pulse 110, and blood pressure 95/60 mm. Hg. Axillary hair was absent and pubic hair thin. The presence of a *Bact. coli* urinary infection was confirmed but she was not uraemic (blood urea 42 mg. per 100 ml., plasma sodium 144 and potassium 4.4 mEq per litre). Shortly after admission a lumbar puncture was performed, following which, and without therapy, she recovered consciousness. The cerebrospinal pressure was normal and the fluid clear, sterile, and acellular, and containing glucose 54 mg., chlorides 650 mg., and protein 70 mg. per 100 ml. She remained febrile—102–104° F. (38.9–40° C.)—despite antibiotic therapy, and two days after admission, following a convulsion, she again became unconscious, with spastic limbs and extensor plantar responses. The blood sugar was then 49 mg. per 100 ml. and the blood pressure 110/70. Continued infusion of 5% glucose caused only a transient return of consciousness, and she died in coma the following day. Several hours before death her blood pressure fell to 65/35. Other preterminal findings were: blood sugar 82 mg. per 100 ml.; plasma protein, 5.8 g. (albumin 3.2 g., globulin 2.6 g.) %; plasma sodium 153, potassium 3.9, and chloride 117 mEq per litre; blood culture negative; cerebrospinal fluid—low pressure, clear and colourless, red blood cells 47, white blood cells 30 per c.mm. (lymphocytes 70%), glucose 51 mg., chloride 740 mg., and protein 50 mg. per 100 ml.

At necropsy (Dr. I. Doniach) there were no abnormal findings in the central nervous system, heart, or lungs. The pituitary gland weighed only 350 mg. (normal 1 g.). There was extensive organized infarction of the anterior lobe, and at the periphery there remained only a few groups of eosinophil and chromophobe cells, which showed abnormal staining reactions. These changes extended into the pituitary stalk. The thyroid gland weighed 23 g. and showed flattened epithelium surrounding hyperchromatic inactive colloid. The adrenal glands showed marked cortical atrophy, involving especially the zona glomerulosa, and a low lipid content. The ovaries were atrophic and showed minimal follicular development. The breasts were poorly developed and showed degenerative changes in the epithelium and periductal fibrous tissue and absence of secretion. The left kidney showed pyelonephritis with multiple small abscesses.

Coma in this case was precipitated by an acute renal infection. Although the patient was hypoglycaemic during the second period of coma, consciousness was restored for only a few hours by continued glucose infusions.

4. Hypoglycaemia

In hypopituitarism, hypoglycaemia may occur spontaneously, as in one of our patients (I. F., blood sugar 43 mg. per 100 ml.), during infections* (Wilson, 1953), or following injection of insulin. Fraser and Smith (1941) stressed the value of the intravenous insulin-tolerance test in the diagnosis of panhypopituitarism. They also gave warning of its possible dangers and advised using only one-third of the standard dose of 0.1 unit insulin per kg. body weight when severe hypopituitarism is suspected. Rolland and Matthews (1952) reported severe hypoglycaemic symptoms in a man with hypopituitarism after 1.5 units of insulin, and Haussmann *et al.* (1951) induced hypoglycaemic shock with 1.75 units of insulin in a woman with Simmonds's disease who then remained semicomatose for two weeks despite energetic treatment.

Although not infrequently there is a normal response to this smaller dose in patients with undoubted hypopituitarism, severe reactions may still occur. One of our patients (I. K.) became comatose within 45 minutes of receiving one-third of the standard dose, and another (S. M.) became pale, sweated, and collapsed in coma with twitching

of the limbs within 15 minutes of receiving half the standard dose of insulin. Consciousness returned with infusion of glucose.

Insulin may also be given for other than diagnostic reasons to patients not yet known to have hypopituitarism. Oliver (1952) described the case of a man with pituitary tuberculoma, who died after two injections of 10 units of soluble insulin, given to promote appetite. Oversensitivity to insulin therapy is also shown by the following very unusual case, in which diabetes mellitus was modified by the progression of hypopituitarism.

E. K. suffered a severe post-partum haemorrhage after the birth of her second child when she was 32. Lactation failed but menstruation returned three months later, to remain scanty and infrequent until it ceased at 39. At 44 she developed diabetes mellitus, which did not require more than 24 units of soluble insulin for its control. At 52, when recovering from severe influenza, she passed into deep coma five hours after an injection of soluble insulin (10 units), despite having taken her normal breakfast and lunch. It needed 100 ml. of 50% glucose, intravenously, to restore consciousness. On then withholding insulin for 48 hours, she became drowsy and ketotic (blood sugar 440 mg. per 100 ml.), and at this point soluble insulin (10 units) again caused hypoglycaemic coma. She had no pubic hair, and hypopituitarism with secondary adrenal failure was subsequently confirmed. After many more hypoglycaemic attacks, her diabetes was eventually controlled by a balanced use of cortisone and insulin. She has since gained 21 lb. (9.5 kg.) in weight and has remained well for over a year.

5. Hypersensitivity to Drugs and Anaesthesia

As in Addison's disease, so also in hypopituitarism, there is hypersensitivity to drugs and anaesthesia. In one of our patients an injection of morphine sulphate, $\frac{1}{4}$ gr. (16 mg.), before a minor operation induced coma which lasted for two days. In another, coma followed quinalbarbitone, $1\frac{1}{2}$ gr. (0.1 g.), and pethidine, 50 mg. Another passed quickly into the third stage of anaesthesia after pentobarbitone sodium, $1\frac{1}{2}$ gr. (0.1 g.), and less than 4 ml. of intravenous thiopentone sodium, recovering in the course of two days.

6. Sodium Depletion

It is still uncertain to what extent the pituitary gland controls the adrenal secretion of mineralocorticoids. Even in advanced hypopituitarism it is unusual to find a classical adrenal crisis in which coma accompanies severe sodium depletion, azotaemia, and circulatory collapse. Laws (1952) has described modified crises of this type in two patients with post-partum pituitary necrosis. Both had been treated for long periods with thyroid extract for supposed primary myxoedema. One died during a second crisis; the other recovered, to die later after influenza.

A sodium-losing crisis, with coma, occurred in two of our cases of pituitary necrosis. In the first (I. F., already described) this happened once in response to pneumonia and again during acute gastro-enteritis (Fig. 2). In the second patient (J. B.) severe sodium depletion was probably precipitated by cortisone therapy.* In this instance coma, acute loss of weight, and extreme circulatory collapse (blood pressure unrecordable) were preceded by psychotic symptoms and probably aggravated by a paraldehyde injection (10 ml.). A few hours before the onset of coma the plasma sodium had fallen to 117 mEq per litre. The coma was corrected within 12 hours by intravenous saline, cortisone, and D.C.A., although full recovery took several days.

Although sodium depletion sufficient to cause collapse seldom occurs spontaneously in these patients, loss of this ion during surgery, infections, or gastro-enteritis is not well tolerated, and may be a critical factor in precipitating coma.

*In Addison's disease and hypopituitarism the sodium excretion may rise greatly during the first few days of cortisone therapy. The same phenomenon occurs, and with greater regularity, in the adrenalectomized dog, and is due to a rise in the glomerular filtration rate (Garrod *et al.*, unpublished observations).

7. Water Retention

Patients with hypopituitarism cannot excrete a water load rapidly, a failure which is readily corrected by cortisone (Garrod and Burston, 1952). They are more prone, therefore, to water intoxication; and this can occur either after a water-loading test or spontaneously, and may be associated with changes in consciousness, as illustrated by the following patient, whose episode of sodium depletion has already been described.

J. B., a housewife aged 53, suffered from severe hypopituitarism following a post-partum haemorrhage at the age of 40. During her first admission to hospital she became drowsy and confused the day after a water diuresis test. She had excreted only 9% of the water dose in four hours, and oliguria had continued. She complained of nausea and anorexia. The blood pressure was 100/70 mm. Hg and the blood urea 21 mg. per 100 ml. The plasma sodium was only 116 and chloride only 85 mEq per litre. She was given 200 mg. of cortisone and 5 mg. D.C.A. during two days, which caused a large water diuresis, loss of weight, and early recovery of her mental state.

When admitted to hospital one year later, having relapsed because she had failed to continue treatment, she gained 2.5 kg. in weight from fluid retention during 10 days without treatment and became drowsy, confused, and irritable, with loss of appetite. The blood pressure was 120/90 mm. Hg and there were no signs of heart failure. The plasma sodium had fallen from 130 mEq per litre on admission to the very low level of 107 mEq. She was given 200 mg. of cortisone by mouth and intravenously and 10 mg. of D.C.A. by intramuscular injection, followed by 75 mg. of oral cortisone daily. During the first two days of treatment she passed 3.1 litres of urine with a minimal sodium content and lost 2 kg. in weight. By the third day her plasma sodium had risen to 130 mEq per litre. Her mental state cleared within a day of starting treatment.

8. Cerebral Anoxia

Six of our patients were subject to hypotensive postural faints which seemed to be due to cerebral anoxia. One patient (S. M.) fainted when he stood up after a hypoglycaemic attack. Another (J. H.) became confused during a short flight at average height in a commercial air liner. Severe postural hypotension is more likely to occur when the hypothalamus is also involved, as seemed probable in the following patient with a craniopharyngioma.

I. K., a tailor's machinist aged 63, was first seen by one of us (O. G.) in 1948. Three years previously he had collapsed unconscious while at work, and had fainted the next day on standing up. His vision had steadily failed until latterly he had been unable to read or write. He had become increasingly inactive and had often lost consciousness for several minutes on rising from his bed. While in another hospital death had twice seemed imminent when he was found cold and pulseless after fainting attacks. On examination, despite his having had testosterone, he was pale and wasted, with dry inelastic skin and diminished facial and pubic hair. He lay apathetically in bed, yawning frequently, and resenting examination. Both eyes contained early cataracts; the right was almost totally blind, the left showed complete temporal hemianopia. His blood pressure, reclining, was usually around 150/80. After three minutes of sitting with his legs dependent it fell to 75/50. One minute later it could not be recorded and he became pale and unconscious. He recovered consciousness within five minutes of raising the foot of his bed, but after reclining for a further 40 minutes his blood pressure was still only 90/60. On further investigation he was found to have a large pituitary fossa, with destruction of the clinoid processes and slight suprasellar calcification, and hypopituitarism with secondary adrenal failure was confirmed (see Table).

9. Hypothermia

These patients are usually intolerant of the cold, and one (I. F.) said that she became mentally confused during cold weather. In one of the post-operative cases the body temperature fell to 96° F. (35.6° C.), but consciousness did not return when this was raised to 99° F. (37.2° C.) by warming for six hours. Cooling of the body is known to cause progressive somnolence and unconsciousness. However, in the example just cited it is unlikely that hypothermia was caused by exposure to cold; more probably there was a failure of

the heat-regulating centres. Injury to the hypothalamus is not essential, since Sheehan and Summers (1952) have described hypothermia in comatose patients with pituitary necrosis. It is uncertain how often hypothermia is a primary factor in initiating the coma. It might, however, be expected to occur during the exposure of an already unconscious patient to cold, and thus be a further factor in prolonging coma. Sheehan and Summers (1952) were able to restore consciousness in two of their patients by immersing them in a hot bath.

Discussion

(a) The Aetiology of Hypopituitary Coma

Many authors have stressed the importance of hypoglycaemia as a cause of "hypopituitary coma." We have found, however, that hypoglycaemia is an unusual finding in the early stages, or, indeed, throughout the comatose attacks, and that when present it is often of too slight a degree to explain by itself the severity of the disturbance of consciousness. Likewise we have failed to find any biochemical disorders that are a constant or even usual feature of these attacks. It is important, therefore, to consider the mechanism of coma in general, understanding of which has been advanced by recent studies of neuronal metabolism.

Consciousness has been defined as an awareness of environment and of self (Cobb, 1948). Although consciousness was once believed to be integrated entirely within the cerebral cortex, it has now been shown to depend also on certain critical centres within the thalamus, hypothalamus, and reticular area of the mid-brain (Cairns, 1952). Any disturbance of neuronal metabolism within the centres of consciousness may affect the mental state. Energy released within nerve cells is derived almost entirely from oxidation of glucose and glutamic acid, a process which may be hindered by interference with specific enzyme systems, by lack of substrate, or by anoxia. In addition, mechanical effects such as trauma, pressure, or oedema may block the delivery of substrate or oxygen to critical areas of the brain (Fazekas and Bessman, 1953). In severe hypopituitarism the centres of consciousness are probably unduly vulnerable because of changes within the cerebral cells resulting from endocrine deficiencies, and from impairment of that part of the defence mechanism which is mediated through the pituitary-adrenal axis. If we can exclude certain post-operative cases in which local factors may be important, it would seem that disorders of consciousness are unlikely to arise in hypopituitarism unless the peripheral endocrine failure is well advanced.

Poor adrenal function is a more constant finding than thyroid failure in these cases; and our experience also points to the effectiveness of cortisone in protecting consciousness during periods of metabolic stress. Although adrenal function in these patients may be just adequate for their lowered metabolic needs, yet in the presence of infection, hypoglycaemia, or other stresses it is probably unable to respond further owing to lack of stimulation by the pituitary gland. We believe that this may be a fundamental factor in allowing the mental changes to occur, and that consciousness can usually be protected if exogenous cortisone be provided. In the post-operative cases of pituitary tumour further factors that may predispose to coma are trauma, local oedema, and a transient mechanical interruption of portal pathways between the hypothalamus and anterior pituitary gland.

(b) Diagnosis of Hypopituitary Coma

The possibility of hypopituitarism should always be considered when the cause of coma is obscure. In a woman the diagnosis would be supported by an earlier history of sepsis or post-partum haemorrhage, followed by a failure of lactation and amenorrhoea, or by scanty menses culminating in a premature menopause. Other symptoms that might be elicited from the husband or other relatives are loss of libido, asthenia, fainting attacks, hypersomnia, and undue sensi-

tivity to cold. In either sex a history of headaches or visual failure, or evidence of primary optic atrophy, should lead to an early x-ray examination of the pituitary fossa.

As hypopituitarism progresses gonadal function is the first to fail, followed usually by adrenal and, finally, by thyroid failure (Garrod and Gilliland, 1954). Adrenal and thyroid failure are not easy to recognize clinically in their early stages, and in order to demonstrate the changes certain tests are needed which we do not propose to discuss in this paper. When the disease is far enough advanced for coma to arise, and if testosterone or oestrogens have not already been given, there should always be some clinical evidence of hypogonadism. In a comatose patient, any of the following signs should arouse a suspicion of hypopituitarism: loss of pubic and axillary hair, atrophy of the labia minora and vaginal epithelium, a small uterus; and in the male, paucity of beard and body hair, a small prostate gland, and soft testes. Further suggestive findings are loss of pigment in the nipples and areolae in the female, and, in both sexes, pallor and a soft thin skin. In severe or long-standing cases the patient may present with a classical appearance of myxoedema, and when coma occurs in a myxoedematous patient a pituitary origin should always be suspected, and cortisone given if there is any doubt.

A combination of hypotension, azotaemia, and haemoconcentration suggests loss of sodium from adrenal failure, in which case the depletion may be masked by haemoconcentration, although urinary sodium excretion should be higher than in shock arising from other causes. In a confused or drowsy patient a very low plasma sodium, with normal blood urea and a normal or only slightly lowered blood pressure, suggest water intoxication.

(c) The Management of Hypopituitarism in Relation to Coma

Study of these cases points the way to a more effective management of hypopituitarism and of the mental changes associated with it. It is not our purpose here to discuss the therapy of hypopituitarism in general, but only in so far as it effects these disturbances of consciousness.

Prevention of Coma.—From our own experience, and from unpublished observations of others, it seems likely that with regular cortisone therapy these patients will be protected from hypersomnia and "hypopituitary coma," provided that the daily dose is increased during intercurrent infections, surgery, and other stresses. The advent of this hormone has undoubtedly improved the general outlook in these patients. Oral cortisone, 12.5 to 25 mg. a day, should be given indefinitely to all patients with hypopituitarism who show signs of diminished adrenocortical function such as hypotension, failure of water diuresis, increased insulin sensitivity, or depressed voltage or low T waves in the electrocardiogram. If in addition there is clinical evidence of hypothyroidism or laboratory evidence such as raised plasma cholesterol or a basal metabolic rate of less than -25%, or if the electrocardiographic abnormalities cannot be corrected by cortisone alone (Garrod and Gilliland, 1954), a daily dose of L-thyroxine 0.1-0.2 mg., or thyroid extract, 1 to 2 gr. (0.06-0.13 g.), should also be given. Testosterone therapy, whilst usually needed to improve sexual function and promote protein anabolism, seems to afford incomplete protection against the risks of coma.

Infections.—We have discussed the hazard of infections such as influenza and gastro-enteritis. Although patients cannot hope to escape these entirely, they can avoid crowds and known infection in other persons. Acute infections, even colds, should be treated promptly, under ideal conditions of rest in bed, and the dose of cortisone increased, temporarily, to at least 50 mg. a day.

Anaesthesia and Surgery.—Whenever possible general anaesthesia should be avoided and surgery restricted to emergencies. When operation becomes inevitable it should be carried out under full cortisone cover of at least 100 mg. a day. Likewise, cortisone should be used in operations on the pituitary gland, whether or not there is prior evidence of hypopituitarism, since it is possible that post-operative

trauma in this region may block hypothalamic-pituitary pathways through which adrenal response to stress is mediated. The effectiveness of cortisone in the surgery of suprasellar tumours has already been shown by Ingraham *et al.* (1952) and by recent experience in the Department of Neurosurgery at Dunedin (Mr. Anthony James).

Insulin.—In view of the great susceptibility of these patients to insulin and the difficulty there may be in correcting hypoglycaemic coma, even when the blood sugar has been restored, we feel that the insulin-tolerance test is probably an unjustifiable risk when the diagnosis of hypopituitarism can be made by other means. Its main application would seem to be in doubtful cases with little evidence of adrenocortical failure. Unfortunately, a negative response to the smaller test dose does not exclude hypopituitarism.

Drugs.—Hypnotics and analgesics must be used sparingly, and morphine and allied compounds should not be given.

The Treatment of "Hypopituitary" Coma

Opinions have varied regarding the optimal management of this condition, and the assessment of therapeutic measures is made difficult because of a tendency to spontaneous recovery once the precipitating factors have ceased to act. Also it is possible that irreversible changes within the brain may have occurred by the time therapy is instituted (Wilson, 1943). Allott and Simmons (1951) described a patient whose coma failed to respond to D.C.A. and infusion of glucose-saline, but who regained consciousness within 24 hours of receiving cortisone, and Decourt *et al.* (1954) have described a similar response. Caughey *et al.* (1952) reported three cases of coma: in one there was a good response six days after starting treatment with testosterone and thyroid extract, 1½ gr. (0.1 g.) a day; the second responded to cortisone alone, and the third to combined cortisone and A.C.T.H. If cortisone had been given orally, rather than by intramuscular injection, the response would probably have been more rapid.

As a result of further experience we now recommend the following therapeutic plan. As soon as coma is found to be associated with hypopituitarism, and especially when there is fever, search should be made for signs of a precipitating infection such as influenza, pneumonia, pyelitis, or gastro-enteritis, and appropriate antibiotic therapy started at once. If the body temperature is very low the patient should be immersed in a warm bath (Sheehan and Summers, 1952). In all cases the rectal temperature, pulse rate, and blood pressure should be checked at short intervals. Blood should be taken early for estimation of blood sugar, plasma sodium, urea, bicarbonate, and haematocrit or plasma specific gravity. Without waiting for the results, and on the supposition that hypoglycaemia may be present, glucose should then be given by mouth if the patient can be roused, or by intravenous injection (50 ml. of 50% glucose followed by a steady infusion of 5% glucose). To get the quickest glucocorticoid effect, hydrocortisone (compound F) is preferable to cortisone; and, because absorption from the gut may be delayed, intravenous therapy is more effective than oral. An infusion of 50 to 100 mg. of hydrocortisone alcohol dissolved in 250 to 500 ml. of isotonic saline should be given as soon as possible. If hydrocortisone is not available, 50 to 100 mg. of microcrystalline cortisone acetate ("cortone") can be given intravenously. Thereafter, 50 mg. of cortisone acetate should be given six-hourly by nasal tube, which should be kept *in situ* for feeding purposes, until consciousness has been regained.

Further treatment must be regulated by the clinical and biochemical findings. If hypoglycaemia is present, intravenous or oral glucose should be continued. The presence of hypotension, haemoconcentration, azotaemia, and sodium depletion (the latter may be masked by haemoconcentration) calls for intramuscular injection of 10 mg. of D.C.A. and an adequate sodium intake. In any event it may be wise to give 5 mg. of D.C.A. during the first few days because cortisone may initially increase the sodium output, probably by raising the low glomerular filtration rate, and is too weak a

sodium-retainer to correct quickly any serious depletion of this ion.* If there is excessive water retention cortisone will correct this by allowing the selective excretion of water in excess of sodium (Garrod and Wynn, 1954).

Since coma occurs in patients with hypopituitarism who are already receiving thyroid extract and testosterone, it is doubtful whether these hormones are of much value in the acute management of this condition. However, if there is obvious myxoedema, L-thyroxine or thyroid extract should be given as well as cortisone and D.C.A., with full awareness that their metabolic effects will be delayed.

Summary

Disturbances of consciousness which varied from hypersomnia, mild confusion, and impaired cerebration to stupor and profound coma were encountered in 17 patients with hypopituitarism.

There were many factors which precipitated coma, and these included cerebral surgery, pituitary apoplexy, infections, hypoglycaemia, drugs and anaesthetics, electrolyte disturbances, water intoxication, and cerebral anoxia.

Except in some of the post-operative cases, severe endocrine failure, especially of the adrenal cortex, seemed to be an essential factor in lowering the threshold of consciousness. Cortisone was more effective than thyroxine or testosterone in the prevention and correction of coma.

In obscure cases of coma the possibility of hypopituitarism should always be considered. The diagnosis, prevention, and treatment of "hypopituitary coma" are discussed in the light of further experience.

We are grateful to many physicians in New Zealand and the United Kingdom who have given us access to their cases; to Mr. Anthony James, neurosurgeon of the Dunedin Hospital; and to Dr. C. L. Cope and Dr. T. Russell Fraser, under whose care some of these patients were studied. We are grateful for secretarial assistance from Miss D. E. Hunt and Miss G. M. Turner.

ADDENDUM.—Since this paper was submitted for publication Whittaker and Whitehead (1954) have described a case of hypopituitary coma arising from water intoxication, and a case of coma due to hypothermia in a patient with hypopituitarism who was already receiving cortisone therapy.

REFERENCES

- Aitken, R. S., and Russell, D. S. (1934). *Lancet*, 2, 802.
 Allott, E. N., and Simmons, J. H. (1951). *British Medical Journal*, 2, 568.
 Cairns, H. (1952). *Brain*, 75, 109.
 Caughey, J. E. (1953). *Proc. Univ. Otago med. Sch.*, 31, 6.
 — (1954). *Aust. Ann. Med.*, 3, 26.
 — James, A., and Macleod, E. K. (1952). *British Medical Journal*, 1, 1216.
 Cobb, S. (1948). *Foundations of Neuropsychiatry*, p. 89. Williams and Wilkins, Baltimore.
 Decourt, J., David, M., Michard, J. P., and Weil, B. (1954). *Bull. Soc. méd. Hôp. Paris*, 70, 110.
 Fazekas, J. F., and Bessman, A. N. (1953). *Amer. J. Med.*, 15, 806.
 Fraser, R., and Smith, P. H. (1941). *Quart. J. Med.*, 10, 297.
 Garrod, O., and Burston, R. A. (1952). *Clin. Sci.*, 11, 113.
 — and Gilliland, I. C. (1954). Communication to Royal Society of Medicine, March 24, 1954. (To be published in *Proc. roy. Soc. Med.*)
 — and Wynn, G. (1954). To be published.
 Grant, F. (1948). *J. Amer. med. Ass.*, 136, 668.
 Haussmann, W., Kalinowski, S., and Le Marquand, H. S. (1951). *British Medical Journal*, 1, 924.
 Ingraham, F. D., Matson, M. D., and McLaurin, R. L. (1952). *New Engl. J. Med.*, 246, 568.
 Laws, J. O. (1952). *Guy's Hosp. Rep.*, 101, 280.
 Oliver, L. C. (1952). *Lancet*, 1, 698.
 Peters, J. P., German, W. J., Man, E. B., and Welt, L. G. (1954). *Metabolism*, 3, 118.
 Rolland, C. F., and Matthews, J. D. (1952). *British Medical Journal*, 1, 1220.
 Sheehan, H. L., and Summers, V. K. (1952). *Ibid.*, 1, 1214.
 Simmonds, M. (1914). *Dtsch. med. Wschr.*, 40, 322.
 Summers, V. K., and Sheehan, H. L. (1951). *British Medical Journal*, 2, 564.
 Whittaker, S. R. J., and Whitehead, T. P. (1954). *British Medical Journal*, 2, 265.
 Wilson, L. A. (1953). *Lancet*, 1, 203.

EFFECT OF CHLORPROMAZINE ON THE BEHAVIOUR OF CHRONICALLY OVERACTIVE PSYCHOTIC PATIENTS

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Reports of the varied central effects of chlorpromazine hydrochloride ("largactil") (Laborit and Huguenard, 1951; Courvoisier *et al.*, 1953; Brand *et al.*, 1954), its reputed potentiating action on central depressants (Laborit and Jaulmes, 1952; Courvoisier *et al.*, 1953), and the clinical response observed in various psychiatric states (Delay, Deniker, and Harl, 1952a, 1952b; Delay, Deniker, Harl, and Grasset, 1952; Delay and Deniker, 1953; Sigwald and Bouttier, 1953) have encouraged a limited trial of this drug in regard to its effect on the behaviour of a small group of chronically overactive psychotic patients in a large and overcrowded mental hospital.

Clinical Material

The material (Tables I and II) consisted of 12 male patients and 15 female patients drawn from the disturbed ("refractory") wards of the hospital. These patients were chosen less according to diagnostic category than because of the degree of overactivity they exhibited, which was sufficient to make them a persistent and difficult nursing problem. Of the 27 patients, 10 were diagnosed as schizophrenics and 3 as paraphrenics. These are grouped together in our assessment as suffering from schizophrenic disorders. Seven cases (Nos. 2, 5, 8, 9, 10, 11, and 14) suffered from recurrent or chronic hypomania, one (Case 13) was a manic-depressive, and three cases (Nos. 4, 7, and 24) were chronic agitated melancholics; these formed the affective group. The remaining three (Cases 20, 21, and 22) were confused, restless, overactive female senile dementes. Three cases (Nos. 5, 13, and 14) in the affective group and one paraphrenic (Case 15) showed signs of organic cerebral deterioration, and one chronic melancholic (Case 24) had had a leucotomy performed six years ago, after which she had become more destructive and even incontinent.

The medical and nursing staff were thoroughly familiar with the pattern of each patient's illness, and this was taken into account when assessing results.

Design of Trial

The patients were mostly observed in their own wards, but where they were transferred from one ward to another an equilibration period of two weeks was allowed. During this time patients were given an opportunity to adjust to their new environment, and full account was taken of any day-to-day variation shown. Within seven days of the beginning of the trial all sedatives were withdrawn. Chlorpromazine tablets and inert control tablets were then administered to the same patient in alternating periods for the duration of the trial. Only one observer (C.E.) and the dispenser knew which patients were receiving the active or

*See footnote on p. 557.