THE TREATMENT OF PROLONGED INSULIN COMA*

By

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INTRODUCTION

THIS thesis gives an account of the use of cortisone and adrenocorticotrophic hormone (ACTH) in the treatment of prolonged comas occurring in the course of deep insulin coma treatment. Cases in which neither hormone was used are also included. The pathology and aetiology of this type of prolonged coma are discussed and a classification of the cases seen is made.

The account is divided into nine parts:

I Normal insulin coma: biochemistry.

II Prolonged insulin coma: types, former treatment, aetiology, pathology.

III Experimental treatment: case material, treatment method, laboratory investigations.

IV Results and their evaluation.

V Biochemical findings.

VI Summary of treatment method.

VII Conclusions.

VIII Summary.

IX Appendix: protocols.

From 1949 onwards my assistance was sought from time to time when patients undergoing deep insulin coma treatment, after being given glucose to interrupt their coma, either recovered with difficulty or failed to recover and a prolonged coma ensued. Previous studies (Thorley and Kay, 1951; Kay and Thorley, 1951) suggested that there might be abnormal states of blood electrolytes in these cases, possibly related to adrenocortical dysfunction. Clinical observations indicated that a deficiency of the coenzymes derived from B-vitamins might be an important factor. Experience soon showed that although electrolyte disturbances and B-vitamin deficiencies were present, their correction was not an adequate answer to the problem of arousing a patient from prolonged hypoglycaemic coma.

Observations on two successive cases (Cases 2 and 3) in which coma lasted almost 4 weeks in the first and over 2 weeks in the second, led me to the conclusion that it was imperative to prevent lapses into hypoglycaemia in the early stages of treatment. As glucose administration alone did not do this, and it was thought that the lapses might be due to the unopposed action of insulin, it was decided to try the effects of cortisone and/or ACTH, both of which have anti-insulin effects and can raise and maintain blood-glucose levels.

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Of the complications that beset deep insulin coma therapy, perhaps the most disconcerting, and by far the most serious, is the failure of the patient to emerge from coma in response to the usual method of "interruption". Each such case is potentially fatal. Lester (1939), quoted by Kalinowsky and Hoch (1953), calculated that a prolonged coma occurred once in 1,877 individual treatments and found that the death rate in 25 cases was 16 per cent. In a large series of insulin-treated cases he found that the death rate due to prolonged coma was 0·33 per cent. Kinsey (1941) in a collected survey of 12,234 cases treated with deep insulin coma attributed 38 deaths (0·31 per cent. of cases) to protracted coma, irreversible coma, hypoglycaemic shock and hyperinsulinism. In a series of 5,882 coma treatments administered to 108 patients, Goldman (1940) reported 23 prolonged ("post-hypoglycaemic") comas, i.e. one (0·4 per cent.) in 256 treatments in 17 per cent. of the patients.

In the series of 62 cases of prolonged coma on which this report is based, it has not been possible to calculate the rate of incidence of prolonged coma in relation to total coma treatments. A rough estimate would be one prolonged coma to 2,000 normal ones. The cases have been collected from thirteen hospitals over a period of three and a half years and it is impossible to assess accurately the total number of coma treatments and of patients undergoing treatment. Not all prolonged comas occurring in these hospitals were brought to my notice, but only those not responding to the usual methods of treatment. There were 4 deaths (6·45 per cent.), a rate about two and a half times better than that found by Lester.

I. Normal Insulin Coma

Biochemistry

According to Thorley and Kay (1951) and Kay and Thorley (1951), there is an orderly sequence of changes in blood components during deep insulin coma. The blood glucose rapidly falls to and is maintained at a low level, about 30 mg./100 ml.

The serum potassium, chloride, bicarbonate and inorganic phosphate fall. The first three remain low, but the phosphate increases when the clearance of glucose from the blood ceases. The falls in serum potassium and phosphate can be related to the removal of glucose from the blood. If there is any attempt to recover in the prodromal stages, further falls in potassium and phosphate occur, probably owing to the removal of more glucose from the blood following attempts at restoration of the blood glucose by gluconeogenesis.

In contrast with the four components mentioned above, the serum sodium and proteins increase. This may be attributed to dehydration as the coma proceeds, since both components fall to a lower concentration after interruption. The loss of fluid, especially by sweating, probably accounts for the progressive fall of serum chlorides and to some extent of serum bicarbonate. The latter may be due to accumulation of organic acids normally metabolized to water and carbon dioxide, but whose destruction is retarded by the interruption of normal metabolism in deep coma. This is supported by the increase in serum base-acid difference as coma proceeds (Kay and Thorley, 1951).

Bliss, Migeon, Nelson and Samuels (1954) have shown that the blood corticoids increase during coma, whether through extra secretion or non-usage is not determined. The increase in corticoids could account partly for the fall in serum potassium and increase in serum sodium; on the other hand it could not account for the falls in serum chloride and bicarbonate. There is some

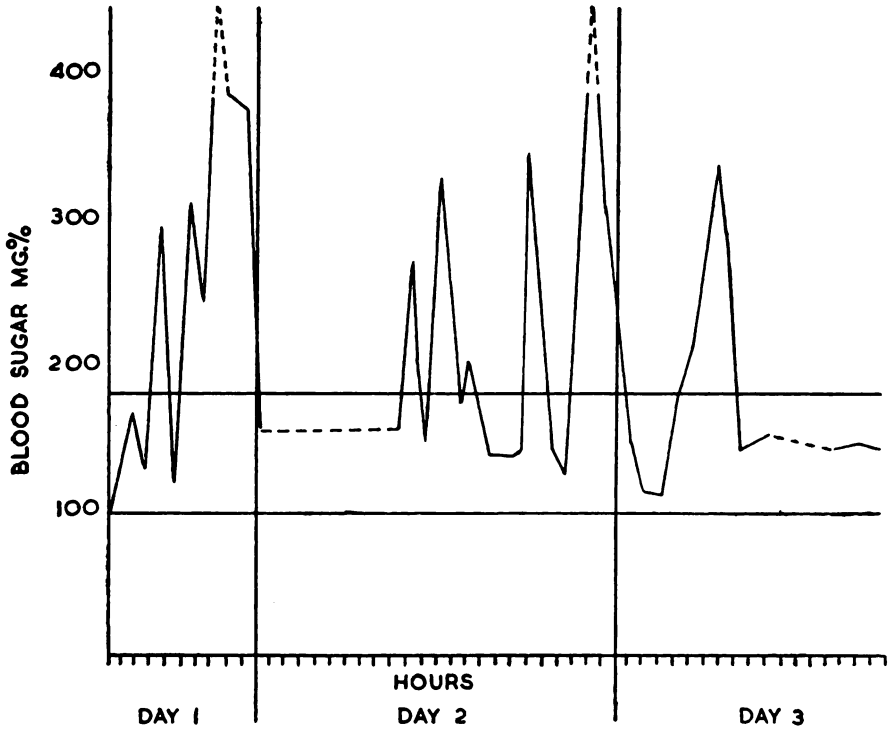

FIG. 1.—Blood sugar in early stages of prolonged insulin coma. Case 2.

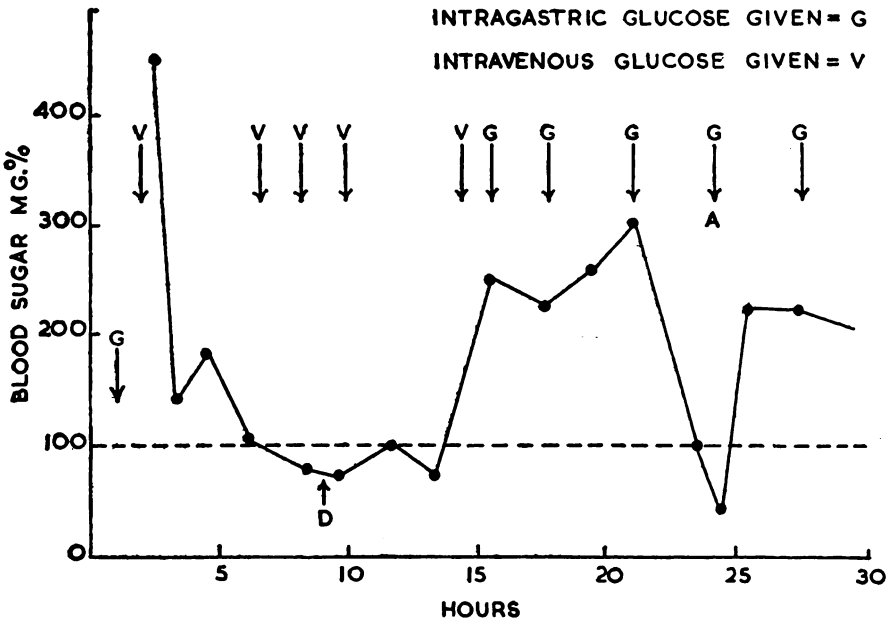

FIG. 2.—Blood sugar in early stages of prolonged insulin coma. Case 3. At D, coma deepening.

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evidence that the corticoids are ineffective at coma-producing levels of hypoglycaemia (Kay, 1958).

In the early stages of hypoglycaemia, there is a fall in blood adrenalin (Weil-Malherbe, 1954). There is an increase in blood corticoids which appears to be inffective and there are paradoxical changes in blood chemistry as the coma proceeds. It is evident that the high dose of insulin breaks down the body's natural defensive mechanisms to produce a continuing state of hypoglycaemia accompanied by adynamogenesis and a state of minimal metabolic activity, which by some workers is described as "near death".

On giving glucose to interrupt coma, several concomitant events occur. The blood glucose is raised to normoglycaemic levels or over, and this stimulates the production of adrenalin (Weil-Malherbe, 1954) and brings the anterior pituitary and adrenal cortex into action (Reiss, Hemphill, Early, Maggs, Cook and Pelly, 1951; Kay, 1958). Normal metabolic activity is also restored. The restoration of normal endocrine activity is the main factor in the maintenance of the normal metabolism and with it the state of normal mental activity. Other factors are involved in the restoration of normal metabolism, e.g., the presence of adequate co-enzymes, etc. These play their part, along with endocrine activity, and with the failure of the latter may be involved in causing prolonged coma.

II. Prolonged Insulin Coma

Types of prolonged insulin comas

Various authors have attempted to define and classify the types of prolonged insulin coma, and various descriptive names have been given such as "continued hypoglycaemia", "delayed awakening", "post-hypoglycaemic coma", "hyperglycaemic coma" and so on. The term "irreversible coma" has gradually been dropped for the general term "prolonged coma", since strictly "irreversible" should mean "fatal". None of these classifications appears to have helped to guide treatment.

For the purpose of this thesis, the term "prolonged insulin coma" has been adopted, since it simply means those cases which failed to recover from insulin coma by the usual methods of treatment and which I was asked to see and treat. When seen, some had hypoglycaemia, some hyperglycaemia; some had transiently recovered from coma and relapsed, some had not recovered at all and continued in coma. The facts common to them all were that they had had a deep insulin coma and in spite of attempts to rouse them they were still in coma when I first saw them, sometimes many hours after the first attempt at interruption.

There are a number of symptoms associated with prolonged coma, not all of which may be present in any one case, except, of course coma: hyperventilation with hyperpnoea and/or tachypnoea; motor excitement; rigidity; spasms of extremities and opisthotonus suggestive of tetany; dilated or contracted pupils, usually varying with the glycaemic state; fever, sometimes high. By appropriate laboratory examinations the following can be detected: haemoconcentration; leucocytosis with marked increase in polymorphoneutrophils; hypo- or hyper-chloraemia; loss of plasma bicarbonate. It is frequently assumed that the hyperventilation leads to alkalosis and tetany. In my experience this is rare; it is the loss of plasma bicarbonate that underlies the hyperventilation and the latter does not compensate for the acidosis.

In my experience the possible types of prolonged coma cannot be satisfactorily differentiated on clinical evidence alone. In the present series, however, four types have been encountered:—

(A) a failure to respond to a maintained hyperglycaemia;

(B) a state of intense dehydration with normo- or hyper-glycaemia;

(C) a state of subnormal glycaemia;

(D) a state of grossly fluctuating glycaemia with a corresponding fluctuation of the coma state.

In any of these four types, abnormalities of blood chemistry may occur, of which loss of blood bicarbonate is the second commonest and perhaps the most important. Of the four types, the last is by far the commonest in the series now reported. Probably this is because cases of the first three types recover fairly easily, often with haphazard treatment, and have not been brought to my attention.

Review of treatment of prolonged insulin coma (excluding the use of ACTH and cortisone)

The aetiology and pathology of prolonged coma are not fully determined. The factors involved are numerous and not all related causally to each other. As a result, treatment has never been systematized. A further difficulty is that not many doctors see more than one case. A doctor faced with a case of prolonged coma may not have had to deal with one before. He has then to depend on his book-knowledge, with or without the help of equally inexperienced colleagues. Should his patient recover, he is ineffably relieved and apt to ascribe the recovery largely to the last therapeutic measure he applied. Should his patient not recover, he may esteem all the measures taken as valueless and those not taken as at least worth trying should he have to deal with another case. Probably to this sort of reasoning is to be attributed the many lines of treatment listed in text books and amplified by verbal advice.

Undoubtedly, the first essential treatment is to raise the blood glucose level by intravenous infusion of glucose solution, usually 33⅓ per cent. in physiological saline. How often this should be repeated is disputed. The guiding principle should be to maintain a glycaemia at least above normal and control it by repeated blood sugar estimations. Surprisingly enough, few doctors have the blood glucose level determined; treatment is thus carried out blindly.

Basing his observations on over 30 cases of prolonged coma, Biskupski (1954) claims that the repeated injection of 300 ml. of 33⅓ per cent. glucose-saline intravenously every two hours, plus a rectal drip of 5 per cent. glucose-saline and warm blankets around the patient in bed, gives in nearly every case, recovery in two to six hours. In one of his cases coma lasted 30 hours, because the treatment was not started immediately. In the series now reported, adequate intravenous glucose had been given in almost all cases without effecting recovery; I was only called when this type of treatment had failed. In my experience, when adequate laboratory investigations are done, there is no evidence that saline is absorbed from a rectal drip, and very little evidence that glucose is. The rectal route is therefore not used.

Other recommended forms of treatment are lumbar puncture; electro-convulsion, metrazol-induced convulsion, convulsions induced by coramine; blood transfusion; administration of adrenalin, thiamine, nicotinic acid, calcium salts, potassium chloride, saline solutions of varying strength, cortin, atropine,

singly or in various conjunctions. Many of these had been tried without effect in the present series of cases before I was called upon. None of the measures listed can be regarded as reliable or effective. Some are even dangerous; a few have a useful place in treatment when their need has been demonstrated by chemical tests. It is odd logic to add the insult of a convulsion to an already damaged brain in the expectation of restoring cerebral function.

Not all of these therapeutic measures can be dismissed as useless, although most are discredited. Vitamin-B administration helps in those cases where there is a vitamin-B deficiency but not in others. Additional glucose is only necessary if there is hypoglycaemia; if there is hyperglycaemia, it may aggravate the patient's condition. Large quantities of fluids help if there is dehydration, but may cause pulmonary oedema if there is normal hydration. Intravenous saline is almost always needed, usually as a vehicle for glucose. Venesection seems irrational unless it causes enough shock to jolt the pituitary-adrenocortical system into activity. If blood transfusion helps, it may be because the blood, especially if fresh, contains adrenocorticotrophic and adrenocortical hormones.

Goldman's (1940) advocacy of adrenocortical extract was disregarded probably because of the variable potency of available preparations. I regret that Goldman's work only came to my notice during the process of reviewing the literature for this thesis.

As the purpose of this thesis is to give an account of personal experience of a new and systematized approach to the treatment of prolonged insulin coma, it is proposed not to discuss recorded methods of treatment any further. Whatever form of treatment is applied, three things are essential:

(i) to restore and maintain the blood glucose level to at least the physiological range;

(ii) to support and maintain the circulatory and respiratory mechanisms;

(iii) to control and manage fits.

To these basic essentials is to be added some form of treatment aimed at restoring consciousness.

At any time a sudden circulatory collapse, with or without respiratory collapse, may occur and will call for heroic efforts to combat it and keep the patient alive. In comas extending beyond, say, twenty-four hours further measures must be taken

(*a*) to control the blood chemistry, especially the electrolytes,

(*b*) to feed the patient,

and (*c*) to prevent pneumonia.

Aetiology of prolonged insulin coma

Although, as has been said, the aetiology of prolonged insulin coma is not settled, certain facts are established by clinical experience and pathological investigations.

(1) B-vitamin deficiency. Some patients undergoing deep insulin coma therapy show signs of B-vitamin deficiencies as their coma course progresses: paraesthesia, tingling of fingers and feet, tenderness and weakness of muscles, clumsy hand movements, e.g. when dressing, slight ataxia, red, sore tongue, angular stomatitis, scaly roughness, pigmented sometimes, of the backs of the hands and feet. This deficiency, especially of thiamine, has been attributed to

the necessity to metabolize the unusual amounts of carbohydrate given during the treatment course.

In due time, these patients are sluggish in recovering from coma and eventually may fail to respond to glucose administration and have a prolonged coma in spite of a sustained high blood glucose (see Case 1). They belong to Type A above. In cases where the vitamin deficiency was diagnosed, administration of B-vitamin complex has abolished the signs of deficiency and enabled the patients to complete their coma course without further difficulty. It was soon found that cases of prolonged coma of this type were exceptional and, in any case, the use of vitamin-B supplements prevented them.

In a few cases, it was possible to investigate the blood electrolytes, lactate, pyruvate and co-carboxylase before and after administration of B-vitamins. The following case illustrates this.

Case (a) A.H. Female aged 31. Had had 14 comas. Coma dose of insulin 60 units i.v. Roused with difficulty after intravenous glucose. Complained of numbness of fingers and back of head, and difficulty in controlling hand actions in dressing. Hands had to be watched to "see they went into the right place". Skin on backs of hands rough; lips sore; tongue edges red. These suggested B-vitamin deficiency. The patient was therefore treated with full doses of mixed B-vitamins. In one week's time the symptoms complained of had disappeared completely and the physical signs almost. The blood chemistry before and after treatment is given in Table I. There was normal gastric acidity. The coma course (39 comas in all) was completed without further difficulty.

TABLE I

Blood chemistry in thiamine deficiency

Case (a)

		Normal range	Before	After
Serum:				
Sodium	mN	135–150	150	150
Potassium	mN	3·6–5·1	4·6	—
Chloride	mN	95–105	103·4	—
Bicarbonate	mN	25–35	26·5	26·5
Inorganic P	mN	0·6–1·6	1·4	1·5
Blood:				
Lactate	mg./100 ml. . .	6–18	14	13
Pyruvate	mg./100 ml. . .	0·5–1·2	1·2	0·5
Co-carboxylase	μg./100 ml. . .	5·0–12·0	5·2	12·5

"Before" = when first seen and before treatment with vitamin B was started.
"After" = after 7 days' treatment with B-vitamins and rest from coma treatment.

(Note: mN = mEq/lit.)

(2) Water loss. Some patients lose large amounts, e.g. 3–5 litres of water during a coma. Although this is a common experience, I have verified it by weighing patients before and after coma. An undue loss of fluid may lead to a prolonged coma with dehydration—type B; but as all who lose a lot of fluid in coma do not have a prolonged coma, some other factor or factors must also play a part in causing the prolonged coma of type B. (Case 6.)

(3) Failure to maintain carbohydrate intake. Some patients, roused by the usual method of interruption, relapse through failing to maintain their intake of carbohydrate. They may refuse their breakfast or vomit after taking it; they may even vomit their intra-gastric glucose. After a period of stubbornness and confusion, they may relapse into sopor and into coma, if not treated at once with intravenous glucose. Usually prompt and adequate intravenous administration of strong glucose solution rouses them, but it is as well to

continue the infusion till they are well awake and to give them glucose drinks followed by breakfast again. These patients correspond to type C. (Case 5.)

(4) Sensitization to insulin. During their course of insulin comas, most patients become more responsive to insulin, a phenomenon generally described as "sensitization". Adequate reduction of insulin dose is usually enough to combat this form of adaptation. However, the sensitization does not always follow a smooth pattern and is affected by recent exercise, intake of carbohydrate and so on. If there is an undue disturbance of such factors, relative overdosage with insulin may occur and be related to the precipitation of a prolonged coma. Type D includes cases arising in this way.

Sensitization may be the result of many factors, but two sets of factors can be identified, one psychological and the other endocrinological. Some patients, possibly through deep unrevealed fears, appear to be able to resist going into coma, in spite of coma-producing blood-glucose levels. If these fears are dispelled they go into coma more easily, require less insulin and appear to be "sensitized". Case (*b*) illustrates this.

Case (b). A man aged 38 failed to go into coma with doses of insulin up to 800 units given intramuscularly in spite of adequate hypoglycaemia and all its attendant discomforts. Finally, he was given 800 units of insulin intravenously. The prodromata to coma were shortened and his resistance broken through. He went rapidly into a profound coma from which he was aroused by intravenous infusion of glucose solution. When assured that he had "had a coma", he asked if that was "all that it was" and confessed his previous fear. Thereafter he went regularly into coma on an intramuscular dose of 350–450 units of insulin.

Sensitization from endocrine causes is commoner and more complicated. This aspect is more fully discussed later under "Pathology", but some comment may be made here (see also Kay, 1958). Deep insulin coma is a form of stress acting on the endocrine system as an integrated whole, but mainly on the pituitary and adrenal cortex. The effects of stress are first to stimulate and then to fatigue. In an organ already fatigued, stimulation may not occur and fatigue may be intensified to the point of exhaustion. The gradual fatiguing of the anterior-pituitary-adrenocortical axis can be shown by following the changes in the excretion of 17-ketosteroids (Batt, Kay, Reiss and Sands, 1957) and 17-ketogenic corticoids. When this occurs, the main antagonists of insulin become less and less available to the body and the patient becomes sensitized to insulin, in the same way as the patient with Simmonds' or Addison's disease is. The intermittent hyperglycaemia in the recovery phase from coma is likely to stimulate the β-cells of the islets of Langerhans and so facilitate the production of endogenous insulin. (Anderson and Long, 1947a.) These two factors may augment each other to cause the observed sensitization of the patient to insulin.

(5) Formation of loculi of insulin. Another possible factor in sensitization is the formation of loculi of unused insulin given intramuscularly which release insulin in an uncontrollable manner. There has been much speculation as to whether such loculi can occur, but the work of Burkinshaw *et. al* (1958) establishes the possibility of their occurrence. Obviously when insulin is given intravenously, similar loculi are unlikely.

Pathology

(1) Morbid anatomy. As deaths from prolonged insulin coma have to be referred to the coroner, who arranges his own post-mortem examinations, it has not been possible to make any personal investigations in the four deaths in the present series. Lawrence, Meyer and Nevin (1942) have reported on the

pathological changes in the brain in fatal hypoglycaemia and reviewed the relevant literature. Two of their six cases were deaths from prolonged coma in deep insulin therapy for schizophrenia. They found that there was widespread damage, degeneration and necrosis of nerve cells with corresponding microglial and macroglial proliferation, chiefly affecting the cerebral cortex, the caudate nucleus, the putamen, the striate body, the globus pallidus and thalamus. Changes in the brain stem and cerebellum were less marked. Vascular lesions were not present, although other observers have reported them. Lawrence *et al.* attributed the cerebral damage to the interruption of cell metabolism through lack of glucose during hypoglycaemia and coined the word "oxyachrestia" to describe the phenomenon. Kay and Thorley (1951) used the word "adynamogenesis" in the same connection. The cortical damage could account for the difficulty the patient had in making contact with his environment when the coma state had passed off.

(2) Nuclear damage and pyrexia. Early in prolonged coma there is pyrexia, sometimes high, 103–106°F, with polymorphonuclear leucocytosis, which later subside without special treatment. These are very likely due to the cerebral damage. The pyrexia may also be due to the increased metabolism of carbohydrate caused by the unopposed (by gluco-corticoids) action of insulin (c.f. after hypophysectomy and adrenalectomy) and to the effect that the administration of glucose has in raising the respiratory quotient and in increasing the efficiency of insulin (Dohan and Lukens, 1948). In the late stages of recovery, there is marked "hangover", confusion and headache, often severe, resembling a post-concussional state. Very high blood uric acid concentrations are sometimes observed both in normal and prolonged comas. These also may be related to nuclear damage.

(3) Gastric stasis and achlorhydria. Neutral stomach contents are sometimes found at the end of normal comas, but in prolonged comas both gastric stasis, with probable pyloro-spasm, and arrest of acid secretion are very frequently found. Both these may be related to failure of the anterior pituitary or adrenal cortex or both. In interruption by gavage, gastric arrest may be the event which determines the failure to awake from coma, since the glucose feed does not pass into the parts of the intestine from which it can be absorbed to raise the level of the blood glucose. Thus the period of hypoglycaemia is prolonged and a state of prolonged coma may be set up. Once gastric stasis is established, it is not easily abolished since it does not respond to drugs, such as pilocarpine, Mechothane, etc., which normally stimulate gastric and intestinal movement, nor to drugs, such as atropine, which abolish spasm. It may respond to ACTH or cortisone injections (Porrúa *et al.* 1954 and Castro-Rial *et al.* 1954). Often, but not always, resumption of gastric movement and recovery from prolonged coma coincide, or nearly do, thus suggesting that the stasis and prolonged coma may be causally related or have a common cause, such as failure of the anterior pituitary and/or adrenal cortex. Both may be of central nervous origin. On the other hand, the stasis, and the failure to secrete hydrochloric acid which often accompanies it, may also have a local origin in damage to or exhaustion of the nerve plexuses associated with gastric function, caused directly by insulin or mediated by the prolonged hypoglycaemia. In this connection it should be noted that Schereschewsky *et al.* (1929) (quoted by Lawrence *et al.*, 1942), found changes in the sympathetic ganglia in the solar plexus, following death from prolonged hypoglycaemia.

The initiation of gastric stasis may be related to insulin or to increased

secretion of adrenalin, which latter may occur when glucose is given to terminate hypoglycaemic coma (Weil-Malherbe 1954). Insulin in small doses stimulates gastric movement and secretion of acid. It has, however, been shown (Olson and Necheles 1955), that, in the hypoglycaemic phase produced by moderate doses (25 units) of insulin, the volume and acidity of gastric secretion are significantly reduced. When the blood sugar begins to rise, the acidity and volume of gastric secretion rise also. Secretion, if not movement, and glycaemia thus appear to be interrelated. Hypertonic solutions introduced into the stomach reduce gastric motility. The glucose or sugar solutions introduced into the stomach to interrupt coma are very hypertonic, 33 per cent. to 50 per cent. solutions being habitually used. Since prolonged comas are infrequent, it is evident that such hypertonic solutions do not always produce gastric stasis. When there is gastric stasis in prolonged coma, it is likely that there is some factor other than the effect of hypertonic solutions which causes the stasis or which has "conditioned" the stomach and made it unusually susceptible to the hypertonic solution. It is suggested that this factor is most frequently hypofunction or failure of the anterior-pituitary-adrenocortical system.

Prolonged comas may occur even when glucose is given intravenously, at the normal time, to interrupt coma. This occurred in 19 cases (almost one-third) of the present series. Gastric stasis may have been present, it certainly was in some, but it had no part in the failure to terminate the coma by preventing glucose reaching the blood stream. Gastric stasis does not appear to be present in prolonged comas associated with dehydration, since the glucose given by gavage has usually been sufficiently absorbed to rouse the patient were there not some other defect. It seems that gastric stasis, and failure of acid secretion when it occurs, is part of the prolonged coma state, rather than its primary cause, and is referable to hypofunction or failure of the anterior pituitary-adrenocortical system.

(4) Disturbances of blood chemistry. Personal studies, discussed later, have revealed disturbances of blood chemistry in addition to the disturbed glycaemia and dehydration. One very serious disturbance is lowering of plasma bicarbonate, which may contribute to or aggravate the cerebral damage. The corresponding loss of plasma chlorides is usually masked by the intravenous salines used. In addition to the thiamine deficiency previously discussed, there may be a disturbance of the thiamine-using mechanisms, since often an increase of blood pyruvate persists when the blood thiamine level has been raised to normal. A similar condition has been observed in alcoholics with thiamine deficiency, whose blood co-carboxylase has become normal after thiamine medication (Kay, Murfitt and Glatt, 1959).

(5) Fluctuations in glycaemia. More serious, and more enlightening, are the rapid falls in blood-sugar content which occur in the early stages of prolonged coma when glucose is given intravenously to raise the blood sugar (See Figs. 1 and 2). If repeated estimations of blood sugar are not done, or if repeated intravenous administration of glucose at short intervals is resorted to, this phenomenon is not detected. The course of events is as follows. When the patient fails to awake after attempted rousing by the usual method, glucose is given intravenously. This produces a rapid hyperglycaemia, sometimes extreme. The coma is observed to lighten. Soon relapse into deep coma occurs, hypoglycaemia has followed the hyperglycaemia, more glucose is given intravenously and the cycle of events is repeated. If this sequence is repeated, hopefully, often enough, the patient may recover; often he does not.

The explanation of this series of events appears to be that when the induced hyperglycaemia is being reduced by the action of insulin, at normoglycaemic levels the usual mechanisms for arresting the further action of insulin, so preventing hypoglycaemia, do not act; hypoglycaemia again ensues and perpetuates and aggravates the coma.

The mechanisms for preventing hypoglycaemia in the intact person are, broadly:

(a) the cessation of the secretion of insulin,

(b) counter-action by the pituitary and adrenal glands and probably the thyroid.

Besides stimulating gluconeogenesis, the outflow of hormones from the pituitary counteracts the peripheral action of insulin in the tissues, and probably inhibits the secretion of insulin (Anderson and Long, 1947b) thus diminishing the uptake of glucose from the blood and mitigating the competition of the muscles with the brain for the available blood glucose, upon which the metabolism of the brain almost entirely depends. In addition, by its hormones the pituitary stimulates the adrenal cortex and the thyroid and appears to have a stimulating effect on the cerebral cortex, either directly or through its effect on other endocrine organs (cf. the euphoria associated often with ACTH or cortisone treatment, e.g. of rheumatoid arthritis). If the pituitary is fatigued or damaged, its actions are abolished or diminished. It does not respond to the stimulus of raising the blood sugar, so that its normal functions, necessary in recovery from insulin coma, are in abeyance. Moreover, the fasting animal, of which the patient in hypoglycaemic coma is a special type, is more than normally sensitive to insulin and less responsive to adrenalin.

(6) Dysfunction of the anterior-pituitary-adrenocortical system. In view of its relationship to some parts of the brain damaged in fatal hypoglycaemic coma, it may be inferred that the pituitary itself is damaged, and/or in a state of dysfunction from lack of stimuli from the rest of the brain, if therapeutic hypoglycaemic coma is unduly severe or prolonged. Pituitary failure or dysfunction may play an important part in the perpetuation, if not in the causation, of prolonged hypoglycaemic coma.

There is evidence of adrenocortical dysfunction at the end of a normal coma. Kay and Thorley (1951) argued that the changes in the blood chemistry at the end of a normal coma are more consistent with the effects of adrenocortical failure than with the effects of adrenocortical stimulation. They suggested "that the adynamogenesis produced by large doses of insulin, especially coma-producing doses . . . inhibits the function of those organs, such as the adrenals, that normally are responsible for counteracting insulin." This view was challenged by Shattock and Micklem (1952), but in interpreting their results they ignored the fact that the patient roused from coma is a relatively intact organism and some of the phenomena they recorded, especially the fall in circulating eosinophils, were most likely due to the effect of hyperglycaemia on the restored anterior pituitary and adrenal cortex (Reiss *et al.*, 1951).

Studies of 17-ketosteroid and corticoid excretion on any chosen day of coma are difficult, because of the proneness to urinary incontinence in coma, and are likely to be inconclusive, because the period of hypoglycaemia is relatively short in relation to the rest of the day, with its many factors that affect steroid output. On the other hand, serial studies of steroid excretion in patients undergoing deep insulin coma therapy, are informative (Batt, Kay, Reiss and Sands, 1957; Kay, 1958). Some results are reproduced in Figures 3, 4, 5. These

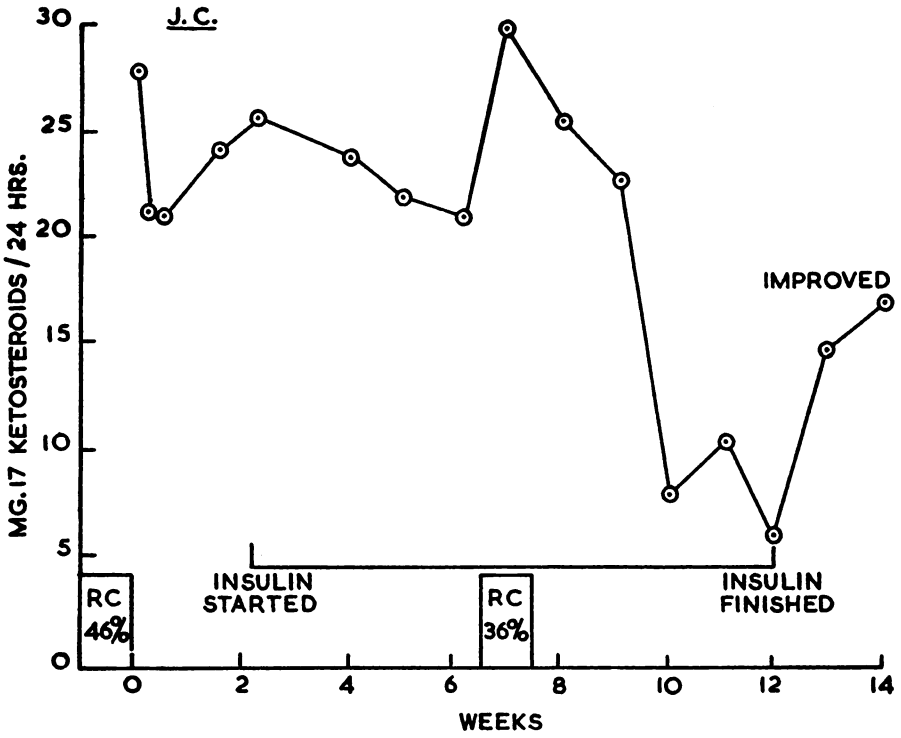

FIG. 3.—Initial values high, final values low. (RC refers to thyroid function.) Steroid excretion in deep insulin coma treatment. (Batt, Kay, Reiss and Sands, 1957.)

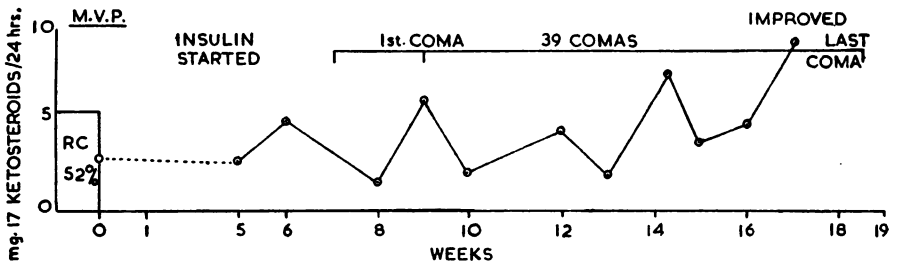

FIG. 4.—Initial values low, final values normal.

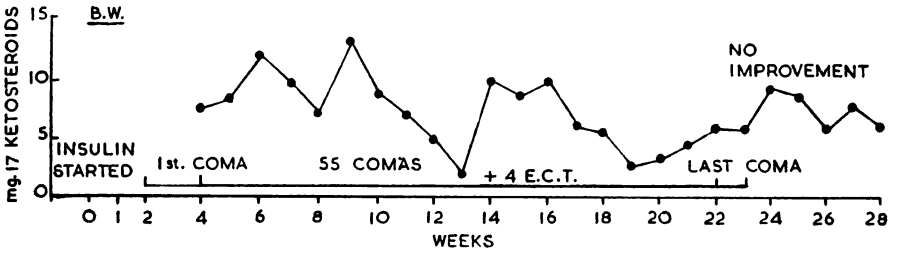

FIG. 5.—Initial and final values low.

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indicate that there are various levels of activity of the adrenal cortex, and of the anterior pituitary too, at the start of the treatment course, followed by phases of stimulation and depression of adrenocortical response as the course proceeds. Often there is stimulation in the early stages, fatigue or depression in the middle stages, whilst at the end there may be stimulation or depression. The course of events depends on the initial state of the adrenal cortex and its reserve of reactivity. Further similar studies amplified by estimations of 17-ketogenic corticoid excretion confirm these findings (personal observations).

In the cases of prolonged coma here reported, where it was possible to determine steroid excretion, it was invariably low. Some patients showing difficulty in recovering from coma, especially those going into coma on low doses of insulin, say 40–80 units, were found to have low 17-ketosteroid and 17-ketogenic corticoid excretions. In these cases doctors were usually advised to discontinue coma treatment because of the poor adrenocortical function and the risk of prolonged coma.

From blood corticoid determinations during therapeutic insulin coma, Bliss *et al.* (1954) concluded that the adrenal cortex was stimulated since the blood corticoids increased. Examination of their results shows that they had three types of corticoid response, shown with their average curve in Fig. 6, which were masked by their taking averages. It will be observed that in the hyper-responsive and normo-responsive types there is a tendency for the blood corticoids to fall at the end of coma, whilst the hypo-responsive type shows a state of fluctuating activity of the adrenal cortex at a relatively lower level. In one patient, investigated twice in this work, the level of blood corticoids in the later

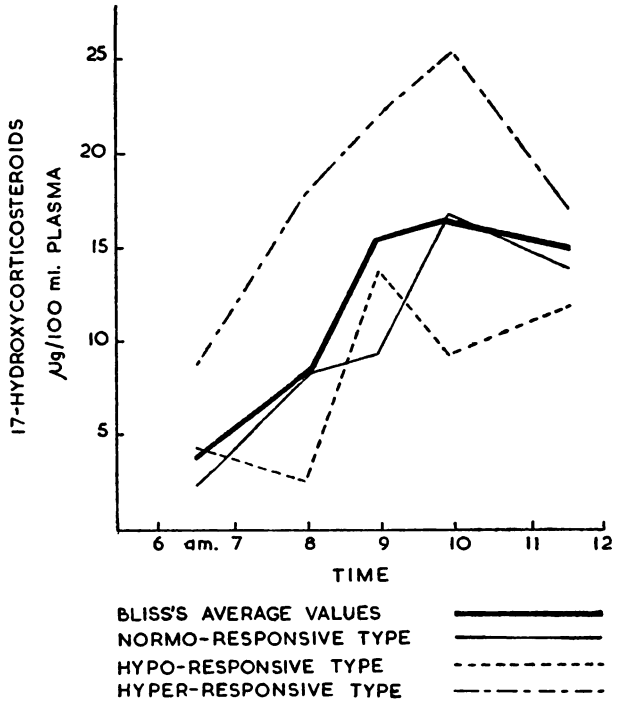

FIG. 6.—Effect of insulin coma on level of 17-hydroxycorticosteroids in plasma. (Bliss *et al.*, 1954 and Kay, 1958.)

coma was lower than in the earlier, suggesting that his pituitary-adrenocortical system was becoming fatigued.

From studies of the effects produced by injected ACTH and cortisone on the patient and on the blood glucose in normal insulin comas, it seems probable that ACTH and the adrenocortical hormones are ineffective in hypoglycaemia (Kay, 1958). This may account for the increase of blood corticoids observed by Bliss: the corticoids secreted were not used and accumulated in the blood. There may not have been extra secretion, especially in the later stages of coma.

The achlorhydria and gastric stasis found in prolonged coma, especially of the fluctuating glycaemic type (type D), have already been related to hypofunction of the anterior pituitary-adrenocortical system.

Goldman (1940), in a patient in prolonged post-insulin coma, observed bronzing of the skin. This suggested to him that adrenal cortical deficiency was an element in the cause of the syndrome. He then began to use adrenocortical extract (Eschatin, Parke, Davis & Co.) and large quantities of saline in treating prolonged insulin comas. Thereafter, no prolonged stupors were observed in spite of the occurrence of 17 post-hypoglycaemic comas. Reporting his success he concludes "These therapeutic observations are probably as strong evidence as can be obtained to support the theory that adrenal cortical deficiency plays the determining role in causing this syndrome." This may be *post-hoc* reasoning, but exactly the same could be said about the cases successfully treated with hormones in the present series. The failures suggest, however, that there may be other not yet determined factors involved in the causation and perpetuation of prolonged insulin comas.

Whether the presumed loss of adrenocortical function is primary or dependent on pituitary failure is not important since the result is the same either way. What is suggested is that there is a probable failure or low state of function of the anterior-pituitary-adrenocortical system in some cases of prolonged hypoglycaemic coma and that this failure or hypofunction may even be gross and continued. It would also account for the phenomenon of sensitization to insulin that frequently occurs during the treatment course.

In prolonged coma, it would appear that, in addition to any residual circulating administered insulin, endogenous insulin is being secreted by the pancreas in response to the hyperglycaemia induced by the administration of glucose, and its secretion is not arrested at normoglycaemia; otherwise the recurrent hypoglycaemia would not occur. In addition, any intramuscular loculi of unabsorbed injected insulin, which slowly drain their insulin into the circulation, could help in producing or aggravating the recurrent hypoglycaemia. Prolonged comas occur even when insulin is given intravenously to induce coma; loculi cannot reasonably be postulated in such cases. The readily available exogenous insulin should eventually be used up by the administered glucose. It seems, then, that the most probable cause of the recurrent hypoglycaemia in prolonged coma is the uncontrolled endogenous secretion of insulin following the repeatedly induced hyperglycaemia. The adrenal cortex, fatigued or exhausted by the stress of the patient's illness, the stress of the prolonged pre-coma state or the repeated stresses of insulin coma treatment, fails to mobilize enough glucocorticoids, both during the coma and in response hyperglycaemia, to cope with the circulating insulin, whether endogenous or exogenous. The adrenal failure may be primary, associated with, or secondary to pituitary failure of similar origin. Such a condition calls for the administration of cortisone or similar adrenocortical hormones to supplement the natural secretion, or of ACTH to evoke a natural secretion from the residual power that even a fatigued adrenal cortex

may have, to assist the impaired physiological regulatory processes that prevent hypoglycaemia.

In so far as the pituitary and adrenal cortex are concerned, prolonged insulin coma bears some relation to wound shock, where the anterior-pituitary-adrenocortical mechanisms are first stimulated and then fatigued and the administration of exogenous hormones is needed to supplement and correct their hypofunction.

(7) *Summary*. My theoretical approach to the problem of prolonged insulin coma of the fluctuating glycaemic type (type D) can now be summarized. Whatever the primary cause of the failure to respond to the usual method of interruption may be, the early stages of the prolonged coma are characterized by hypoglycaemia relapses which aggravate the state. These relapses are probably mainly due to failure to control residual exogenous insulin and endogenous insulin secreted in response to the induced hyperglycaemia. This failure to control insulin at normo-glycaemic levels is referable to failure of the anterior-pituitary-adrenocortical system, due to temporary exhaustion or even damage. Administration of effective pituitary and/or adrenocortical hormones should correct the imbalance between the pituitary-adrenal system and insulin, thus stabilizing glycaemia and establishing conditions for recovery. Supplies of adrenocorticotrophic hormone (ACTH) and cortisone (acetate) were therefore obtained from the Medical Research Council, in April, 1952.

(It may be mentioned here that according to Alexander (1953), Clower and Niswander, in a paper read before the Massachusetts Society for Research in Psychiatry, 2nd November, 1951, reported having given cortisone intramuscularly and by gavage in prolonged insulin coma. Their results are not stated. This information did not reach me until late in 1953 when I had by then used cortisone and ACTH in a number of cases.)

III. Experimental Treatment

Case material

By the courtesy of doctors in a number of mental hospitals, I was called to their cases of prolonged coma, preferably as soon as possible after the prolonged coma was diagnosed. This report is based on 62 consecutive cases, 18 male and 44 female, seen and treated in 13 hospitals over a period of 3½ years.

The mean ages of the patients, the mean numbers of comas they had had up to and including the prolonged one and the mean doses of insulin used to induce the coma that became prolonged, are set out in Table II, together with ranges and standard deviations. The sex groups are comparable from these three aspects, the differences between means of ages, numbers of comas and insulin doses not being statistically significant. For purposes of later discussion, therefore, males and females can be treated as one homogeneous group.

Table II

Numbers of patients and means of ages, of numbers of comas (including the prolonged one) and of doses of insulin (units)

	Males	Females	All
Numbers of patients ..	18	44	62
Ages:			
means and S.D. ..	29·6±4·96	28·3±6·07	28·7±5·8
ranges	24–39	17–40	17–40
Numbers of comas:			
means and S.D.	10·6±9–6	11·8±10·2	11·4±10·0
ranges	1–35	1–38	1–38
Insulin doses:			
means	256±157	209±96	222±118
ranges	20–600	40–480	20–600

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The cases can be divided into four groups according to the type of treatment they had (see later): general, cortisone, ACTH and both hormones. The numbers of patients in the four treatment groups and the means of their ages, numbers of comas and doses of insulin are given in Table III. There are no statistically significant differences between any pairs of age means, means of numbers of coma or means of doses. The four treatment groups may, therefore, be compared with each other when the results of treatment are evaluated.

TABLE III

Numbers of patients and means of ages, of numbers of comas and of doses of insulin (units) in the four treatment groups

	Treatment group				
	General	Cortisone	ACTH	Both hormones	All
Numbers of patients ..	7	16	33	6	62
Means:					
Ages	29·7	28·7	28·5	30	28·7
Numbers of comas ..	13·1	12·8	11·5	5·7	11·4
Insulin doses	267	202	218	251	222

The doses of insulin used were those ordinarily in general use; for example, Thorley and Kay (1951) used a mean dose of 290 units (S.D.156) for men. As is usually found, the mean dose for women was rather less than that for men but not statistically significantly so.

40 per cent. of the cases occurred in the 1st, 2nd, 3rd, 4th or 5th coma the patient had had. Of the men, 47 per cent. had their prolonged coma in the first 5 of their treatment course, as compared with 37 per cent. of the women. This difference is not statistically significant. In the ACTH-treated group, the mean number of comas for the men was 8 and for the women 13 (the difference is not statistically significant). This was because the prolonged coma was the first coma for 4 of the 10 men in this treatment group as compared with only 1 of the 23 women in the same group.

In all, for 5 men and 1 woman their first coma was a prolonged one. This sex difference may be accounted for by the naturally higher dose of insulin required by men and by the possibility that they exhibit a greater resistance to going into coma than women do and so require an exaggerated dose for their first coma (cf. Case (b)).

The relationship of the prolonged coma to the coma treatment course is shown in Figs. 7 and 8. Fig. 7 shows the incidence for both sexes. In Fig. 8 the numbers of prolonged comas are related to successive quintuplet groups of numbers of comas in the treatment courses.

A point of interest is the distribution of the prolonged comas on the days of the week, shown in Fig. 9. Contrary to many opinions, Monday is by no means the day on which most prolonged comas occur. Wednesday holds this dubious distinction. A greater number of cases occur in the second half of the week than in the first half. The small number on Saturday is due to the fact that most hospitals prescribe a rest day on Saturday for their coma patients.

Without added information it is not possible to explain the daily distribution of prolonged comas. It may be, however, that the break in treatment at week-ends allows a recovery of the stressed anterior-pituitary-adrenocortical system which may then call for an increased dose of insulin on Monday. The next two days then intensify the burden on the fatigued defensive mechanisms, leading to a greater number of breakdowns at the middle of the week.

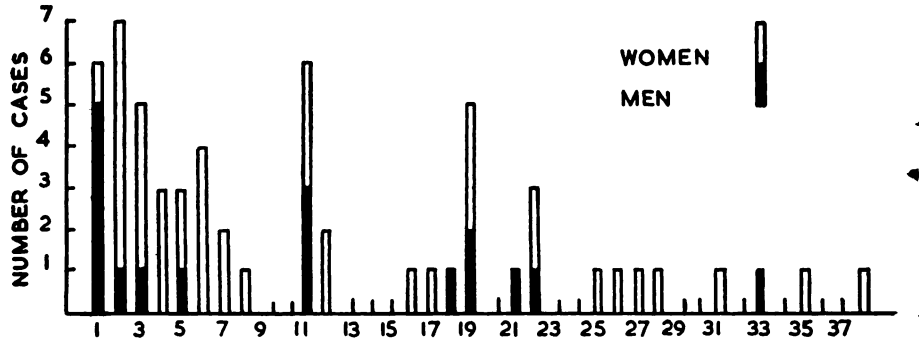

FIG. 7.—Relation of prolonged coma to treatment course. (59 cases.)

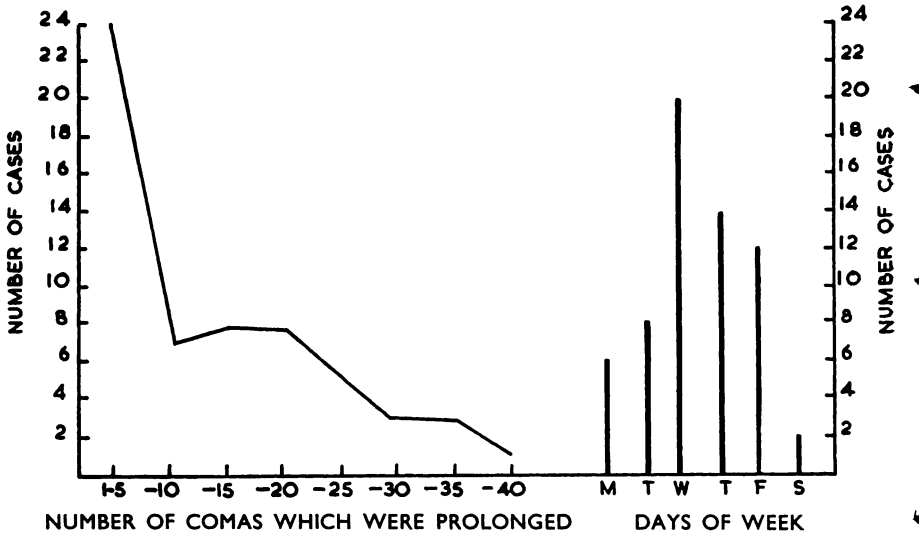

FIG. 8.—Relation of prolonged coma to coma course. (59 cases.) (Kay, 1958.)

FIG. 9.—Days on which prolonged comas occurred.

Treatment

(1) *General observations.* It is necessary to keep in mind the four types of cases previously discussed. My first approach to the problem of treatment was along the lines of the part played by the gradually growing deficiency of B-vitamins, which are essential for the co-enzymes required for glucose metabolism. One case (Case 1) responded spectacularly to the intravenous administration of a mixture of the principal B-vitamins. Subsequent cases, however, soon indicated the limitations of this form of treatment. Moreover, more use was being made of B-vitamin supplements for patients undergoing deep insulin coma therapy, and among the first remedial measures used in cases of prolonged coma was the administration of large doses of mixed B-vitamins. It was soon evident that the cases to which I was being called were those in which both glucose administration and B-vitamin medication had failed to bring about recovery.

Of the other types of prolonged coma discussed, one case (Case 6) of type B (intense dehydration) and one case (Case 5) of type C (simple glucose lack) were encountered. They responded respectively to intravenous administration of saline (with glucose) and of 33 per cent. glucose solution. The remaining cases all fall into type D. Dehydration is a frequent feature of prolonged coma, but not necessarily a determinative one, and has to be treated as it occurs.

The 62 cases are divided into four groups according to treatment. Seven cases are included in a "general" group. Four of these were treated symptomatically, three have just been referred to above. None of these seven had either cortisone or ACTH. Sixteen cases were treated with cortisone, thirty-three with ACTH and six with both hormones.

It was advantageous to see cases as early as possible after the establishment of the prolonged coma state, but in many cases several hours had elapsed, and in two cases a whole day, before hormone treatment was applied.

(2) *Method of treatment.* The routine approach to a case was to obtain the history of the coma leading up to the prolonged coma, a brief history of the previous comas and recovery therefrom, and an account of treatment given since the first attempted interruption. Note was taken of the amount of glucose given intravenously and of whether gastric stasis had been shown to be present by withdrawing fluid previously given by gavage. An assessment of the clinical state of the patient was next made, especially in regard to depth of coma, circulatory and respiratory state, dehydration and reactiveness to stimuli such as supra-orbital pressure. Blood was taken by venepuncture for laboratory investigations and serial capillary blood sugar estimations started, if not already being done.

Treatment was then decided on in accordance with the guiding principles previously stated. General treatment, such as raising the foot of the bed, providing warmth (if necessary) in the form of hot water bottles or electric blanket, was instituted at once. Mixed B-vitamins (thiamine, riboflavine, nicotinamide, pantothenic acid and pyridoxine) were given parenterally if not already administered, and measures taken that appeared obviously necessary to correct dehydration or hypoglycaemia, if established by blood-glucose estimation. If there was still no indication of recovery, hormone was then given by intramuscular injection (55 of the 62 cases). At first, since the effect of neither cortisone nor ACTH was known, doses of 25 mg. were used; later attempts were made to vary the dose according to the insulin dose (hormone dose range 25–100 mg.), but this did not appear to help. Eventually, 50 mg. of either cortisone or ACTH was accepted as a useful first dose, to be repeated an hour or so later if the patient had not recovered. In 6 cases ACTH was given first and followed after an interval by cortisone, especially as the latter was thought to have a better stabilizing effect on the blood-glucose level.

In cases where there was not a prompt recovery after hormone or other treatment, steps were taken to correct any abnormalities in blood chemistry revealed by laboratory tests. Adjustments were required chiefly to plasma bicarbonate and potassium and blood glucose. Correction for the first two was attempted by intragastric feeding, but sodium lactate and potassium chloride were given intravenously when necessary.

Low blood-glucose values were corrected by giving $33\frac{1}{3}$ per cent. glucose in normal saline intravenously. The aim was to maintain the blood glucose in the range 100–300 mg./100 ml. The use of normal saline for intravenous infusion tended to raise the plasma sodium chloride. This rarely passed into dangerous levels, but if it did, correction was made by using weaker saline.

An intra-gastric tube was passed, usually intranasally, and the stomach emptied. A feed consisting of glucose in water was introduced into the stomach. With experience of treating a number of cases, the following formula was adopted as a routine feed:

Water	10 oz. (300 ml.) (half-pint)
Glucose	2 oz. (50 g.) (4 tablespoonsful)
Sodium bicarbonate	60 grains (4 g.) (1 teaspoonful)
Potassium chloride	30 grains (2 g.) (½ teaspoonful)

The intragastric tube was usually kept *in situ*. Two hours after the first feed, the contents of the stomach were withdrawn and measured. Loss of volume usually meant that the stomach movements were beginning again. The removed feed was replaced by a fresh one of the same composition. This two-hourly change of gastric contents was maintained till the patient was capable of drinking. The potassium chloride was omitted from feeds if the plasma potassium warranted this.

There was no need to give feeds containing other nutrients than glucose until it was certain that recovery would be delayed beyond 24 hours. Even then the chances of vomiting had to be taken into account. In such extended comas, fluid diet with a prepared milk (citrated or pre-digested) basis and necessary salts and accessory factors was started and given by the intragastric tube. Ordinary milk is an abomination because of its clotting. The proneness to vomiting, especially early in the prolonged coma, makes milk clots a lethal menace. If inspired, clots seem invariably to initiate pneumonia.

Nikethamide, strychnine, oxygen and the usual resuscitatory measures were kept immediately available in case of a sudden respiratory and/or circulatory collapse.

(3) *Laboratory investigations.* If not already instituted, on my arrival serial blood-sugar estimations at approximately hourly intervals were started at once. In view of the known effects of insulin coma and of both hormones on the blood chemistry, especially on the electrolytes sodium, potassium, chloride and bicarbonate, appropriate investigations were started at once, blood samples being collected before treatment started and at intervals after. Usually a final check was made after recovery. The essential estimations were those indicated above, blood sugar and plasma electrolytes, to which were added serum total proteins, a full blood count including haemoglobin and packed cell volume as a basis for controlling dehydration and blood volume changes. It was not possible in all cases to do all these estimations; in one or two cases it was impossible to take venous blood.

Further investigations were carried out at leisure to obtain added information about the changes in the blood in prolonged coma.

All the methods used were those ordinarily in use in my laboratory. They were as follows:

Serum:		normal range	
bicarbonate		25–35 mN	van Slyke (1922).
chloride		95–105 mN	Whitehorn (1921).
potassium		3·6–5·1 mN	by flame photometer.
sodium		135–150 mN	by flame photometer.
proteins:	total	5·9–7·5 g./100 ml.	modified biuret method; albumen-globulin separation by 27·8 per cent. ammonium sulphate adjusted to pH 6·5–7·0. electrophoresis in Antweiler micro-Tiselius apparatus.
	albumin	3·6–7·5 g./100 ml.	
	globulin	1·8–2·8 g./100 ml.	
	a/g	1·5–2·3/1	

inorganic phosphate		0·6–1·6 mN	Kuttner and Lichtenstein (1930).
uric acid		2–4·5 mg./100 ml.	Brown (1945).
cholesterol:	total	150–250 mg./100 ml.	Sperry and Webb (1950).
	free	40–80 mg./100 ml.	
	ester	100–180 mg./100 ml.	
	f/e	1/2·0–3·0	
Blood:			
urea		15–40 mg./100 ml.	Archer and Robb (1925).
glucose		70–120 mg./100 ml.	various (Folin and Wu (1920). Hagedorn and Jensen (1941). Nelson (1944)).
cholinesterase		over 45 units	manometric at 30°.
cocarboxylase and thiamine		5–12 μg./100 ml.	Kay and Murfitt (1956).
glutathione		24–37 mg./100 ml.	Kay and Murfitt (1960).
pyruvate		0·5–1·2 mg./100 ml.	Friedemann and Haugen (1943).
lactate		5–20 mg./100 ml.	Barker and Summerson (1941).
Urine:			
steroids	(men)	9–19 mg./24 hrs.	Paterson, McPhee and Greenwood
	(women)	5–13 mg./24 hrs.	(1942) modified.

(Note: mN = mEq/lit.)

In order to be able to do the emergency estimations it was necessary to assemble and take the requisite special laboratory equipment and to take members of my technical staff to supplement the laboratory staff at the hospital where the case of prolonged coma was located. It is not inappropriate at this point to acknowledge the great help given by biochemists and laboratory technicians, often in prolonged spells of work after normal working hours, sometimes throughout the night and always under the stress and drive of an exacting emergency.

IV. Results and their Evaluation

Results

These are classified according to the time taken for a full recovery, that is, when the patient was again in touch with his surroundings and able to drink eat and speak. The times are defined as follows:

Recovery Group 1 prompt—recovery in less than one hour;
2 hours—recovery after one hour, but on same day as the coma started;
3 next day—recovery by the day following the coma, usually, by next morning;
4 days—recovery after the next day but in less than a week;
5 weeks—recovery after more than a week;
6 death.

The results, in gross form, and grouped according to method of treatment, are given in Table 4.

Table IV

Results of treatment in the 4 treatment groups

Treatment group	Total cases	Numbers of cases in recovery group No. 1 Prompt	2 Hours	3 Next day	4 Days	5 Weeks	6 Death
General	7	2	1	1	—	3	—
Cortisone ..	16	5	3	4	3	1	—
ACTH	33	7	6	13	3	2	2
Both hormones ..	6	—	1	1	2	—	2
Totals ..	62	14	11	19	8	6	4

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(1) The general treatment group. The three cases that recovered promptly and within two hours were exceptional and were not duplicated in the rest of the series. They belonged to types A, B and C.

Type A. Case 1. 4.5.51. Male aged 28. Nearing end of coma course. Insulin dose 230 units (reduced from 250 units on previous day). At 10.25 a.m., after 30 minutes of coma he was given 180 ml. of 33⅓ per cent. glucose in saline intravenously. There was partial recovery followed by relapse into coma. A further intravenous infusion of 500 ml. of 33⅓ per cent. glucose was given at 11.0 a.m., followed by 50 mg. nicotinic acid i.v. at 11.30 a.m. and an intragastric feed of 100 g. glucose and 2 g. of potassium chloride in water. The patient did not recover but remained quiet in coma. Further glucose, 1 pint of 5 per cent. glucose saline and 100 mg. nicotinic acid were given i.v. at 1.35 p.m. with intramuscular atropine and penicillin. I saw this patient at 3.0 p.m. He was then in coma and had been restless but his physical condition was well maintained. The blood glucose was 165 mg./100 ml. Two doses of 10 mg. of thiamine given intravenously at 25 minute intervals were followed by lightening of the coma and rapid progress to recovery within an hour. Next day the patient was well, but complained of paraesthesia, tingling fingers and feet and said that he had had these for some days before the prolonged coma. Treatment with mixed B-vitamins was continued with full recovery from these in about a week. The patient felt well enough to decline further coma treatment.

The blood chemistry is reported in full in the Appendix. The significant abnormalities at 3.0 p.m. on the day of the prolonged coma were:

Plasma bicarbonate	21 mN (m.Eq/litre)
Blood pyruvate	2·5 mg./100 ml.
Blood lactate	60 mg./100 ml.

There was moderate loss of plasma bicarbonate but not enough to cause serious embarrassment of the patient. The blood glucose had been well maintained. The blood pyruvate was high enough to indicate a deficiency of cocarboxylase. (In order to obtain definite evidence about blood cocarboxylase, a method (Kay and Murfitt, 1956) was being developed but was not available for this case.) The fact that this patient did not recover with nicotinic acid injections indicates that B-vitamin deficiency is not confined to a single vitamin. There were no clinical signs of pellagra in this case, the main signs present being referable to thiamine deficiency. The increase in blood lactate was probably due to some restlessness just before the blood sample was taken

The other case of prompt recovery was a case of simple glucose lack.

Type C. Case 5. 5.5.52. Male aged 21. 21st coma. Insulin dose 350 units. 15 minute coma interrupted by 125 ml. 33⅓ per cent. glucose i.v. (usually he required about 225 ml. of 33⅓ per cent. glucose to get him fully round). He awoke promptly but was stubborn and uncooperative. He refused breakfast, vomited his dinner and insisted on taking a bath. He then relapsed into coma. Further intravenous glucose was given i.v., 250 ml. 33⅓ per cent., followed by his regaining consciousness promptly, only to become comatose again. About 4.0 p.m. he was physically distressed, with temperature 102°, pulse 140/min. and respirations 48/min. I saw this man about 4.30 p.m. On the history, a probable diagnosis of glucose lack was made. The blood glucose was then 45 mg./100 ml. A further 200 ml. 33⅓ per cent. glucose i.v. brought him out of coma at once. Thereafter, his condition was well maintained and he ate a "breakfast" and later a full supper. The temperature and pulse and respiratory rates returned to normal. This patient had an acute respiratory infection with cough and blood-stained sputum. A streptococcus viridans was isolated. Infections of this type upset insulin mechanisms and maybe this had played a part in this case. The infection cleared up rapidly with penicillin treatment.

The case recovering in 2 hours was one of dehydration.

Type B. Case 6. 10.9.52. Female aged 22. 22nd coma. Insulin dose 260 units. Earlier in the course, she had required 320 units for coma. This had been gradually reduced to 260 units: (mild degree of sensitization to insulin). She had had several difficult recoveries from coma. After 15 minutes' coma, an intragastric feed of 10 oz. strong glucose solution was followed by partial recovery. An hour later the residue of the interrupting feed was withdrawn from the stomach and 225 ml. of 33⅓ per cent. glucose given i.v. This raised the blood glucose to 300 mg./100 ml. which thereafter was maintained, only falling slowly to 139 mg./100 ml. at 4.30 p.m. Mixed B-vitamins were given and a fresh intragastric feed given at 5.50 p.m. At 5.15 p.m. 44 oz.

of urine had been withdrawn by catheter. I saw this patient shortly after 6.0 p.m. She was very dehydrated, restless and rather exhausted. In view of the steady blood-glucose level this case was assessed as suffering mainly from dehydration. 700 ml. 5 per cent. glucose-saline, 300 ml. normal saline and 200 ml. 33⅓ per cent. glucose-saline given rapidly i.v. were followed by prompt partial recovery and in 2 hours by full recovery. The blood sugar remained high, the last reading at 11.0 p.m. being 260 mg./100 ml.

In this case there was no prolonged hypoglycaemia following interruption and although the blood glucose was well maintained and adequate glucose was given, there was no permanent recovery until adequate fluid was given i.v. to correct the dehydration.

The patient who did not recover till next day was misjudged clinically.

Type D. Case 17. 21.3.53. Female aged 27. 4th coma. Insulin dose 400 units i.v. Her coma had been interrupted by 300 ml. 33⅓ per cent. glucose given i.v., which produced partial recovery followed by relapse into coma. Glucose solution was given intragastrically without effect, followed by further glucose i.v. When first seen, at 5.0 p.m., the patient's blood sugar was 305 mg./100 ml., her general condition was good, there was some dehydration, and she responded purposefully to stimuli. It was felt that cortisone or ACTH would not help. (In the light of fuller experience, this decision is felt to be wrong.) A nasal tube was passed to explore the stomach contents. This evoked much struggling and aroused the patient. The last previous fluid put into the stomach was entirely withdrawn (evidence of gastric stasis), and a fresh feed of water (10 oz.), glucose (100 g.), potassium chloride (2 g.) and sodium bicarbonate (8 g.) given. Withdrawal of the nasal tube produced further stimulation and lightening of coma and the patient appeared to have almost recovered and was able to sit up and drink. As an attempt to complete awaking, 10 mg. of methedrine were given i.v. and repeated in about half an hour. This produced only slight advancement. The blood sugar fell to 45 mg./100 ml. at 8.0 p.m. and intravenous glucose was given. Gastric movements returned and the patient was maintained throughout the night by intragastric glucose with potassium chloride and sodium bicarbonate. Next morning she had recovered. To some extent, this case serves as a control to the hormone treated cases. It is highly probable that either cortisone or ACTH would have produced a prompt recovery, as there was no undue prolongation of the therapeutic hypoglycaemia, interruption having been first attempted by intravenous glucose.

The remaining three cases were treated on general lines; administration of glucose, intravenously and intragastrically, to maintain the blood-sugar level, and of saline, potassium chloride and sodium bicarbonate as indicated by blood analyses. Two were encountered before ACTH and cortisone were available.

One (Case 2. March 1952. Male aged 24. 19th coma. Insulin dose 120 units) was in coma for 3–4 weeks and the second (Case 3. April 1952. Female aged 23. 2nd coma. Insulin dose 280 units) 2–3 weeks. For early blood-glucose values see Figs. 1 and 2. The experience gained in these two cases was valuable in learning the management of long term comas. Observation of the fluctuating glycaemia that occurred led to the conclusion that ACTH or cortisone might help if used early in treatment.

The third (Case 26. September 1953. Female aged 39. 11th coma. Insulin dose 230 units) of these cases was not seen until she had been in coma for over 24 hours. The blood glucose was relatively stable and it seemed unlikely that either ACTH or cortisone would help. Routine general treatment was instituted and the patient recovered in the third week of coma. In all these three cases, the primary interruption was by intragastric glucose, followed by intravenous glucose when recovery did not occur. As a result, the period of hypoglycaemia was prolonged by 80, 70 and 65 minutes respectively, beyond the usual treatment period. For blood chemistry of Case 3 see Appendix.

In this group, then, there were one case of prolonged coma associated with B-vitamin deficiency (Type A), one of simple glucose deficiency (Type C) and one of dehydration (Type B). In none of these was the period of hypoglycaemia longer than was intended for therapy and recovery was quick in response to treatment. The other four cases were of Type D, fluctuating glycaemia. One, having a therapeutic period of hypoglycaemia only, recovered by the next day; recovery could probably have been hastened by cortisone or ACTH. The remaining three cases had hypoglycaemia prolonged far beyond the therapeutic period and recovered only after 2–4 weeks. All the other cases treated fell into Type D and received hormone treatment.

(2) The cortisone treated group. Sixteen cases were treated with cortisone, 8 of whom recovered quickly, 5 in less than one hour and 3 within a few hours. Four of the remaining 8 recovered by the next day, and 4 after longer periods.

Typical cases will be described.

Prompt recovery. Case 4. 1st May, 1952. (The first case treated with hormone.) Male, aged 28. 33rd coma. Insulin dose 380 units. Nothing abnormal was noted during the coma. After 25 minutes' deep coma, 250 ml. of 33⅓ per cent. glucose in saline were given i.v. to interrupt the coma but did not rouse the patient. One pint of 40 per cent. glucose was given intragastrically, still without effect. The patient became very distressed and was given nikethamide and adrenalin by injection and oxygen by inhalation. One and a half hours after the attempted interruption there was slow recovery and the patient was able to sit up in bed but began to relapse into coma. Further glucose, 5 per cent. solution in saline, was given i.v. When I saw this patient at 4.0 p.m., five hours after the first attempted interruption of coma, the patient was comatose and gradually slipping back into deep coma. Blood chemistry is given in the Appendix. He had had 96 g. of glucose i.v. and 200 g. intragastrically. His general condition was good, blood sugar was 65 mg./100 ml. and electrolytes normal. B-vitamins (as Becosym) were given intramuscularly without effect. The blood pyruvate was normal at this time. The stomach was empty, acid was present, enabling 20 oz. of 40 per cent. glucose solution to be given intragastrically. As there were no signs of recovery, 25 mg. of cortisone were given intramuscularly, the time being 5½ hours after the first attempt at interruption. There was a rapid lightening of the coma and in 10 minutes the patient was able to sit up and drink. He was still drowsy, but rousable and soon able to speak in a confused manner. He continued to make good progress, his blood sugar increased and was maintained and in due course he was able to eat a normal supper. This patient had a blood uric acid of 13·6 mg./100 ml. (? evidence of nuclear damage) which slowly fell. The day following coma, the white blood cell count was 16,500/cu.mm. (75 per cent. polymorphs). His ketosteroid excretion was just subnormal (8·4 mg./24 hrs.) the day after his prolonged coma, suggesting poor adrenocortical function. A week later it had risen to 12·7 mg./24 hrs. For blood chemistry see Appendix.

Recovery in hours. Case 12. 16.12.52. Female, aged 34. 4th coma. Insulin dose 40 units. Uneventful coma. After 20 minutes' deep coma, 100 ml. of 33⅓ per cent. glucose in saline given i.v. failed to rouse the patient. A further 80 ml. were given at once. There was slight lightening of the coma followed by a deepening. A further 180 ml. of 33⅓ per cent. glucose solution given i.v. with mixed B-vitamins (Becosym) produced lightening of the coma with much restlessness. This was the state of the patient when seen by me 90 minutes after the first attempted interruption. The blood electrolytes were normal and the blood sugar 70 mg./100 ml. Cortisone, 25 mg. given intramuscularly produced a rapid response. Ten minutes after the cortisone the patient opened her eyes and appeared to be rousing. After a further ten minutes she was able to drink freely but was not progressing as quickly as was desired. Three hours after the first attempt at interruption a second dose of 25 mg. of cortisone was given i.m. At this point the blood electrolytes were still normal and the blood glucose was 83 mg./100 ml. Progress was now steady, the patient taking glucose drinks freely. After a short period of hysterical weeping, the patient roused herself into a sitting position and appeared to be fully roused about 2¾ hours after the first dose of cortisone. The blood sugar was then 115 mg./100 ml. When first seen, this patient had a blood pyruvate of 1·8 mg./100 ml., a value which suggested that there was some thiamine deficiency. She also had a low 17-kestosteroid excretion, 2·4 mg./24 hrs. on the day following the prolonged coma. For blood chemistry see Appendix.

Recovery by next day. Case 16. 25.2.53. Female, aged 28. 2nd coma. Insulin dose 250 units. Uneventful coma. After 10 minutes' deep coma, interruption was attempted by intragastric administration of 50 g. of glucose in 8 oz. of water. There was no response to this, and 400 ml. of 33⅓ per cent. glucose in saline with 2 ml. of nikethamide were given i.v. 80 minutes after the onset of deep coma, without effect. An intragastric tube was passed 2 hours and 40 minutes after the first attempt at interruption by intragastric feed, and the whole of this feed was withdrawn and replaced by a similar fresh one. Three hours later 500 ml. of 33⅓ per cent. glucose in saline with nikethamide and Becosym were given i.v. I first saw the patient about 6 hours after the onset of deep coma. The patient as still in moderately deep coma and in good physical condition. Blood was taken for chemical estimations and 50 mg. of cortisone given i.m. The blood sugar just before this was reported to be 394 mg./100 ml. Twenty minutes after the cortisone the patient was recovering and could be roused by slapping and calling to her. She sat up and was able to drink with difficulty, but remained somnolent and tended to go to sleep again. The blood glucose was being maintained, the value being 348 mg./100 ml. one hour after the first test. In view of the marked somnolence, 20 mg. of Methedrine were given i.v. Instead of waking the patient, the Methedrine evoked uncontrolled violent motor activity which lasted for about half an hour. At this point the plasma bicarbonate (sample taken just before giving the cortisone) was reported to be 14·5 mN, the other electrolytes being normal. Bicarbonate of soda, 8 g. in solution, was given by gavage to correct the acidaemia. This appeared to be absorbed rapidly, for in about a quarter of an hour the plasma bicarbonate had

risen to 23 mN. By this time (about 8½ hours after the onset of deep coma) the patient's condition appeared to be stabilized, but she had not fully recovered and was still restless. Glucose was given by gavage, but the blood glucose slowly fell and a further intravenous infusion of 450 ml. of 33⅓ per cent. glucose in saline had to be given. Gardenal gr. iv. was given as a sedative. Glucose drinks were given at intervals during the night. By morning the patient was rousable, able to speak when addressed and by mid-day was fully awake, in good condition, but with a "hangover".

Recovery after a few days. Case 59. 17.8.55. Female, aged 36. Habitually slow in recovering from coma. 12th coma. Insulin dose 260 units. Uneventful coma. After gavage, the coma lightened for a time, then suddenly the patient relapsed into deep coma. Intravenous infusion of 25 ml. of 33⅓ per cent. glucose in saline, given with difficulty 45 minutes after gavage, had little effect. Later larger amounts failed to rouse the patient, although the blood glucose was raised to 300 mg./100 ml. When seen by me about 5 hours after the first attempted interruption, the patient was in moderately deep coma. The plasma sodium, potassium and chloride were normal, but the bicarbonate was low, 19 mN. Cortisone, 50 mg., was given i.m., followed by lightening of the coma and partial rousing of the patient, so that she was able to drink a little. The blood glucose appeared to be stabilized at 120 mg./100 ml. Emptying of the stomach by intra-nasal tube showed that little, if any, of the feed given to interrupt coma had been absorbed. A fresh feed, 10 oz. of water, 30 g. of glucose, 4 g. of sodium bicarbonate and 2 g. of potassium chloride, was introduced into the stomach. As the patient appeared to be nearly roused but not making progress, 30 mg. of Methedrine were given i.v. This produced violent, purposeless physical activity lasting 30–35 minutes, but no restoration of mental activity. Withdrawal of stomach contents showed that there was still gastric stasis, and it was decided to give 100 ml. of 33⅓ per cent. glucose in saline i.v. with 35 ml. of 50 per cent. sodium lactate to raise the plasma bicarbonate. This was followed by a second 50 mg. of cortisone given i.m. Stable blood-glucose values were by this time attained, but the patient was still not rousable. A regime of two-hourly intragastric feeds, the same as the last previously given, was arranged, with intravenous glucose infusions as indicated by the blood glucose values or the state of the patient, and a course of penicillin (Estopen) started. The blood glucose was well maintained throughout the night and the patient slowly progressed. On the second day, however, her blood pressure fell to 90 mm. Hg. systolic and 70 mm. Hg. diastolic. As the plasma chlorides fell to 88 mN and the plasma potassium rose to 5·1 mN, the asthenia of this period was probably due to renewed temporary adrenocortical failure. At this stage, further cortisone would probably have helped. Instead, sodium chloride was added to and potassium chloride omitted from the i.g. (intragastric) feeds, as fluids were now being passed on by the stomach. The regime of i.g. feeds described was continued and by the end of the day the systolic blood pressure had risen to 120 mm. Hg. and the patient was progressing towards recovery. By the middle of the next (third) day, she was able to speak and drink and pass urine normally. Complete recovery was not attained until the fifth day. For blood chemistry, see Appendix.

Recovery after weeks. It is not necessary to describe any of these cases in detail, as their early course closely resembled that of Case 59. There are, however, two additional requirements (a) to continue the prophylactic use of penicillin, and (b) to arrange a fluid diet adequate in composition and calorie value to maintain strength. The basis of this is milk, reinforced by dried or concentrated milk or milk preparations, with added glucose, salts and vitamins, and made up to 3–4 litres with water. In the early days, when there is a danger of vomiting, citrated milk, or milk preparations that do not clot, should be used. A fluid balance chart should be kept. Treatment is directed to maintaining the patient in good physical condition to enable restoration of cerebral cortical function to occur naturally. The blood chemistry should be checked daily at first and then less frequently as normal values are maintained.

(3) ACTH-treatment group.

(4) "Both hormones" treatment group. Only one illustrative case from these groups will be quoted, as the principles of treatment are the same as those indicated in the cortisone treatment group. The cases in the "both hormones" treatment group may be regarded as failures or partial failures of ACTH treatment, since in all six cases ACTH was given first and cortisone later.

ACTH-treatment group. Case 13. 17.12.52. Female (Indian), aged 28. Rather undernourished. 3rd coma. Insulin dose 190 units. Uneventful coma. Intravenous glucose-saline, 170 ml. of 33⅓ per cent. glucose, given after 15 minutes' deep coma, failed to rouse the patient. Further infusions to a total of 700 ml. of 33⅓ per cent. glucose-saline, had little effect. There was slight lightening after administration of Becosym. When first seen by me 1½ hours after the first attempt at interruption, the patient was still in deep sopor and could not be roused. The blood glucose was 605 mg./100 ml. and the plasma bicarbonate 20·5 mN; the other electrolytes were in normal concentration but the pyruvate was raised, 1·7 mg./100 ml. ACTH, 25 mg., was given i.m. For almost ten minutes the patient lay prone without apparent change

in her condition. Then suddenly she turned over in bed, sat up and appeared fully awake. She drank readily and in a few minutes was in full touch with her surroundings and able to speak. Very shortly she was able to take a light meal. This recovery, if it had occurred as the result of a normal i.v. interruption, would have been accepted as a normal recovery. This patient's ketosteroid excretion in the 24 hours following recovery was 8·5 mg., a low value since it included the steroids produced in response to the ACTH.

Evaluation of results and of treatments

(1) Comparison of results of hormone treatment with those when hormone was not used. One of the difficulties in evaluating the results here presented is the absence of adequate controls. In investigating a form of treatment of prolonged insulin coma, it is not possible to omit the treatment from alternate cases, as can be done in some other therapeutic trials, because there is no adequate alternative form of treatment and each case is potentially fatal. If the experimental method offers a hope of success or is found to work, every patient must have the advantage of receiving it. Furthermore, cases vary so much between themselves that selection of alternate cases for treatment would not necessarily give comparable series. The three special cases in the "general" treatment group illustrate this. They are different in character from all the others and do not form a strict control group for all the others.

On the other hand, the other four cases in the "general" treatment group do form a small control group for the 55 hormone-treated cases. As has been pointed out, Case 17, which recovered by the second day, would probably have recovered in a few hours or even less after hormone had this been used. The remaining three cases recovered only in 2–4 weeks. These contrast markedly with the 55 hormone-treated cases, 40 of which recovered by next day or earlier and only 3 failed to recover until the 3rd or 4th weeks (excluding the 4 deaths).

Taking Table IV as it stands, there is no statistically significant difference between the results from the four treatment groups, the distribution being therefore within the range of chance. It may be reasonably argued, however, that since the 55 hormone-treated cases had had adequate "general" treatment and failed to recover within "hours" after the first attempt to interrupt their coma and there was usually some interval before hormone was given, to make sure that the patient was not recovering, they form a control series for comparison with hormone treatment. Table IV could then be revised to give Table V. According to this table 5 per cent. of the control cases recovered in "hours" or less, as compared with 40 per cent. in the hormone treated series. It scarcely needs a statistical test to establish the significance of this difference between the series. (When tested by the χ^2 test P is $<0{\cdot}001$.)

TABLE V

Distribution of results of treatment using the 55 hormone-treated cases as failed general treated cases., i.e. as controls for the hormone-treated cases

Series	Form of Treatment	Recovery Group 1—2	3—6	Total
Control	General	3	4	7
	General followed by hormone	—	55	55
	Total	3 (5 per cent.)	59	62
Experimental ..	Hormone	22 (40 per cent.)	33	55
Both		25	92	117

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Except that the cases which recovered early tended to have shorter periods of hypoglycaemia than those that recovered after days or weeks, there was no clinically apparent difference between the cases.

(2) Relation of results of treatment to dose of insulin used to induce coma. The means of the doses of insulin for the sex and treatment groups have been given in Tables II and III. The means of the doses of insulin used in the cases in the various treatment and recovery groups are given in Table VI. The only significant difference between means is that the mean of the doses of cases in recovery group 2, 179 units, is significantly lower than 308, the mean of the doses in group 4 ($P < \cdot 05, > \cdot 02$). There seems to be no rational explanation for this finding. There is no significant overall correlation between mean dosage and types of recovery and between dosage and numbers of comas patients had had. There is no significant difference between the mean dosages of those who recovered quickly (groups 1 and 2) and of those who recovered less easily (groups 3–6) in the cortisone and ACTH treatment groups or between the mean dosages of those who recovered well (groups 1 and 2) in these two treatment groups, or between the mean dosages of those who recovered less easily in these two treatment groups.

TABLE VI

Means of doses (units) of insulin used to induce the comas in the various recovery and treatment groups

Recovery Groups	Treatment Groups				
	General	Cortisone	ACTH	Both Hormones	All
1. Prompt ..	290	226	214	—	229
2. In hours ..	260	153	178	180	179
3. Next day ..	400	175	216	120	212
4. Days	—	243	310	400	308
5. Weeks ..	210	180	250	—	218
6. Death ..	—	—	208	205	206
All	267	200	218	252	222

If the deaths (cases in recovery group 6) are excluded from the ACTH-treated cases, the correlation between mean dosage and type of recovery in the ACTH-treated cases becomes almost statistically significant (P slightly $>0 \cdot 05$), the tendency being for patients who had the lower doses of insulin to recover most easily from their prolonged coma.

On the whole, however, the dose of insulin can be said not to have determined the type of recovery. This is to be expected, since the coma-producing dose is personal to each patient and reflects his reaction to the treatment as conditioned by his endocrine status and his mental resistance to or acquiescence in coma. It will be seen later that the factor determining the type of recovery is the length of the extra period of hypoglycaemia.

(3) Relation between numbers of comas patients had had and type of recovery. In Table VII, the means of the numbers of comas patients had had are analysed in relation to form of treatment and type of recovery. There is an obvious tendency for the patients who recovered quickest (recovery group 1) to have had the greatest number of comas. The mean number of comas of patients in recovery group 1 (21·6) is not determined by the route of primary interruption and is statistically significantly greater than the mean number of comas of

patients in each of the other five recovery groups, which latter do not differ significantly among themselves.

TABLE VII

Relation between mean numbers of comas patients had had (including the prolonged one) to form of treatment and type of recovery

	Means of numbers of comas in recovery groups						
Treatment Groups	1	2	3	4	5	6	All
General	21	22	4	—	10·7	—	13·1
Cortisone ..	29·3	7·7	5	8·3	7	—	12·8
ACTH	16·7	12·5	9·7	5·7	4·5	21	11·5
Both hormones ..	—	2	2	12	—	3	5·7
All	21·6	11·1	8	8·3	8	12	11·4

Although there is no significant overall correlation between means of numbers of comas and types of recovery, yet if deaths are excluded, the correlation between means of numbers of comas and type of recovery becomes significant for the ACTH-treated cases and the cases as a whole. If the cases are grouped according to the numbers of comas they had had (1–5, 6–15, and over 15 comas) and into two main recovery groups (good: groups 1 and 2; not so good: groups 3–6) Table VIII can be constructed. Although the distribution of cases in this table is not quite statistically significant, there is an obvious tendency for cases who had had most comas to recover quickest from prolonged coma and for those who had had fewest comas to recover less easily.

TABLE VIII

Numbers of cases in recovery groups related to numbers of comas they had had

Numbers of Comas	Numbers of cases in recovery groups 1—2		3—6		Total (100%)
1—5	6	25%	18	75%	24
6—15	4	27%	11	73%	15
15—38	12	60%	8	40%	20
All	22	40%	37	60%	59

The probable explanation of this tendency and for the high mean number of comas in recovery group 1, is that insulin dosage was better stabilized and the pattern of return to consciousness better known in those patients who were most advanced in their treatment course than in those who had had fewer comas. In other words, relative over-dosage with insulin is easier and more probable and failure to awake more difficult to recognize during the earlier comas than in the later ones when doctors have had longer opportunities of observing patients' reactions and patients had become better adjusted to the type of treatment. This links up with the incidence of prolonged comas in relation to the treatment course (see Figs. 7 and 8). The greatest number of prolonged comas occurred in those cases where the dose was most recently arrived at and the patient's adaptation to and acceptance of the coma process and recovery had not fully developed.

It is worth relating these facts to the evidence of the state of the adrenal function in patients undergoing insulin coma treatment (as examples, see Figs. 3, 4 and 5). Many patients enter upon their coma course with their

anterior-pituitary-adrenocortical system already fatigued (cf. Figs. 4 and 5) by the stress of their illness. This fatigue is aggravated by the new stresses of the dosage building-up period before the first coma. These are potential cases for the prolonged comas that occur early in the treatment course. As the coma course proceeds, there is first, stimulation or depression and later, fatigue of the anterior-pituitary-adrenocortical system, with fluctuations in the functioning state, depending on the reserve reactivity of the system. During the periods of depressed function, the prolonged comas in the later part of the treatment course occur. Note the increase in the numbers of prolonged coma about the 11th and 19th–22nd comas (Fig. 7).

The relation of the incidence of prolonged comas to the days of the week is also relevant when considering the effects of the coma stress (see Fig. 9). Statistical analysis shows that the distribution of prolonged comas in Fig. 9 is not due to chance; distribution by chance may be expected to give the same numbers of prolonged comas on each day of the week, except Saturday, since the numbers of comas given on each of the five days, Monday to Friday, can be expected to be the same.

The distribution of types of recovery does not differ significantly on the different days of the week (excluding Saturday with only 2 cases) and there are no significant differences between the means of the number of comas per prolonged coma per patient on the different days of the week. Yet more prolonged comas occur in the middle and later days of the week than in the earlier part. The week-end without comas gives an opportunity for the anterior-pituitary-adrenocortical system to recuperate so that the first coma of the week is well managed by the patient. Thereafter, the accumulating stress of the comas tends to produce breakdown and prolonged comas later in the week. This explains the greater incidence of prolonged comas on Wednesday to Friday. If, however, Wednesday is passed without a prolonged coma, there is a reasonable chance of the patient's completing the week without trouble. The only hospital that gave deep coma treatment on Saturdays provided the third highest number of prolonged comas of all the thirteen hospitals, and of them, the number occurring in the first two days of the week was disproportionately slightly high.

Ten patients with prolonged comas were having their second or third coma course. It seems a reasonable surmise that 10 is a much higher proportion of the number of patients having a second or third coma course than is 52 (the remainder who had a prolonged coma in their first course) of the number of patients having their first course of coma treatment. The mean dose of insulin these patients had was 212 units (mean dose for all 62 patients, 223 units) but their mean number of comas was 5·8, only half the mean number (11·4) for all the 62 prolonged comas. None of these 10 patients had a prompt recovery, three were in recovery group 2 and the rest in groups 3 (4 patients), 4 (1 patient) and 5 (2 patients). The chronic schizophrenic, such as those who have repeated courses of deep insulin coma treatment, is prone to have poor endocrine reactivity at a low level. Therefore, he is likely to react badly to stress. He appears more prone to prolonged comas and does not make as good a recovery from them as does the schizophrenic in an earlier stage of his disease.

From our consideration of the incidence of prolonged coma in relation to the coma treatment course, it is possible to conclude that the stresses in the early part of the course precipitate prolonged comas in those who are just entering upon their series of therapeutic comas and in the later part of the course the stresses precipitate prolonged comas in those whose endocrine defensive mechanisms are becoming fatigued. The weekly fluctuation of stresses mediated

in part by the week-end break in treatment plays a part in shifting the greater incidence of prolonged comas into the middle and second half of the week.

(4) Relation of results of treatment to interval between onset of therapeutic coma and giving of hormone in cases treated with one hormone. In most cases it was possible to calculate the interval between the recorded time of onset of the therapeutic stage of the deep coma and the time of giving hormone. Excluding two cases seen first on the second day of their prolonged coma, the mean intervals for all cases and for the ACTH- and cortisone-treated groups are given, and related to type of recovery, in Table IX. There are no statistically significant differences between any pairs of means and no statistically significant correlation between the intervals before giving hormone and the results of treatment. The small group treated with both hormones shows no difference from the bigger groups.

TABLE IX

Means of periods (in hours) between onset of coma and giving of hormone

Recovery Group	Treatment Group		
	Cortisone	ACTH	Both Hormone
1. Prompt	5·0	4·8	4·88
2. In hours	3·2	3·8	3·56
3. Next day	5·5	4·5	4·75
4. Days	4·5	5·3	4·91
5. Weeks	4·75	*	—
6. Death	—	4·25	4·25
All	4·67	4·53	4·58

* Not known

The results of treatment are not determined by the interval elapsing before giving hormone in the ranges of time covered by these cases (1·5–9·25 hours). Cases in recovery group 2 tended to have a shorter time interval before hormone was given, just as they also tended to have lower insulin doses than did other cases.

(5) Effect of duration of hypoglycaemia. The relationship between the extra period of hypoglycaemia and the type of recovery is shown in Table X. Five cases are omitted because the extra period could not be determined. This extra period is measured in minutes elapsing between the first attempt at interruption and the first i.v. administration of glucose. In cases where interruption was by the i.v. method, this "extra period" is nil (0 in Table).

TABLE X

Relation of extra period (minutes) of hypoglycaemia in the treatment groups to type of recovery

Treatment Group		Recovery Group					
		1	2	3	4	5	6
General	range	0·0	65	0	—	65–80	—
	mean	0			—	72	—
Cortisone	range	0–40	0–25	15–70	40–50	25	—
	mean	8	8	36	45		—
ACTH	range	0–100	0–40	0–170	0–85	45	55
	mean	26	21	30	42		
Both Hormones	range	—	30	20	60	—	95,300
	mean						
All	mean	16	22	29	40	57	150

Where means not given, only one case available. Five cases omitted.

Although the groups in the table are too small for full statistical analysis, the figures do show a definite trend: the cases that recovered "promptly" and in "hours" had had shorter extra periods of hypoglycaemia than had those which recovered "next day", later or not at all. This is emphasized if one case which had 100 minutes' extra hypoglycaemia is excluded from the ACTH-treated "prompt" recovery group, the mean for the remaining 7 cases being 13 minutes. The mean duration of the extra hypoglycaemia for the 25 cases in the "prompt" and "hours" recovery groups was 18 minutes; for all the other cases it was 48 minutes. The difference between these means is statistically significant in the range $P < \cdot 05 > \cdot 02$.

There is a significant correlation between the shortness of the extra period of hypoglycaemia and the type of recovery in the ACTH-treated cases ($\rho = 0 \cdot 9$) and an almost significant one for the cortisone cases ($\rho = 0 \cdot 7$). Taking all the cases, there is a complete inverse correlation between type of recovery and mean extra period of hypoglycaemia.

Table X, then, supports the clinical impression that those patients recovered quickest whose failure to awake after primary interruption was detected earliest and who had been given i.v. glucose promptly, i.e. had had the shortest periods of extra hypoglycaemia. This inference is also supported by comparing the rates of recovery according to the method of primary interruption. Of the 19 cases that received i.v. glucose for primary interruption, 13 (68·4 per cent.) recovered on the first day, 5 by the second day and 1 later. Of the 43 cases that received i.g. glucose at the first attempt at interruption, only 12 (27·9 per cent.) recovered on the first day, 14 on the second day, 9 in days or weeks, and 4 died. These results are summarized in Table XI. The distribution of these results is statistically highly significant ($P = < \cdot 01 > \cdot 001$). Clearly, i.v. administration of glucose to interrupt coma is better than i.g. However, the practical difficulties of its continuous use—poor veins, risk of thrombosing veins and so on—and the fact that glucose can be given i.g. by nurses, account for the more general use of the i.g. route.

TABLE XI

Relation of types of recovery to routes of primary interruption

Route of Primary Interruption	Recovery Groups		Total (100%)
	1 and 2	3 to 6	
Intravenous	13 (68·4%)	6 (31·6%)	19
Intragastric	12 (27·9%)	31* (72·1%)	43
Both	25 (40·3%)	37 (59·7%)	62

* Includes 4 deaths

Since the i.v. route for primary interruption is so much better than the i.g., it is necessary to examine the results of treatment taking into account the method of primary interruption. All the 19 cases that had i.v. primary interruption had "general" treatment; 2 recovered early, 17 did not. These 17 had hormone treatment; 11 recovered early, 6 later. These figures are shown in Table XII.

TABLE XII

Relation of types of recovery to treatment in cases that had intravenous interruption

Treatment	Recovery Groups		Total (100%)
	1 and 2	3 to 6	
General	2 (10·5%)	17 (89·5%)	19
Hormone	11 (64·7%)	6 (35·3%)	17
Both	13 (36·1%)	23 (63·9%)	36

All the 43 cases that had i.g. primary interruption had "general" treatment; 1 case recovered early, 42 did not. Of these 42, 38 had hormone treatment; 11 recovered early, 23 later, and 4 died. These figures are shown in Table XIII.

TABLE XIII

Relation of types of recovery to treatment in cases that had intragastric interruption

Treatment	Recovery Groups		Total (100%)
	1 and 2	3 to 6	
General	1 (2·3%)	42 (97·7%)	43
Hormone	11 (28·9%)	27 (71·1%)	38
Both	12 (14·8%)	69 (85·2%)	81

The distribution of the results in both these tables is statistically highly significant ($P = < \cdot 001$). Thus the value of hormone treatment is again established whatever the method of primary interruption.

It is, therefore, possible to conclude that in prolonged comas, i.v. primary interruption gives a better chance of early recovery than does i.g., that the shorter the period of extra hypoglycaemia the better are the results of subsequent treatment, and that over and above these, hormone treatment gives better results than general treatment.

(6) Comparison of results with ACTH and with Cortisone. The method of primary interruption must be taken into account when comparing the results obtained with cortisone with those with ACTH. Of the 8 cortisone-treated cases that recovered on the first day, 6 had had i.v. glucose to interrupt their coma, whereas of the 13 corresponding ACTH-treated cases, only 5 had had i.v. glucose at the normal time of interruption. Against these are to be set 6 ACTH treated cases that had had i.v. glucose at the first attempt at interruption, yet did not recover till the next day or for a few days. The results for the 49 cases treated with a single hormone are analysed in Tables XIV, XV and XVI.

The distribution in Table XIV is probably significant (the value 0 in one box makes testing of doubtful value, but on the figures, $P < \cdot 05, > \cdot 02$), but in Tables XV and XVI the distribution is not better than would be due to chance, ($P < \cdot 5, > \cdot 3$). It seems probable that cortisone could be expected to give better results after primary i.v. interruption than ACTH, but not after primary i.g. interruption. This can be further tested by examining the cases that recovered "promptly" and "in hours" (recovery groups 1 and 2) according to the hormone used and the method of primary interruption. This is done in Table XVII.

TABLE XIV

Results in cases that received intravenous primary interruption and hormone treatment

Treatment	Recovery Groups		Total (100%)
	1 and 2	3 to 6	
Cortisone	6 (100%)	0	6
ACTH	5 (45·5%)	6 (54·5%)	11
Both	11 (64·7%)	6 (35·3%)	17

TABLE XV

Results in cases that received intragastric primary interruption and hormone treatment

Treatment	Recovery Groups		Total (100%)
	1 and 2	3 to 6	
Cortisone	2 (20%)	8 (80%)	10
ACTH	8 (36·4%)	14 (63·6%)	22
Both	10 (31·3%)	22 (68·7%)	32

TABLE XVI

Results in all cases treated with a single hormone

Treatment	Recovery Groups		Total (100%)
	1 and 2	3 to 6	
Cortisone	8 (50%)	8 (50%)	16
ACTH	13 (39·4%)	20 (60·6%)	33
Both	21 (42·8%)	28 (57·2%)	49

TABLE XVII

Relation of route of primary interruption to hormone used in cases that recovered in the first day

Hormone	Route of interruption		Total (100%)
	Intravenous	Intragastric	
Cortisone	6 (75%)	2 (25%)	8
ACTH	5 (38·5%)	8 (61·5%)	13
Both	11 (52·4%)	10 (47·6%)	21

Again the groups are small for statistical analysis, but the distribution is not different from chance ($P < \cdot 2$, $> \cdot 1$). There is then no evident statistically significant difference between the various combinations of hormone and route of primary interruption, although cortisone seems to give better results than ACTH after i.v. primary interruption. This being so, it is reasonable to act on the inference that cortisone and ACTH appear to give similar results whatever the method of primary interruption. Better results can be expected with either hormone if the primary interruption was by i.v. glucose than if it was by i.g.

(7) Deaths. There were 4 deaths in the series, one from broncho-pneumonia, one from renal failure and two from shock or exhaustion.

Case 18. 24.4.53. Female, aged 23. 5th coma; insulin dose 210 units. Normal coma. Attempted interruption by gavage at 10.45 a.m. was followed by a major fit and the patient made a slow apparent recovery. She vomited her dinner, became shocked and at 3.45 p.m. was in coma again. Intravenous 33⅓ per cent. glucose at 4.30 p.m. and 6.30 p.m. produced lightening of the coma but not recovery. When I first saw her at 7.30 p.m. she was deeply shocked. ACTH, 100 mg., given by i.m. injection produced lightening of coma followed by attempts to sit up but not full awaking. Methedrine, 10 mg., i.v. was without perceptible effect. Gastric stasis persisted and more glucose was given i.v. and Becosym i.v. At 11.40 p.m., 50 mg. of cortisone was given but without apparent effect and the patient was in a profound collapse. Glucose continued to be given by both routes. On the morning of the 25th, the blood chemistry was as follows: serum sodium 158·7 mN, potassium 10·5 mN, chlorides 121·8 mN, bicarbonate 28 mN, uric acid 18 mg./100 ml., urea 39 mg./100 ml., pyruvate 4·6 mg./100 ml. Allowing for the i.v. saline given, the potassium value suggests adrenal failure. The pyruvate indicates failure of co-enzyme mechanisms, in spite of the B-vitamins given. There was no improvement and she died on the evening of the 25th.

In this case, a major fit provoked a deceptive pseudo-recovery, but the increase in blood glucose that usually follows a fit was apparently not maintained because of the gastric stasis that was responsible for the vomiting. There was a long period (about 5½ hours) of extra hypoglycaemia which was not rectified till late in the afternoon. These conditions were responsible for the collapse in a poorly reactive subject.

Case 33. 4.2.54. Female, aged 30. 26th coma, insulin dose 240 units reduced from 260 units on previous day. Usually recovered easily from coma. After an apparently normal coma of 20 minutes' duration, i.g. glucose failed to produce a response. Glucose, 250 ml. of 33⅓ per per cent., given i.v. 35 minutes after the attempted interruption failed to rouse her. The extra period of hypoglycaemia was thus short. Further 33⅓ per cent. glucose with Becosym was given i.v. one hour later without result. Gastric stasis was proved by withdrawing stomach contents. I saw her about 4 hours after the first attempt at interruption. She was then deep in coma, shocked, cyanosed and giving the appearance of acute cardiac failure and breathing deeply as if in acidosis. The blood chemistry results were: plasma sodium 130 mN, potassium 3·3 mN, chloride 115 mN, bicarbonate 17 mN, urea 24 mg./100 ml., uric acid 12·8 mg./100 ml., pyruvate 3·1 mg./100 ml. and cocarboxylase 13·7 μg./100 ml. There was some dehydration with gastric stasis and achlorhydria. ACTH, 50 mg., followed by a second dose of 50 mg. forty minutes later produced lightening and some improvement. Improvement was not maintained although the blood glucose was kept in the range 98·418 mg./100 ml. The patient died on the 6th about 49 hours after the first attempt to interrupt her coma. Shortly before death the blood chemistry was: serum sodium 148 mN, potassium 8·5 mN, chloride 137 mN, bicarbonate 17 mN, urea 96 mg./100 ml., uric acid 8·1 mg./100 ml. and pyruvate 4·6 mg./100 ml. Death was apparently due to exhaustion with some adrenal and cardiac failure and early broncho-pneumonia.

Case 48. 7.10.54. Male, aged 31, of south-east Asian stock. 1st coma, insulin dose 200 units. As this was the patient's first coma, interruption was attempted as soon as deep coma was diagnosed. Intragastric glucose produced an apparent recovery and the patient sat up. He shortly relapsed into coma, was given more glucose i.g. without effect as there was gastric stasis, and then 33⅓ per cent. glucose i.v. with Becosym 95 minutes after the first attempt at interruption. Methedrine, 30 mg. i.v., was ineffective. I saw this patient about 3 hours after the first i.g. glucose was given. The only abnormalities in the blood chemistry were serum bicarbonate 17 mN and uric acid 8·2 mg./100 ml. The W.B.C. was 18,500/cu.mm. ACTH, 50 mg., followed in ¾ hour by cortisone, 50 mg., produced only slight lightening of coma. Mechothane was given i.g. but did not start gastric movements. There was some respiratory distress. This patient seemed to be completely devoid of that drive that the patient whose coma lightens must exert to recover. His mental illness was characterized by severe depression and an intense desire to die which did not express itself by attempts at suicide. During the following days he remained unconscious, and his blood chemistry changed fairly steadily. On the 4th day (10.10.54) there was haematuria. Cortisone, 25 mg., i.m. on the 12th and 13th was ineffective. The serum sodium rose to a value of 160 mN on 15th October; the bicarbonate rose to 34 mN and then fell to 16·5 mN on the 15th; the inorganic phosphate rose to 4·0 mN, the uric acid to 13·2 mg./100 ml. and the blood urea to 420 mg./100 ml. on the 15th, in the evening of which he died. This was apparently a death from renal failure probably due to the effects of the prolonged coma, associated with a terminal broncho-pneumonia. Renal damage does occur in insulin comas prolonged more than about 48 hours. There was an increase in blood urea in Case 33. Case 2, a man aged 24, whose coma lasted 3–4 weeks, had a moderately severe toxic nephritis in the second week of his coma, with albumen, granular casts and red blood cells in the urine, blood urea 91 mg./100 ml. and raised diastolic blood pressure. As this nephritic episode subsided, he gradually improved.

Case 50. 3.11.54. Female, aged 22. 16th coma, insulin dose 176 units. This patient failed to respond to i.g. glucose and to i.v. glucose given later. She had been in coma about 6 hours when I saw her and was very collapsed. The only significant abnormality in her blood chemistry was in the serum bicarbonate, 15 mN. She failed to respond to two separate doses of 50 mg. of ACTH and died in the 4th week of coma from apparent exhaustion.

Along with the cases in recovery groups 4 and 5, where coma was prolonged into days and weeks, the four cases that died raise the question of whether it would be useful to continue using hormones after the first day of coma. In case 48, cortisone given late did not help. It might have helped in the other three. This would be easily practicable now that long-acting ACTH is available. Death may arise from other causes than adrenal exhaustion, as is shown by case 48, and each case would have to be treated according to its needs.

(8) Value of B-vitamins. The B-vitamins are undoubtedly of value, if given in adequate amounts. The commonest abnormality in the blood found in the early stages of prolonged insulin coma is an increase in pyruvate. It was found in 34 (80 per cent.) of 42 cases in which it was estimated, and in most of these the blood cocarboxylase was artificially high as a result of vitamin injections. In some cases the pyruvate increased as the coma was extended and more and

more glucose was given. Low blood cocarboxylase was found in 2 cases. As has been pointed out previously, quoting Kay, Murfitt and Glatt (1959), the raising of the blood cocarboxylase by giving thiamine does not necessarily immediately restore to normal the enzyme activity which depends on the presence of adequate co-enzyme formed from thiamine. This is particularly true if activity or the metabolism of extra glucose occurs.

In B-vitamin deficiencies, usually more than one factor is deficient. Although tests for deficiencies of factors other than thiamine were not carried out in this work (except for co-enzyme I in a few cases), it was best to act on the assumption that there was depletion of the remaining B-vitamin factors. (It should be noted that the method of estimating blood cocarboxylase (Kay and Murfitt, 1956) was worked out for use in this study of prolonged insulin coma.) The three B-vitamins required for co-enzyme synthesis, thiamine, nicotinamide and riboflaving must be included. Pyridoxin was used, since claims are made that it has value in toxic comas. Pantothenic acid was included because there is some evidence that it is necessary for proper function of the adrenal cortex and the production of its hormones (Bean *et al.* 1955, Eisenstein, 1955). Vitamin B_{12}, even in milligram doses, did not appear to have any effect on the course of recovery.

(9) Accessory treatment. The other therapeutic measures taken were chiefly for the purpose of restoring the blood glucose and electrolytes to normal levels and to keep them there. Both hormones, and repeated i.v. infusion of salines, tend to raise the plasma sodium and chloride, excessive elevation of which may cause oedema of the lungs. Intravenous infusion of glucose tends to lower the concentration of the plasma potassium; so do the hormones. Low plasma potassium concentrations are a danger to proper cardiac action. Often in prolonged coma the plasma bicarbonate falls, sometimes to dangerous levels. Acidosis embarrasses respiration and probably facilitates cerebral damage. When the plasma bicarbonate is moderately low or very low, i.v. infusion of 50 per cent. sodium lactate is invaluable. Dehydration, or increase of blood concentration may occur and embarrass the circulation. All these variations in the "milieu interne" can only be accurately detected by appropriate laboratory investigations, upon which rational treatment can be based.

In addition to the foregoing, the usual routine measures for treating shock and collapse were applied as appeared clinically necessary.

V. Biochemical Findings

Brief summary of abnormalities found

Biochemical investigations were carried out in 56 of the 62 cases to help in assessing the state of patients' "milieu interne" and to guide treatment. Examples of results are given in the Appendix.

In addition to their use in guiding treatment, the systematic chemical investigations have cleared up some uncertainties. Alkalosis, often said to occur, was never found; on the contrary, a low plasma bicarbonate was so frequent as to make it safe to act on the assumption that it was present, when treatment had to be started without laboratory results. Deficiency of B-vitamins was very frequent, as judged from blood pyruvate values, even though the blood cocarboxylase was artificially high as the result of administering B-vitamins.

It was not possible to apply the full battery of tests in every case, but in most cases, especially in those with delayed recovery, repeat tests were done. I am not aware of any published similar systematic work with which comparisons

can be made. It is proposed now only to summarize the most important findings in the early investigations in each case, the meanings of which will be self-evident.

Serum sodium:	low in 6 cases; high in 1.
Serum potassium:	low in 6 cases; high in 3.
Serum chloride:	low in 0 cases; high in 14.
Serum bicarbonate:	low in 25 cases; high in 0.
Serum uric acid	low in 0 cases; high in 22.
Blood pyruvate:	low in 0 cases; high in 34.
Blood cocarboxylase:	low in 2 cases; high artificially in many.
Urine ketosteroids:	low in 6 cases; high in 0.

It is evident that the main findings are the loss of plasma bicarbonate, which is related to changes in oxidation processes (oxyachrestia) and, with low serum sodium, to adrenocortical failure, and the increase in blood pyruvate, which is evidence of disturbed enzyme reactions dependent on thiamine. It is essential to deal with both these disturbances to aid recovery.

Knowledge of the blood glucose level is, as has been pointed out, essential for treatment. Results are not discussed here because most patients had had i.v. glucose when first seen.

The raised serum uric acid is a new finding. The highest value found was 20·8 mg./100 ml. Raised values decline in course of time after recovery. I have found raised values, sometimes as high as this, in some normal insulin comas, the initial level being normal but followed by a steady increase throughout the coma with a fall after recovery following successful interruption of coma. This does not occur in all comas. The increase in blood uric acid may be related to nuclear damage caused by the coma process and to low activity of the adrenal cortex.

It was possible to investigate ketosteroid output in only 7 cases. All values except one were low. The one exception was in the normal range, but represented the 24-hours' excretion following the injection of ACTH to rouse the patient from prolonged coma (Case 13). The results support the argument for adrenocortical fatigue. In some cases, as the patient recovered from the effects of the prolonged coma, the 17-ketosteroid output rose.

Serum cholinesterase values were mostly normal but two cases had high normal values of pseudo-cholinesterase. This has also been found in normal insulin comas (personal observations).

There was occasionally an increase in serum globulins, especially in the longer cases. This may be related to the toxic state.

Not many estimations of blood glutathione were done. In two cases results were normal (29·8, 31·2 and 33·9 mg./100 ml.). On the other hand, one patient had values of 77–90 mg./100 ml. and another 65 mg./100 ml. These values did not seem to be related to blood glucose level or be affected by giving hormone. Blood glutathione is concerned in some oxidation reactions and may be related to the secretion of insulin. Further investigations are needed on this aspect of coma.

Although not biochemistry, the haematological findings may be referred to here. The red cell count, haemoglobin estimation and packed-cell volume are useful in conjunction with the total serum protein value to assess the state of hydration of the body. One difficulty in interpretation is the absence of values in the normal state of the patients. Almost invariably the white blood cell count

increases in comas lasting more than a few hours. The increase is chiefly in the polymorphoneutrophils. This phenomenon usually subsides as the patient recovers and may be due to tissue damage, or as some say, to the toxic effects of insulin. It is accompanied by a pyrexia, sometimes high, which is due in part to tissue damage, especially cerebral, and in part to the increased combustion of glucose. This early pyrexia subsides without special treatment. Leucocytosis and pyrexia occurring later, say after 3 or 4 days in the longer comas, usually indicates an infection, most likely pneumonia.

VI. Summary of Treatment

Summary of treatment

It is possible now to summarize the method of treatment in cases of prolonged insulin coma which have failed to respond to glucose given intravenously.

(1) Assess the case clinically.

(2) Take blood for laboratory investigations: estimations of blood glucose, plasma electrolytes and proteins, blood count, haemoglobin and packed-cell volume. Repeat these as required, but blood glucose estimations should be done approximately hourly.

(3) Give adequate mixed B-vitamins, if not already given.

(4) If the blood glucose is low, give 33⅓ per cent. glucose in saline i.v.

(5) Give 50 mg. of cortisone or ACTH i.m. Repeat in about 1 hour if necessary, making sure that the blood glucose is over 100 mg./100 ml. In cases that need a second dose of hormone, an additional dose of 100–120 mg. ACTH-gel is useful for an effect of long duration.

(6) If recovery does not occur within about half an hour, institute intragastric feeding: water 10 oz. (300 ml.), glucose 50 g., potassium chloride 2 g., sodium bicarbonate 4 g., repeating every two hours, first withdrawing and measuring any residues of the feed last given. Adjust content of meals in accordance with changes in blood chemistry. Use i.v. sodium lactate to correct low plasma bicarbonate. Continue until recovery or for 24 hours then start nutrient feeds.

(7) Should recovery not take place by the second day, institute a regime of regular i.g. feeds based on milk, which should be citrated or otherwise treated to prevent clotting till the risk of vomiting has passed. The feeds should provide adequate proteins, glucose, salts, vitamins, calories and water.

(8) Use penicillin in adequate doses from the first day to prevent pneumonia.

(9) At all times be ready to treat cardio-respiratory collapse.

(10) Watch for distension of the bladder and catheterize if necessary.

(11) Adjust intake, intravenous and intragastric, in accordance with blood chemistry.

(12) Avoid high glycaemia, dehydration and low plasma bicarbonate especially.

VII. Conclusions

Conclusions

(1) Two important factors related to the onset of prolonged insulin coma are fatigue of the anterior-pituitary-adrenocortical system and disturbance of the oxidation mechanisms dependent on co-enzymes derived from B-vitamins.

(2) The administration of cortisone or ACTH to patients in prolonged insulin coma after raising the blood glucose to at least normoglycaemia assists their recovery, quickly rousing a large proportion to full recovery and stabilizing the blood glucose in others, thus preventing relapses into hypoglycaemia. Both hormones are valuable therapeutic agents in this connection and worth routine use when necessary.

(3) B-vitamins, preferably thiamine, nicotinamide, riboflavine, pyridoxine and pantothenic acid, are useful for routine use.

(4) Recovery is not affected by the dose of insulin used to induce coma, nor by the interval between onset of coma and giving of hormone up to a period of about 9 hours. On the other hand, the less the period of hypoglycaemia is prolonged, the better is the chance of quick recovery. Primary interruption by intravenous glucose is better than by intragastric. The patients who had had most comas tended to recover quickest.

(5) Prolonged comas tend to occur most frequently in the early part of the treatment course, at periods when low ketosteroid excretion occurs, and in the middle and second half of the week.

(6) Some patients having a second or third course of comas are likely subjects for a prolonged coma.

(7) Death, when it occurs, may be due to collapse, exhaustion or pneumonia.

(8) Treatment, apart from using hormones and vitamins, should be controlled by adequate laboratory investigations.

(9) Management of the blood glucose and electrolytes is essential where recovery is delayed beyond 2–3 hours after giving hormone. Sodium bicarbonate by gavage or sodium lactate i.v. corrects low plasma bicarbonate.

(10) Gastric stasis, almost invariably present in prolonged coma, does not respond to the usual drugs used to relieve spasm or produce movement of the alimentary tract.

(11) Methedrine does not rouse patients but causes excessive motor activity which may exhaust the patient. It should not be used.

The conclusions that both cortisone and ACTH are useful and an advance on previous empirical methods of treatment is inescapable, especially when one has seen the dramatic recovery made by some patients within 15 to 20 minutes after injecting the hormone. The 55 cases treated with hormone had failed to recover after the usual methods of treatment. Twelve of these recovered within an hour after being given hormone and in many cases their recovery was little different from the normal manner of recovery they had shown in their previous uneventful comas. Ten cases recovered within a few hours after receiving hormone, having first shown early progress by the lightening of their coma and by developing a stable blood glucose, and 18 cases recovered by the next day. The relief of anxiety over these cases is inestimable.

Little attempt was made to choose a hormone for any case. Cortisone appeared to act better than ACTH when the extra period of hypoglycaemia was short, especially after i.v. primary interruption. In other cases it was at least as good as ACTH. It was therefore acceptable as first choice to use in any case, especially when it was more generally available than ACTH. Now that both hormones are available, either can be used with almost equal hope of success. ACTH-gel (long-acting) is now available and is useful to give slow, continuous

stimulation of the adrenal cortex when the first dose of hormone fails to rouse the patient in 3–4 hours.

During the course of this work, it soon became apparent that although both hormones stabilized the blood glucose level, and sometimes even raised it, they did not rouse patients from coma unless the blood glucose was near, in or above the normal range. This was confirmed by investigations on a series of patients undergoing insulin coma treatment (Kay, 1958). ACTH or cortisone was given at different stages of coma in different patients. Both hormones sometimes roused patients from light coma but not from deep coma until glucose was given i.v. Then a normal recovery occurred even though the deep coma had been prolonged at least an hour.

The "prompt" recoveries induced by ACTH and cortisone suggest that both hormones have some action besides that of counteracting insulin and stabilizing the blood glucose level. They roused the patient so quickly and so completely that they appeared to have a stimulating effect on the cerebral cortex. Methedrine, a known cerebral cortical stimulant, did not rouse patients; it produced excessive and unwanted motor activity.

One hospital still using insulin coma treatment, that provided many of the cases included in this report, has accepted hormone treatment as a routine for patients who do not respond normally to their primary interruption and has found it very satisfactory.

VIII. Summary

Summary

(1) The types, treatment, aetiology and pathology of prolonged insulin comas are discussed.

(2) The significance of fatigue of the anterior-pituitary-adrenocortical system and of the disturbance of the oxidative enzyme systems depending on B-vitamin co-enzymes in relation to prolonged insulin comas is indicated.

(3) An account is given of experience of 62 cases of prolonged insulin coma, 55 of which were treated with cortisone and/or ACTH.

(4) Twelve of these cases recovered in less than one hour after receiving hormone, and ten others within a few hours after. Four deaths occurred.

(5) Initiation of recovery by both hormones appears to be an improvement on previous methods of treatment.

(6) The rationale of the use of hormones in treating prolonged coma and some factors affecting results are discussed.

(7) The method of treatment is stated together with an account of the laboratory investigations that should accompany it.

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Case No. 1. Male, aged 28. Insulin 230 units. 4.5.51.

Blood Glucose:	165 mg.%	Serum Proteins:	Total	6·0 g.%
			Albumin	5·1 g.%
Serum Sodium:	156 mN		Globulin	0·9 g.%
			A/G	6·0/1
Serum Chloride:	106 mN	Blood Lactate:		>60 mg.%
Serum Bicarbonate:	21 mN	Blood Pyruvate:		6 mg.%
Serum Phosphates:	0·8 mN	Blood Urea:		25 mg.%
Blood P.C.V.:	42%			

Case No. 3. Female, aged 23. 2nd coma: insulin 280 units.

			2.4.52 1.15 p.m.	2.4.52 3.40 p.m.	3.4.52 11.50 a.m.	4.4.52 10. 20 a.m.	7.4.52 10.05 a.m.		16.4.52 12.15 p.m.	29.4.52
Serum Chlorides:	mN	.. ..	103·5	104	105	103	102		102	96
Serum Bicarbonate:	mN	.. ..	28	25	28	25	29		27	27
Blood Glucose:	mg.%	.. ..	111	77	206	82	—		—	—
Serum Potassium:	mN	.. ..	4·6	4·1	3·8	3·5	4·9		4·6	4·5
Serum Sodium:	mN	.. ..	152	150	155	154	141		150	143
Serum Phosphates:	mN	.. ..	0·6	0·5	0·9	0·7	1·35		1·35	1·35
Serum Urea (Blood):	mg.%	.. ..	17	14	29	31	29		27	24
Serum Protein: Total	g.%	.. ..	—	5·9	6·0	—	—		6·3	7·4
Albumen	g.%	.. ..	—	4·1	4·0	—	—		4·2	4·5
Globulin	g.%	.. ..	—	1·8	2·0	—	—		2·1	2·9
A/G ratio		.. ..	—	2·3	2·0	—	—		2·0	1·5
Blood Co-enzyme I:	μg.%	.. ..	37·0	32·5	36·9	32·0	34·2		37·6	33·6
Blood Pyruvate:	mg.%	.. ..	2·18	3·26	2·12	0·61	0·54		1·42	1·1
Blood Carboxylase:	μg.%	.. ..	21·5	18·3	23·2	22·5	18·6		11·6	15·9
Serum Cholinesterase:	units	.. ..	55·6	54·4	49·7	44·0	45·8		—	53·0
Serum Cholesterol: Total	mg.%	.. ..	—	—	—	—	—		105	265
Free	mg.%	.. ..	—	—	—	—	—		40	85
Ester	mg.%	.. ..	—	—	—	—	—		65	180
F/E ratio		.. ..	—	—	—	—	—		1/1·4	1/2·1
			7.4.52	9.4.52	25.4.52	6.5.52	26.6.52		8.7.52	Recovered
Urine 17-Ketosteroids:	mg./24 hrs.	.. ..	4·4	3·2	6·8	5·3	9·5		13·7	
Urine volume:	ml./24 hrs.	.. ..	900	900	790	2230	1400		980	

Slight albuminuria with few r.b.c's

True cholinesterase normal throughout.

Case No. 4. Male, aged 28. 33rd coma: insulin 380 units.

		1.5.52 Coma day					2.5.52 Post-coma
		4.5 p.m.		5.0 p.m.	6.5 p.m.	8.45 p.m.	11.40 p.m.
Blood Glucose:	mg.%	65		90	115	250	147
Serum Sodium:	mN	150		158	150	150	144
Serum Potassium:	mN	4·4		3·8	4·3	4·3	4·1
Serum Chloride:	mN	108		112	108	108	102
Serum Bicarbonate:	mN	29·0		27·0	29·0	28·5	29·5
Serum Phosphates:	mN	0·6		0·6	1·0	1·4	1·45
Serum Protein: Total	g.%	7·2		7·3	7·1	6·8	6·6
Albumen	g.%	4·4		4·5	4·5	4·3	4·1
Globulin	g.%	2·8		2·8	2·6	2·5	2·5
A/G ratio	..	1·6		1·6	1·7	1·7	1·6
Blood Urea:	mg.%	34		31	27	31	31
Blood Pyruvate:	mg.%	0·83		0·96	0·92	4·42	1·36
Serum Cholesterol: Total	mg.%	190		185	185	155	160
Free	mg.%	70		60	60	50	55
Ester	mg.%	120		125	125	105	105
F/E	ratio	1·7		2·1	2·1	2·1	1·9
Serum Uric Acid:	mg.%	13·6		12·4	12·0	9·2	7·0
				3.5.52			8.5.52
Urine 17-Ketosteroids:	mg./24 hrs.			8·4			12·7
Urine volume:	ml./24 hrs.			1700			3850

4·35 p.m. 25 mg. cortisone i.m.

Recovered

Case No. 12. Female, aged 34. 4th coma: insulin 40 units.

		16.12.52 12.45 p.m.	16.12.52 2.0 p.m.	16.12.52 3.30 p.m.	17.12.52 2.0 p.m.
		12.45 p.m. Cortisone 25 mg. i.m.		2.05 p.m. Cortisone 25 mg. i.m.	Recovered
Serum Sodium:	mN	149·1	152·6	148·2	146·5
Serum Potassium:	mN	4·3	4·3	4·2	4·5
Serum Chlorides:	mN	103	105	104	106·5
Serum Bicarbonate:	mN	27·0	27·5	27·0	28·5
Serum Phosphates:	mN	1·3	2·1	1·3	1·6
Serum Urea (Blood):	mg.%	24	22	22	21
Serum Uric Acid:	mg.%	4·8	4·9	4·8	4·0
Serum Proteins: Total	g.%	7·1	7·0	6·9	6·9
Albumen	g.%	4·3	4·4	4·4	4·3
Globulin	g.%	2·8	2·6	2·5	2·6
A/G ratio		1·5	1·7	1·8	1·7
Blood Pyruvate:	mg.%	1·8	1·2	—	1·0
Blood Cocarboxylase:	µg./100 ml.	9·4	10·5	—	8·9
Blood Thiamine:	µg./100 ml.	0·4	0·9	—	0·9
Urine 17-Ketosteroids:	mg./24 hrs.	—	—	—	2·4
Urine volume:	ml./24 hrs.	—	83	115	830
Blood Glucose:	mg.%	70			—

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Case No. 13. Female, aged 28. 3rd coma: insulin 190 units.

		17.12.52 12.35 p.m.	17.12.52 1.43 p.m.	18.12.52 12.15 p.m.
		12.40 p.m. ACTH 25 mg. i.m.		Recovered
Serum Sodium:	mN	137·8	146·4	146·9
Serum Potassium:	mN	4·8	3·8	4·8
Serum Chloride:	mN	103·2	108·7	106·0
Serum Bicarbonate:	mN	20·5	20·5	27·0
Serum Phosphates:	mN	1·6	1·6	1·3
Blood Urea:	mg.%	22	21	21
Serum Uric Acid:	mg.%	3·6	4·2	4·0
Serum Proteins: Total	g.%	6·7	7·1	6·0
Albumen	g.%	4·4	4·5	3·6
Globulin	g.%	2·3	2·6	2·4
A/G ratio		1·9/1	1·7/1	1·5/1
Blood Pyruvate:	mg.%	1·7	3·0	1·3
Blood Cocarboxylase:	µg./100 ml.	7·8	8·2	6·5
Blood Thiamine:	µg./100 ml.	0·7	0·4	0·6
Blood Glucose	mg.%	605	350	—
Blood P.C.V.:	%	—	—	34
		19.12.52		
Urine 17-Ketosteroids:	mg./24 hrs.	8·5		
Urine volume:	ml./24 hrs.	2970		

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Case No. 16. Female, aged 28. 2nd coma: insulin 250 units.

		25.2.53 5.50 p.m.	5.55 p.m. 50 mg. Cortisone i.m. 25.2.53 7.0 p.m.	26.2.53	Recovered 6.15 p.m.	7.50 p.m.
Serum Sodium:	mN	147·8	153	153	348	212
Serum Potassium:	mN	—	2·6	3·0		
Serum Chloride:	mN	105·2	104·3	105·2		
Serum Bicarbonate:	mN	14·5	23·0	28·0		
Serum Phosphates:	mN	1·0	2·0	1·6		
Serum Uric Acid:	mg. %	6·4	5·8	3·3		
Blood Urea:	mg. %	—	17	21		
Serum Proteins: Total	g. %	—	—	6·4		
Albumen	g. %	—	—	3·8		
Globulin	g. %	—	—	2·6		
A/G ratio	..	—	—	1·5/1		
Blood Glutathione:	mg. %	—	—	65		
Blood P.C.V.:	%	—	—	38		
		5.30 p.m.	6.15 p.m.	7.50 p.m.		
Blood Glucose:	mg. %	394	348	212		

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Case No. 59. Female, aged 36. 12th coma: insulin 260 units.

		2.53 p.m. Cortisone 50 m.g. i.m.	17.8.55 2.57 p.m.			17.8.55 5.0 p.m.	5.20 p.m. Cortisone 50 mg. i.m.	18.8.55	19.8.55	Recovered
Serum Sodium:	mN		144			146		146	139	
Serum Potassium:	mN		3·2			3·5		5·1	3·9	
Serum Chloride:	mN		105			106		88	98	
Serum Bicarbonate:	mN		19·0			23·0		24·5	22·5	
Serum Phosphates:	mN		1·7			2·5		1·4	1·2	
Blood Urea:	mg.%		22			20		18	27	
Serum Uric Acid:	mg.%		4·2			4·8		3·4	3·8	
Serum Proteins: Total	g.%		6·6			7·0		7·2	7·2	
Albumen	g.%		4·2			4·4		4·2	3·9	
Globulin	g.%		2·2			2·6		3·0	3·3	
A/G ratio			1·9/1			1·7/1		1·4/1	1·3/1	
Blood Pyruvate:	mg.%		3·2			—		4·6	2·5	
Blood Cocarboxylase:	μg./100 ml.		21·8			28·1		16·7	13·3	
Blood Glucose:	mg.%	1.45 p.m. 300		3.15 p.m. 120	4.35 p.m. 120		5.30 p.m. 140	200	210	

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