THE TECHNIQUE AND COMPLICATIONS OF INSULIN THERAPY.

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SINCE there are several excellent accounts of the technique of insulin therapy (1, 2, 3, etc.), and since our method is based largely on the recommendations of Sakel, we do not intend to describe this in detail, but to discuss such variations and points of interest as have developed at Hatton during the completion of treatment in 59 cases.

James (4) first used a pure crystalline insulin and then a gland extract, and found no essential differences in action. We have used Burroughs Wellcome's and Boots' insulin and found both satisfactory. No case of urticaria has occurred with either. Protamine zinc insulin has been tried and found unsatisfactory (5) because of wide variations in the effects produced and the consequent variations in the dosage, the necessity for more frequent laboratory procedures and the occurrence of more after-shocks and fits.

We usually commence with 10 units of insulin, increasing by 10 or 8 units until coma is produced, increasing more rapidly only if there is clearly very little effect produced by previous doses. The opinion has been expressed (6) that if dosage is increased too rapidly, excitement and anxiety with antagonism follow, and we have tried rapid increases, only to return to a more careful approach to the coma dose. There is evidence that rapid increases are justified in stuporose types of schizophrenia, but our experience has led us to believe that the more cautious procedure produces equally good results. Stimulation during the pre-coma phase by examinations or by the necessities of laboratory investigations should be avoided unless it can be justified by the demands of research, for coma is delayed and sometimes rendered unsatisfactory.

The coma dose varies enormously: James (4) recorded coma with 15 units and with over 400 units, and we have recorded a case with a coma dose of 17 units (7). We have seen two emaciated women patients with melancholia become comatose with absent corneal reflexes and extensor plantar responses following a morning dose of 10 units of insulin, given as a stimulant to appetite.

The coma dose, when found, does not often remain stable—in only 14% of our cases; increased sensitivity allows a reduction in the dose in a further

https://doi.org/10.1192/bjp.84.352.718 Published online by Cambridge University Press

35%, while in 42% the dose has to be increased, but in about a half of these it can be brought down later in the course. The remaining cases show a fall in coma dose followed by an increase, or several variations up and down that do not allow of description under one type of response. Day (6) believes that schizophrenics are usually resistant to large doses of insulin, even when the blood sugar has fallen below 20 mgrm.%, but Sakel says that this is noticeable in old cases only. We agree with James (4) and Swiss observers that there is little difference in the average coma dose between old and recent cases, and that mental improvement bears no relation to the necessary dose.

The average daily dose for patients with a history of eighteen months or less was 117·4 units of insulin in our cases, and James (4) found it to be 104·5. For cases with a history of over eighteen months our figure was 107·5 and James's 105·6. Our average for women was 112·1 and for men 107·6.

When the coma dose has been regularly high for some time we usually try the effect of halving the dose, and have done this 50 times with 37 patients. On 28 occasions the half-dose was followed by a shock or a fit and 22 times the manœuvre failed. Of the 28 successes, in 11 instances the coma dose remained at the low level or was reduced still further, in 13 the dose had to be increased to the original level or something lower, and in 4 the original level was finally exceeded. This procedure is well worth trying at intervals; in one patient it failed twice, but the third time effected a permanent reduction in dose.

Sensitivity to pain and hyperacusis are said to exist during the pre-coma phase, and care as to what is said and done during this period is advised (8). Without taking anything more than ordinary precautions we have never had any difficulties of this kind, and discussion with intelligent patients who have recovered makes it clear that there is an amnesia for a great part of the pre-coma phase.

Pullar Strecker (8) has stated that during the pre-coma phase smoking will precipitate a fit or a coma, often before the cigarette is finished, and that this can also occur after the feed and recovery. We have tried to precipitate coma when this seemed delayed by persuading the patient to smoke, but only one of seven became too drowsy to hold his cigarette, and the actual coma did not follow for some time, while no patient had a fit. Strecker cautions against allowing smoking within an hour of the interruption of the coma by glucose, but we have permitted smoking as soon after coma as the patient wishes without any ill-effect that we have been able to observe, although it is often almost an hour before a cigarette is wanted.

The Duration of Coma.

The criteria of coma are usually taken as absent corneal reflexes and extensor plantar responses, but there is sometimes difficulty in deciding whether coma has really developed; in one of our patients the corneal reflexes

disappeared while the patient was still responsive to loud speech. Complete unconsciousness must be present before coma can be taken as having begun, and in cases of doubt we demand absence of any response to pin-pricks and forcible supra-orbital pressure. We have not taken the term "light coma" as having much meaning, and our comas and their duration are measured from the onset of the complete coma referred to above.

The first coma period should be short, and the duration of coma should gradually be extended in succeeding shocks (4) up to an absolute maximum of 1½ hours (9), but the patient must rouse easily and have no unpleasant after-effects, and frequently the optimum duration of coma is considerably less than 1½ hours. We have occasionally exceeded 1½ hours of deep coma, but only when the closest personal supervision could be given by an extra physician present in the insulin ward. The early comas must be watched very carefully, particularly for confusion after the shock, for mild symptoms of this nature may be the first indication of a dangerous prolongation of coma after the next shock. After complete recovery from one coma the dose for the next day is decided; only close attention to individual reactions can give useful indications for dosage and duration.

As a rough rule we calculate our dose of insulin to produce deep coma some time before 10 a.m. The average duration of deep coma for all our patients was 53 minutes.

Sakel (1) lays stress on the importance of terminating coma in a suitable phase, that is, in a stuporose patient when he is restless and in an excitable patient when he is quiet, believing that the state at the time of interruption is carried on into consciousness. We have not been impressed by either the necessity or the possibility of this, for many of our patients have come round depressed, excited, confused, quiet or pleasant in turn and irrespective of their state when sugar was given. A grandiose paranoid, whose comas were always quiet, was restless and awkward after his early comas; later he came round boastful and elated, then noisy and singing, then quiet, and finally, after his last few comas, he was quiet and pleasant, the third phase of noisiness and singing overlapping the fourth and fifth phases to some extent. A confused and stuporose patient was extremely restless after the seventh, ninth, twenty-fifth and thirtieth comas, elated and excited after the first, eleventh, thirteenth and fourteenth, and depressed and tearful after the nineteenth, twenty-first and twenty-sixth; after the remainder she was quiet and apathetic; but these varying conditions had no relation that we could determine to the state when she was fed. One patient always came round excited and aggressive, and although every effort was made to interrupt in a quiet phase, and on twenty occasions ergotamine tartrate or ammonium chloride or both were given before the feed, his manner of recovery remained unchanged.

We have tried various experiments with adrenaline, and have even given ɱxx of the 1: 1000 solution subcutaneously during a tonic spasm with great

restlessness, but we have never seen a patient awake from coma excited because of it, and the tonic spasm referred to passed off in the usual time. Adrenaline was given to ten patients just before the feed, and in one the corneal reflexes returned and another seemed to awake very quickly after the feed, but in the others there was no change. There is little doubt that hypoglycæmia is followed by sympathetic impulses from the central nervous system, which increase the secretion of adrenaline, but we doubt if this mechanism deserves all the importance that is sometimes attached to it.

We have terminated coma six times on account of absent light reflex of the pupils, three times with a feed and three times with intravenous glucose.

The Feed.

Modifying and adding to the recommendations of Frostig (10), the indications for the termination of hypoglycæmia by a nasal tube glucose feed are :

(1) Hunger riot, a demand for food accompanied by extreme excitement. Sakel described this, but we have never observed it.

(2) Coma of the required duration, the duration having been decided by experience with previous comas.

(3) Spontaneous awakening in the fifth hour, the patient being too drowsy to drink voluntarily.

(4) Prolonged inspiratory dyspnœa with moderate cyanosis.

(5) Irregular soft pulse with pallor and respiratory distress.

(6) Early and sustained extensor spasms. Sometimes this indication can be ignored if the patient's reactions are familiar.

(7) Individual danger signs ; thus one of our patients showed a fixed staring face and snored before developing right-sided heart failure.

(8) An attempt to bring the patient round in a certain phase. We have already indicated that we do not lay much emphasis on this.

The limit of assimilation of sugar from the bowel is 1·8 grm. per kgrm. per hour, which is about 115 grm. per hour in a person of 10 st. (11), and if a patient is willing to take food when conscious we use 125 grm. (5 oz.) of glucose in 150 c.c. (6 fl. oz.) of water as the feed for the interruption of coma. If there is no tendency to vomit and difficulty is experienced in later feeding, larger quantities of sugar can be given.

Larkin (12) suggested passing a precautionary nasal tube during coma, but we have never found this necessary. Larkin also suggested tapping the larynx if any difficulty is experienced in passing the tube. When the tube has been passed it is important to empty the stomach of as much fluid as possible before giving the glucose solution. We have observed one case where a tube-feed was always followed by an awakening accompanied by confusion and aggression, but clear and easy recovery from coma followed intravenous injections.

Number of Shocks.

Frostig (10) defines a shock as either a coma of sufficient depth or else a fit, and we adopt this definition in counting shocks, except that only a fit occurring before coma is counted as a separate shock, a fit during deep coma being ignored.

Sakel (1) recommends a minimum of 50 shocks unless cure or some other good reason makes it inadvisable to continue treatment, and we have adopted this as our basis in treatment. James's (1) 12 discharges had from 7 to 59 shocks, averaging 27·9; our 39 discharges had from 2 to 62 shocks and averaged 35·5.

Table I.—*Shocks in Discharged Patients.*

Shocks.	James *et al.*	Gillman and Parfitt.
50 or more	2	17
30 to 50	4	11
10 to 30	5	7
Less than 10	1	4

James's 12 failures had from 11 to 63 shocks and averaged 40·2, and our 20 failures had from 22 to 54 shocks and averaged 45·0.

Table II.—*Shocks in Patients Not Discharged.*

Shocks.	James *et al.*	Gillman and Parfitt.
50 or more	3	9
45 to 50	1	7
Less than 45	8	4

Where less than 50 shocks were given to failed cases it was because dangerous complications made it inadvisable to continue, or because the patient was deteriorating under treatment, or because experience made it plain that it was useless to continue, as in cases showing a slight initial improvement with a rapid relapse completely unaffected by further shocks.

There is a generally accepted minimum of treatment of 60 insulin days (4), but if one starts with a low dose and increases it very gradually, the number of insulin injections may be excessive and bear no relation to the intensity of treatment. Thus, in one of James's successes there were 7 shocks in 94 insulin days, and in one of his failures there were 11 shocks in 58 days. Our 39 successes averaged 53·2 injections and the 20 failures 61·4 injections, and 15 of the latter group had over 60 injections. Although we have observed a patient in whom comas were not produced by very large doses of insulin (over 400 units), but who, nevertheless, improved considerably, we do not attach so much importance to the number of insulin injections as to the number of deep comas.

Interesting data have been collected about blood-sugar levels (6), but such estimations can be safely ignored in practice unless complications develop.

Since complications necessitating a day's rest are fairly frequent, we have adopted the practice at Hatton of giving the treatment five days a week only, omitting the treatment on Wednesdays and Sundays, and we have found that most patients can be given five shocks a week in this way.

Some physicians prefer to stop all visiting to patients during this treatment and in the early days of insulin therapy at this hospital we followed this advice, but we are now of the opinion that visits by relatives within reasonable limits are more often than not beneficial.

Complications.

Müller (13) lays stress on the essential safety of insulin therapy, and quotes Swiss figures which show a death-rate of 0·5% in 495 cases treated; he thinks this death-rate should be reduced still further. James (4) believes that there is a tendency to magnify the dangers, but utters a warning against any false sense of security, for serious complications are apt to arise with dramatic suddenness. Küppers (14) reports a mortality of 1·5% in 400 cases, but Lemke (15) had 4 deaths in 46 patients and only 6 of his patients had a smooth course of treatment. Lemke suggests that the dangers and complications are greater and more frequent than the literature would lead one to suppose, and that the method is not nearly so safe as it is claimed to be, and although we have found that improved technique and added experience have effected a considerable reduction in unpleasant complications, we have some sympathy with Lemke's point of view. We have given 662 intravenous injections for various complications during the treatment of 59 cases, which is much higher than James's figures of 64 intravenous injections for 24 patients. We had one death in this series.

Rise in Temperature with Malaise.

We have given intravenous sugar more than 300 times to patients who were not sufficiently conscious 30 minutes after the nasal feed, usually with satisfactory results, but fairly frequently a certain amount of confusion, mild headache and malaise have remained for several hours, and in the evening the temperature has risen a degree or two; sometimes the only sign is the slight evening temperature, the patient being otherwise comfortable. Great care should be exercised in such cases when deciding the dose and duration for the next shock, for we believe such conditions are often the forerunners of delayed recovery of a serious kind. When this malaise and rise of temperature has developed with successive shocks, we have lately stopped treatment for a time and given a course of T.A.B. vaccine, 6 to 8 injections intravenously

at intervals of three or four days, a temperature of 102° F. or less being aimed at. We have completed this procedure in 3 cases of the first 59 and in 2 more of patients now under treatment and it has been completely successful in every case ; when insulin is resumed the course is smooth and uneventful.

Delayed Recovery.

Grading from the mild cases described above one meets with rather more severe cases, where the transition from coma to consciousness is further delayed and complicated by tonic spasms and respiratory disturbances, and where the malaise is prolonged into the next day. More rarely, and completing the series, coma is prolonged to an extremely dangerous degree, and severe symptoms, opisthotonos, with tremendous muscular spasms, extreme cyanosis or occasionally deathly pallor, protruding eyes, drenching sweats and a weak thready pulse reach a maximum one to two hours after the first nasal feed (16). If this acute stage can be safely negotiated the patient settles into a state of quiet coma with a good pulse punctuated by bursts of restlessness ; the corneal reflexes are absent and the plantar reflexes extensor throughout. Towards the evening the temperature rises to 103° F. or less, but in fatal cases there may be hyperpyrexia. Such cases have been described by Salm (17), who comments on the difficulty of treatment. James (4) records two cases in 24 patients, but only one was serious, and Lemke met 5 in 46 cases. We have given 22 intravenous injections for prolonged coma, but in only 9 cases were the symptoms really severe, with complete coma varying from 7 to 43 hours and averaging 20 hours, and they affected 4 men and 5 women, in contradistinction to Lemke (15), whose complications were found much more commonly in men. The ages of this group of 9 varied from 17 to 30, and seemed to have no significance ; the dosage varied from 80 to 256 units, and averaged 153. The diagnosis is usually evident after some time and the clinical impression is one of great seriousness. The diagnosis of true cases can be made very early if rapid blood-sugar estimations are performed (8), and for this purpose we use the Crecelius-Seifert picric acid method, with a small Zeiss colorimeter, the blood sugar being normal or high despite the coma (4, 18). Usually, however, much sugar has been given intravenously before the blood-sugar is estimated, and it is bound then to be high. We have already indicated that this dangerous complication could generally be avoided by the careful study of previous shocks and the proper management of post-coma confusion and malaise, and this especially applies in the early stages of treatment, for our nine prolonged comas occurred at the second, second, second, fourth, fourth, ninth, eleventh, twenty-second and thirty-second shocks in 9 different patients. In the case recorded by Molony and Honan (18) no further treatment was given until ninety-five minutes after the first nasal feed, and when a nasal tube was passed again practically the whole of the feed was returned. It seems clear that

here the complication followed an excessively prolonged initial coma. Molony and Honan suggest that there is a general disturbance of carbohydrate metabolism, although the blood-sugar of their case fell with insulin and was maintained within normal limits for some days on saline only, both of which facts suggest to us that the carbohydrate metabolism was working satisfactorily. A local disturbance of carbohydrate metabolism (17) especially affecting the mid-brain seems more likely. Alkalosis, which is present so often without causing symptoms, cannot be held responsible.

When the condition is fully recognized a sufficiency, perhaps an excess, of sugar has usually been given intravenously. The limits of assimilation for intravenous sugar are 8 grm. per kgrm. per hour, so that 150 c.c. of $33\frac{1}{3}\%$ glucose is the maximum quantity that need be given in one hour (11).

In the very acute stage developing within two hours of the first nasal feed, coramine (5 c.c. intravenously) can be used and repeated with benefit, and we make a practice of giving this a minute or two before a lumbar puncture, which allows of clear fluid under pressure being withdrawn. In two of our cases the c.s.f. pressure was 114 and 170 mm. of water respectively, and in one the c.s.f. sugar was 135 mgrm.%, although James (4) and Molony (18) have found the c.s.f. sugar over 300 mgrm.%. The normal c.s.f. sugar is less than that in the blood, 45 to 65 mgrm.%, and the barrier action between blood and c.s.f. probably accounts for the persistence of a high c.s.f. sugar in these cases. Bursts of 5% CO_2 in oxygen may be useful, and artificial respiration may be necessary. Adrenaline is generally given, but it is difficult to tell with what result. James (4) recommends blood-transfusion, but since the most dangerous phase develops suddenly, we doubt if it would be of any great service. Following the acute phase the patient is usually safe, although still comatose, and we keep up feeding by tube at regular intervals, although Molony and Honan suggest saline only. We usually precede our feeds with a stomach wash-out, an enema, and tepid sponging when the temperature rises are helpful. If there is retention of urine, catheterization is necessary at intervals ; the urine contains sugar and albumin.

Although Peters (19) found that a deficiency of vitamin B1 produced a disorder of the brain metabolism, probably because it is a catalyst in the oxidation of pyruvic acid, and the use of the vitamin is popular in several nervous disorders, we consider it of very little value in these cases. Freudenberg and James (4) strongly recommend it. Calcium in the form of the chloride or gluconate, given by injection, is also useless, and we have tried intravenous saline without appreciable effect. Molony and Honan give injections of insulin, but we consider this unnecessary.

When the coma lightens the patient is often dull, confused and irritable for some time and complains of headache, and vomiting may be troublesome. Striking recoveries have been reported after this complication, one by James (4) and one by us, but this one was the only instance amongst our nine.

None of our patients died, and perhaps the complication is not so desperately dangerous as it appears.

Occasionally after a nasal tube feed the coma deepens and this may lead to some delay in recovery, but this is quite a different thing to the prolonged comas we have been considering.

CASE.—H. E—, male, aged 24. Six months before admission he had become hesitant and neglectful at work, developed paranoid ideas and finally delusions of persecution, with excitement and exaltation. He was admitted on July 7, 1937, confused and excited, his physical state being excellent.

Insulin therapy was commenced on July 17. On the 28th he had his first deep coma with 88 units at 9.20 a.m., and this was interrupted at 10.30. Half an hour later he was stuporose and confused, but was able to take milk and bread and butter at 11.15.

Insufficient attention was paid to this slow recovery, and the next day he was given 96 units, deep coma developing at 9.45 a.m. At 11 a.m. he vomited 10 oz. of fluid. He was fed at 11.10, after a coma of 85 minutes. At 11.40 a.m. he was still unconscious. He was given betaxan, 1 c.c. intramuscularly, and 40 c.c. of 33⅓% glucose solution intravenously; this injection was interrupted by a tremendous muscular spasm, with opisthotonos, extreme congestion of the face with cyanosis, the eyes being protruded and the pupils widely dilated.

12 noon: The spasms were still severe, alternating with periods of relaxation; 60 c.c. of sugar solution was given intravenously. The corneal reflexes returned momentarily, but the coma was still deep.

12.30 p.m.: The muscular spasm recurred with even greater intensity, every palpable muscle being board-like with rigidity; the pulse became thready and uncountable, cyanosis was extreme and the breathing painfully laboured and stertorous. His condition seemed desperate and death was expected. Adrenaline, ℥x of the 1 : 1000 solution, and 5 c.c. of coramine were given intramuscularly and a further 60 c.c. of sugar solution intravenously, with inhalation of 5% carbon dioxide in oxygen at intervals. The condition improved and the pulse became countable at 160.

1 p.m.: A little better, but still seriously ill. A rectal wash-out produced a good result.

1.15 p.m.: Following coramine 5 c.c., adrenaline ℥v and betaxin 2 c.c., all intramuscularly, and 60 c.c. of glucose intravenously, a lumbar puncture was performed and 20 c.c. of clear cerebro-spinal fluid withdrawn under normal pressure except when a spasm caused a spurt.

2 p.m.: Saline 60 c.c. intravenously, with calcium gluconate 10 c.c. intramuscularly.

3 p.m.: Glucose 100 c.c. intravenously and pituitrin ½ c.c. The patient was now considered out of danger. The prolonged spasms were less frequent and much less severe, but he was still in a deep coma, with absent corneal reflexes and extensor plantars.

4 p.m.: Glucose 100 c.c., saline 60 c.c. Quiet and restful, giving the appearance of a deep sleep, but still in coma. Pulse-rate 128, temperature 101° F. Glucose 100 c.c. was given intravenously every hour for the next three hours, until at 8 p.m. catheterization for retention of urine withdrew 60 oz. which contained a great deal of sugar, but at 9.30 p.m. the blood-sugar was only 120 mgrm.%. Soon after this the stomach was washed

out and a small milk and glucose feed left in. The patient remained completely unconscious, with absent corneal reflexes and extensor plantar responses throughout the night. He received 180 c.c. of glucose solution intravenously and a tube-feed of coffee, milk and glucose. Following the 180 c.c. of glucose, the blood-sugar in half an hour was over 1000 mgrm.%, but had fallen to 195 mgrm. % an hour later and in another hour it was 105 mgrm. %.

9 a.m. of the next day, July 30: Benzedrine 10 mgrm. was given with a feed and catheterization again performed, 40 oz. being withdrawn. The benzedrine was repeated three hours later. The temperature was 99·2° F., and the pulse-rate 105. At mid-day the corneal reflexes were still absent and the plantars extensor, but at 5 p.m. the patient showed the first responses to stimuli, muttering incoherently when shaken and spoken to.

July 31, 4 a.m.: Reflexes normal; able to answer questions but rather sturporose and resistive. Incontinent of urine and fæces. Temperature 100·2° F., pulse-rate 120. At mid-day reasonably clear, taking food well.

In this case deep coma was present for nearly two days and the patient's condition was desperate. The first coma was too long, the recovery slow, and the increased dose producing the second and serious coma was contra-indicated. The mental symptoms disappeared with dramatic suddenness and the patient was soon discharged and returned to work. He relapsed, however, seven months after discharge and was readmitted to hospital.

Laryngeal Spasm.

This dangerous emergency usually develops suddenly during coma, but may develop gradually from tonic spasms and respiratory difficulty. We have seen it develop once during the violent spasms occurring in a prolonged coma about one and a half hours after the feed. The tremendous but useless efforts to breathe are followed by the rapid development of extreme congestion and cyanosis, and the condition soon becomes desperate.

Gillies (20) has described two attacks in the same patient. We have seen ten of these spasms, excluding the attack in prolonged coma referred to above, and seven of these ten were in one male patient, two in another male patient and one in a female patient.

The treatment is the immediate intravenous injection of 60 c.c. of glucose solution, inhalation of CO_2 in oxygen combined with artificial respiration if necessary, and finally, the use of adrenaline and coramine. The possibility of this complication developing makes it obligatory to have a doctor present throughout the coma.

Fits and Status Epilepticus.

Fits were originally thought of as an unpleasant complication to be terminated by intravenous injection of sugar, but there is a tendency at present to believe that they are beneficial. Our opinion is that the supposed antagonism between schizophrenia and epilepsy is far from proved, and that insulin fits

do not affect the ultimate prognosis in schizophrenia, and at most may accelerate expected recoveries. For most of our early cases we used intravenous sugar at once for fits, and have altogether done this 164 times. Later we used a nasal glucose feed for pre-coma fits, and extended this practice to fits in coma when they occurred early and the patient's condition was satisfactory. James (4) says that it is very seldom necessary to hurry interruption of a fit, and in all cases we wait until the fit is over before commencing treatment. James uses intravenous sugar before a threatened fit when experience has shown that the patient is worse after fits, and Frostig uses intravenous sugar for fits occurring late in the fourth or fifth hour. We also inject the sugar for fits occurring after the interruption of coma, together with evipan 0·5 grm. intramuscularly, for the possibility of *status epilepticus* must be remembered at this time. One of the Vienna deaths was due to *status epilepticus*. Gillies (20) has described a case in which ten fits occurred after recovery with sugar. The treatment is sugar intravenously, morphine gr. $\frac{1}{4}$ and evipan intramuscularly, together with lumbar puncture. The fluid is under pressure, and 20 c.c. may be removed and the operation repeated later. Luminal may be given by injection or by the mouth, and lobeline has been suggested following good results obtained in animal experiments (8). Inhalation of carbon dioxide in oxygen may be useful, but adrenaline is contra-indicated (8). In Gillies' case and in our own the *status* developed after a few comas only.

CASE.—D. M—, female, aged 28. Physically healthy. No previous personal or family history of epilepsy. Treatment commenced on August 7, 1937, and the first coma was produced with 64 units. This and subsequent comas were marked by pre-coma excitement, pallor, and a more cold and clammy skin than usual. During the third shock the patient had an epileptic fit and was slow in recovering after glucose. Improvement was shown after the fifth coma, but tolerance for insulin was being established; the dose was raised to 96 units before the sixth shock, on August 24. Following the usual feed after a coma of one hour, recovery was slow. Thirty minutes later she was given 30 c.c. glucose solution intravenously and was completely clear almost at once, but complained of headache, was aggressive and refused food. At 1 p.m. she became drowsy, and soon after had a series of three major fits at 20-minute intervals. She was treated by lumbar puncture and removal of 10 c.c. of cerebro-spinal fluid under diminished pressure, 60 c.c. of intravenous glucose solution, adrenaline 1 : 1000 mvij, coramine 4 c.c. intramuscularly and periodic inhalation of 5% CO_2 in oxygen. This was followed by a stomach wash-out and a feed. She recovered well, but again complained of headache.

The next day, August 25, at 10 a.m. she had another fit, which was followed by four more at 10-minute intervals, producing deep coma with absent corneal reflexes. She was given 60 c.c. of intravenous glucose solution, a glucose feed with 2 gr. of luminal, and some brandy, with coramine, 4 c.c., intramuscularly. Inhalations of CO_2 in oxygen were ineffective, but following an enema and a whiff of pure CO_2 she regained consciousness and soon appeared well.

She remained well until 1.30 a.m. on August 26, when a series of fifteen fits at 10-minute intervals commenced and her condition soon became extremely

grave. Intravenous glucose, tube-feeding, 2 gr. of luminal intravenously, intramuscular betaxan and coramine, lumbar puncture, CO_2 in oxygen and CO_2 alone all failed to produce any improvement. At 4 a.m., with the patient unconscious and breathing stertorously, the temperature and pulse-rate rising, 10 c.c. of evipan was given intramuscularly. There was one fit after this, but it was followed by deep sleep, and at 5 a.m. the corneal reflexes were present. The day passed uneventfully, but in the evening of the same day there were some severe muscular twitchings. Luminal, gr. j, was given twice a day, and small doses of morphine were necessary in addition to control twitching during the next two days; the luminal was continued. As the mental state began to deteriorate the insulin comas were recommenced and the course finished with eventual cure and discharge, the luminal being stopped about a week after the termination of treatment.

Cardio-vascular and Respiratory Complications.

Marked variations in the pulse-rate with periods of dyspnœa and some cyanosis are common, and experience of the individual reaction in such cases must decide whether termination of the coma is necessary. Signs indicating early heart failure must be watched with care, and such appearances can be divided into two rough clinical groups, one suggesting right heart failure and the other left heart failure. In the first group, increasing congestion, cyanosis and dyspnœa persist beyond a few minutes, and later the pulse becomes weak or irregular. We have used intravenous sugar on twenty-one occasions for this complication. In the other group increasing pallor is associated with a thready, weak pulse. We have given intravenous sugar twelve times for this condition; in ten of these there was no great alarm, but in two men there was an almost complete vascular collapse, which developed rapidly and gave rise to great anxiety for some time. In one case the collapse occurred during the second shock and in the other during the twenty-second shock. A case of this kind has been described by James (4), where extreme pallor followed a fit and the patient suddenly became pulseless and the veins collapsed. Both our patients were successfully treated with adrenaline ℥x of the 1: 1000 solution and coramine 5 c.c. intramuscularly, shock blocks at the foot of the bed and periods of carbon dioxide in oxygen inhalation, and this relieved the situation sufficiently to allow an intravenous injection of sugar to be given slowly. We were prepared to give adrenaline intracardially and to apply artificial respiration, but they were not necessary. James gave 2 c.c. of glucose solution intracardially to his case, and got sufficient response to enable intravenous sugar to be given.

Since the use of carbon dioxide is becoming popular in hypoglycæmic emergencies it should be remembered that overdosage with CO_2 produces collapse, with pallor and weak gasping respirations.

Frostig (10) describes generalized rapid muscular twitchings with collapse, which he calls myoclonic vascular collapse, but we have not seen such a case.

In one case we observed regular pulsus bigeminus for several minutes, with no impulse or sound at the apex except before the pulse-beats, and we regard this as a case of heart-block. We have treated three cases with rheumatic heart lesions. Two of them were liable to congestion and cyanosis, and the other to pallor and failing pulse.

For severe apnœa we have used a whiff of pure CO_2 with artificial respiration and intravenous sugar.

Strecker (8) men ions œdema of the lungs, of which four cases have been recorded and which he says is the most dangerous complication. Treatment is by venesection, inhalation of oxygen, and the slow intravenous injection of $\frac{1}{4}$ mgrm. of strophanthin in 20 c.c. of sugar solution. We have not met this complication yet.

Vomiting.

Nausea, with a distaste for food, is common after shocks, and should be noted when dosage and duration of coma are being considered. The nausea is probably of central origin in the main and of local origin in much less degree, and has its basis in central disturbances, but there is a marked personal idiosyncrasy, and in a large group of patients there are only a few who are really troublesome. We had only one difficult case, although 12 of 59 patients vomited at some time. Sometimes vomiting is a complication of fits.

We always empty the stomach carefully before feeding, and in cases liable to vomit we use only 125 grm. of sugar in 150 c.c. of water as the feed. Large quantities of sugar are emptied from the stomach very slowly and increase the local irritation. The necessity of further careful feeding after recovery must be remembered, and we do not hesitate to give intravenous sugar. We give atropine, gr. $\frac{1}{50}$, subcutaneously twenty minutes before the feed if possible, preferring this to atropine by the mouth because it is more certain and there is no danger of its being vomited. Raising the foot of the bed with shock blocks is useful, but we have not been helped by alkaline powders given with the feed, as recommended by Larkin and Hamilton (12, 21).

In troublesome cases a careful review of the patient's reactions is essential. The coma may have to be considerably shortened and then gradually increased, but sometimes vomiting is only in evidence when the coma is not sufficiently deep, and an increase in the dose of insulin is effective. The addition of a diffusible stimulant or some brandy to the feed may be tried.

The immediate treatment of vomiting is to elevate the foot of the bed and give intravenous sugar, together with 5 c.c. of coramine intramuscularly if the patient looks ill. We have given intravenous sugar 43 times for this purpose to 12 patients. Later, if feeding proves impossible, further intravenous sugar and a rectal feed can be given. In severe cases it may be necessary to give a prolonged stomach wash-out, after which a feed is usually retained.

Abdominal Colic Simulating Appendicitis.

Attacks of abdominal colic which have raised the question of appendicitis have occurred once each in 6 patients and following each of 5 successive shocks in a seventh. The attacks come on between 3 and 6 p.m., following a shock in the morning. Severe colicky pain is referred to the lower abdomen, often with tenderness and less often with rigidity ; not uncommonly pain, tenderness and rigidity are most marked in the right iliac fossa. There is a very slight rise of temperature as a rule. In one case the temperature rose to 102° F., and signs and symptoms were so suggestive that an operation was performed and the appendix found a little bulbous at the tip, but otherwise normal. In another case an after-shock with collapse occurred at 4 p.m., and when the collapse had been successfully treated the signs and symptoms suggested appendicitis for a short time. This patient died four days later with signs of pneumonia, and at post-mortem the appendix was normal.

We have treated these cases satisfactorily with intravenous sugar, hot fomentations to the lower abdomen, aspirin and atropine gr. $\frac{1}{100}$ subcutaneously.

Tongue-biting.

The tongue is sometimes held between the teeth during the coma, and we have three times interrupted with intravenous sugar for this when hæmorrhage has developed.

After-shock.

Severe symptoms of hypoglycæmia coming on after full consciousness has been regained following the feed constitute an after-shock. We have observed 30 after-shocks in 59 patients, and for 22 of these intravenous sugar was given. James reported 18 after-shocks in 24 patients and Hamilton 16 in 8 patients. Since all patients undergoing insulin treatment have been kept in one unit under the observation of a trained staff, the incidence of after-shocks has dropped considerably, and they are now extremely rare.

There are two factors in the production of after-shocks. The first is the intake of food, the second the prolonged action of insulin or the stimulus of food to insulin production. We believe that the latter alternative can be decided in favour of the prolonged action of insulin, for although after-shocks do sometimes occur with a satisfactory food intake, they are commonest when the intake is insufficient. Wright states that the lowest blood-sugar level may be present several hours after insulin (11) and with protamine zinc insulin after-shocks are more common (5). Moreover there is a general tendency among patients under treatment to have low fasting blood-sugar levels. This is not because insulin is injected as a deposit and cannot be absorbed at once,

for if the dose is split into several parts and spread about the body the effects are the same, but because the effective action of insulin takes time to develop.

James stated that his cases were due to insufficient food or vomiting, and stressed the importance of training the nursing staff to recognize the symptoms.

Hamilton (21) says his cases had 170 units of insulin at least and averaged 250, but our lowest dose to produce an after-shock was 56 units and the average was 155 units. Thirteen of his 16 after-shocks occurred after 9 p.m., but only 4 of our 30 were after this time. Twelve of our 30 took their meals and did not vomit, but in 4 of these the after-shock developed immediately after the mid-day meal, presumably before it was absorbed, and 5 came on just before tea. The great majority of those who refused food or vomited had their after-shocks round about tea-time. Treatment is usually easy, sugar being given intravenously or by nasal tube. Hamilton recommends 3½ oz. of glucose at 9 p.m. for patients receiving more than 200 units, and 7 oz. if the dose exceeds 250 units.

A peculiar kind of after-shock was observed in a patient who frequently failed to go into coma with doses as high as 464 units. He became drowsy and cyanosed the next day, developed a rise of temperature and complained of headache and malaise.

Increased Liability to Infections.

When insulin treatment was started at Hatton in June, 1937, patients travelled from the main hospital to the insulin unit every morning and returned each evening, a distance of some 150 yds. or more. This was perfectly satisfactory during the summer months, but in September, 3 male patients suffered from diarrhœa without abdominal pain, and ran a temperature of about 101° F. for two or three days. The three cases occurred within a few days of each other, and the attack in each case appeared during the afternoon following a shock in the morning, the illness clearing up in two or three days without special treatment. In October there were 3 cases of tonsillitis in a short time, two men and one woman being affected, and all attacks cleared easily with ordinary treatment. Later a patient developed signs of pneumonia and died in four days, and this death, the only one in the series, led to the transfer of all patients under treatment to the insulin ward. Since then infections have been much less in evidence, and have consisted of two mild attacks of bronchitis and one severe tonsillitis leading to a double quinsy, which needed operative drainage.

Two women have developed boils. Gillies (20) has recorded two cases of pyelitis which cleared satisfactorily with mandelic acid.

There has been one abscess due to faulty technique in giving intravenous sugar.

Weight Changes.

Among 39 discharges the average gain during treatment was 14·1 lb.; 2 were unchanged, and the others gained from 1 to 53 lb. None lost weight. In 20 failures, 2 lost a little weight, 1 was unchanged, and the others gained from 1 to 28 lb., the average gain for all being 10·1 lb. Insulin probably increases weight by accelerating the formation of muscle glycogen, and its stimulant effects on the appetite may also be important. Day (6) has recorded the disappearance of sallowness of the face and of acne, and we have seen similar good results as well as marked improvements in the appearance of the hair in some of the female patients.

Results of Treatment.

Sakel states that the results of treatment depend more on the operator than on the method, and the treatment is consequently not specific as liver is for pernicious anæmia.

In describing results Müller divided them into four categories, and these are usually followed: they are (1) complete recovery; (2) incomplete recovery, with one symptom, such as abnormal affectivity or absence of insight remaining; (3) partial recovery, home and working but plainly schizoid; (4) unimproved. We cannot accept this scheme, because in our view the time factor is most important, and a remission with residual symptoms lasting five years is a better result than a complete remission lasting a few months. We have seen a category 2 remission relapse to category 4 in a few days, and a category 1 remission re-enter hospital as a category 4 in a few months, while a patient discharged in category 3 was found to be in category 1 when seen several months later. Because of these variations results published may be inaccurate long before they appear in print. The exact estimation of the individual results can only be possible if every patient discharged is very carefully examined at frequent intervals, and in practice this is impossible. Category 3, according to Müller, are out working, but category 4 are unimproved. This seems to us a very big gap compared with the gaps between the other groups. We take as our guide the ability or inability of the patient to do his work and react satisfactorily to everyday life situations.

Another difficulty that arises is the question of diagnosis. Clinically we find little difficulty in the cases we meet in diagnosing some kind of schizophrenia, but since spontaneous remissions vary with different observers from 4% to 48%, it is clear that diagnostic standards are far from uniform, and this indicates the importance of comparing results obtained with insulin and other methods by the same observer.

Cook (23) has stated that the remission-rate with the new forms of treatment can be fairly taken as twice as great as that to be expected from spontaneous

remission. Dussik and Sakel (9) report 88% discharges with 70·7% complete remissions in recent cases, and 47·8% discharges among chronic cases with 19·8% complete remissions, and there is plenty of support for these figures (4, 6, 13, 24). Rosenberg and Moersch (25), on the other hand, considered the results no better than those obtained with ordinary methods after comparing the results in thirty-three pairs of cases matched as closely as possible in respect of age, history, symptoms, etc., and Lemke (15) considered that insulin produces good results where the prognosis is already good. This view corresponds closely to our own. We agree with James that the period of treatment is considerably shortened by Sakel's technique, and we think that there may be a slight superiority in the percentage of discharges, but it is certainly not a great superiority. Of our 59 cases 39 were discharged, but these figures have been closely paralleled by our previous results. A few of the failures are brighter and do simple hospital work, but occupational therapists claim to do as much without insulin.

Day (6) has observed that patients very sensitive to insulin do badly, but we have not noticed this among our cases. Sakel reported better results in paranoid schizophrenia, for which he induces deep shocks, than in other types, and we have had 80% discharges with the paranoid group and 59% with the others. A difficulty arises in this connection, for while we believe we can diagnose schizophrenia with some confidence, we often find ourselves in difficulty when trying to group the schizophrenics, for some have symptoms that cannot be forced into any group, and others change from one group to another.

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