# IRREVERSIBLE HYPOGLYCAEMIC COMA IN ISLET-CELL ADENOMA AND IN SCHIZOPHRENIA

By

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As an approach to the problem of schizophrenia it is proposed to compare the effects and after-effects of severe hypoglycaemia due mainly to islet-cell adenoma of the pancreas in otherwise healthy people with the effects and after-effects of severe hypoglycaemia therapeutically induced in schizophrenics.

The difficulties are plain. Personal experience of patients with functioning islet-cell adenoma is limited almost always to a few cases, whereas average experience of insulin coma treatment covers some hundreds of cases; moreover, there is little overlap of experience except in the post-mortem room or in the laboratory for morbid histology. During insulin treatment there is constant supervision by a trained staff, medical and nursing, so that serious developments can be met by immediate intravenous sugar and investigations are continual; with adenomata there is no observation until, perhaps, a general practitioner is called in about alarming symptoms of one kind or another and sometimes months or even years elapse before a patient gets into hospital, where the intensity of observation and even more so of investigation may exceed that available in mental hospitals. Insulin coma treatment has a more or less standard aim, to produce coma of increasing duration up to a maximum of something like an hour which is then repeated thirty times or more; dosage is built up with the greatest care. Adenomata produce conditions varying from the hardly serious to the fatal under the influence of an insulin dosage which is quite unknown.

This comparison is based chiefly on an analysis of 290 serial courses of insulin coma treatment given to schizophrenic patients at Holloway Sanatorium during the four years 1950 to 1953 inclusive, and on the 258 cases of islet-cell adenoma reported by Crain and Thorn (1949) and the 398 cases, all that could be traced up to that date and including the Crain and Thorn cases, analysed by Howard, Moss and Rhoads (1950). Many separate papers have been consulted for more detailed approaches and for extra information, although of course those published before 1950 were included in the reviews already mentioned. Despite the difficulties of this comparison, it can be shown that the similarities between the two groups follow expectation and are very strong indeed, so that the differences which emerge have at least possible significance.

## General Picture

The general picture of signs and symptoms is in fact indistinguishable. It is not necessary here to review the metabolism of the brain and its dependence on oxygen and glucose, but only to say that both islet-cell adenomata and therapeutic doses of insulin produce the same phylogenetically and ontogenetically determined abrogation of brain function which is familiar, say, in progressive alcoholic intoxication, and that the additional intense autonomic disturbances are also common to both groups. Judgment, reason and clarity of mind are steadily diminished, giving way to increasing drowsiness and clouding and



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eventually to coma. Before coma blankets them, mental symptoms of every kind, not only excitement and peculiarities of behaviour but symptoms suggestive of almost every psychosis and psychoneurosis (Sigwald, 1932; Greenwood, 1935) can occur, against a background of normality in the case of patients suffering from islet-cell adenoma, added to the symptoms of schizophrenia in the treated patients. Full descriptions are plentiful (Sakel, 1935; Parfitt, 1937; Himwich *et al.*, 1939 and 1941). The march of events is in line with the richer blood supply to grey matter and to correlative centres as compared with motor centres (Wolff, 1936). In both groups sugar ordinarily produces a very rapid disappearance of the abnormal signs and symptoms caused by the hypoglycaemia.

In both groups there is a grave danger of irreversible damage to the brain and of death (the fact that the danger of death is very much greater than that of irreversible brain damage in the case of islet-cell adenomata will be discussed later).

## Irreversible Coma

Irreversible coma may be defined as a coma which cannot be terminated at will. Put another way, as a coma which persists while the blood sugar is kept consistently at normal or above normal levels. It varies in severity from case to case, from an anxiety-producing situation lasting several hours to a desperate struggle for life going on through several days, if in fact it does not end in death. There is no detectable difference in this recurring situation as it is described for the severe hypoglycaemia of islet-cell adenoma and as it is described for therapeutic hypoglycaemia, the bedside struggle is the same. The differences are found before the event and more particularly after the event.

It is impossible to make a comparison which would prove that one type of case develops an irreversible coma more easily than another, because such comas are universally possible and the unknowns, particularly in cases of islet-cell adenoma, are too numerous, but one can say that the hypoglycaemic experiences of the undiagnosed sufferers from islet-cell adenoma are often astonishingly severe and that the ease with which serious trouble supervenes in schizophrenia is equally astonishing.

The cases of spontaneous hyperinsulinism reported by Black *et al.* (1954) can be taken as typical. Case 1 would be found unconscious and unrousable in the mornings five to six times a week and there was incontinence and tongue biting, but operation effected a cure. Case 2, a young lady aged 22, after a long and testing period of symptoms was eventually admitted to hospital having been in coma for twenty-four hours. She remained comatose and semi-comatose for several days before it was possible to detect that she had developed a left hemiplegia. For some time she was apathetic, unco-operative and emotional, but she returned to her work as a school teacher and had worked steadily for over a year at the time of publication. Case 3 was found unconscious one morning and didn't reach hospital for treatment to begin until four o'clock in the afternoon, but without long-term ill effects. Further confirmation of the prolonged and perilous delays before diagnosis and treatment in non-schizophrenics can be seen in the reports of Layne and Baker (1939), Lidz *et al.* (1949) and Smith and Cochran (1952).

Compare this with by far the commonest setting for an irreversible coma developing during therapeutic hypoglycaemia, which is met in a patient in an acute phase of the malady, suffering a first attack or a further extension of the disease, as a complication of one of the first few comas, when the period of

complete coma lasts only a few minutes, in accordance with the usual technique of increasing the length of coma very cautiously because this danger is so well recognized. Including the time consumed by the failure to respond to gastric glucose, the patient is being given sugar intravenously about three hours after the insulin injection and about two and a half hours after the first symptoms of hypoglycaemia, but the most adequate precautions fail and this does suggest a most unusual sensitivity to hypoglycaemia during certain phases of schizophrenia. Marble's (1952) statement, that "the prognosis of an insulin reaction is almost *invariably* good if it is diagnosed reasonably early" (my italics) hardly holds good for this therapeutic complication.

## Post-mortem Findings

It has been shown by laboratory experiments that the brain uses up its reserve of glycogen after about an hour of severe hypoglycaemia and that damage becomes increasingly likely after that (Kety *et al.*, 1948). Yannet's work on cats (1939) suggested a relationship only between damage and excess insulin in the presence of hypoglycaemia, but there is general agreement that in man there is no reliable yardstick provided by dosage, duration of stupor or of coma, sugar level or any other measure (Rivers and Rome, 1944; Malamud, 1948).

The post-mortem findings appear identical and as Ferraro and Jervis say (1939), nothing specific is revealed by the microscope either in the damaged brain or in schizophrenics as compared with others, and for this reason cases of schizophrenia dying under treatment and fatal cases of islet-cell adenoma tend to be mixed indiscriminately. (Malamud and Grosh, 1938; Moersch and Kernohan, 1938; Ferraro and Jervis, 1939; Baker, 1938; Wilder, 1940; Kerwin, 1940; Malamud, 1948.)

Ferraro and Jervis provide a good review and quote other careful studies (Ehrmann and Jakoby, 1929; Terplan, 1934; Bodechtel, 1933; and Wohlwill, 1938), and the reports bring out the great variability and the widespread nature of the damage to the brain, both in animals and human beings. Alterations to blood vessels, with perivascular changes and very numerous cortical and subarachnoid petechiae, which may render the C.S.F. bloody, are usually prominent (Baker; Ehrmann and Jakoby; Ferraro and Jervis; Morsier and Mozer, 1936) and may lead to softening and cysts (Baker). The cortex suffers severe cellular damage and neuroglial changes are prominent, but sometimes the white matter (Mackeith and Meyer, 1939) or the basal ganglia or the cerebellum (Ferraro and Jervis) seem to suffer most. Malamud and Grosh have reported the chief damage in layers 3 and 5 of the cortex, Malamud has described cases where the temporal cortex or Ammon's horn have shown the most severe changes, sometimes it is the occipital and temporal cortex rather than the parietal and frontal, and sometimes the reverse (Ferraro and Jervis), sometimes striking changes in the corpus striatum or in the caudate and putamen are stressed (Malamud). Hassin (1939) saw vital damage in the medulla and the olivary bodies and attention has been drawn to intracellular lipids (Ferraro and Jervis) and the significance of fatty degeneration of the liver has been considered (Malamud). Quoting Spielmeyer (1930), who had a common vascular origin in mind, Ferraro and Jervis mention similarities between the findings and those discovered in epilepsy, eclampsia, pertussis encephalitis, fat and air embolism, occlusion of the carotids and arteriosclerosis, and they add lead poisoning, malaria, serious infections and toxaemias. Jetter and

Sheflen (1952) regard the neuropathological picture of fatal hypoglycaemia as indistinguishable from that of anoxia caused by other agents. I should like to add one further note to this post-mortem evidence of widespread nervous damage. Ferraro (1942) described evidence from three schizophrenics who had died during insulin coma treatment and gave it as his opinion that the cells showed more damage than the vessels and perivascular areas in schizophrenics as compared with normals, and that this cellular damage showed itself "particularly in the frontal and temporal cortex".

## Fits

Fits associated with islet-cell adenomata and with therapeutic hypoglycaemia occur, as far as can be told, with roughly the same frequency. This aspect was reported in some detail by Parfitt (1937) and taking the present series of 290 cases into account as well, the incidence works out at about 50 per cent., but it is very variable. Crain and Thorn reported that 28 per cent. of the 193 cases of which they felt the clinical histories were satisfactory had fits, but only 58 of the 193 became unconscious and only 40 per cent. went into deep coma and it is reasonably certain that the percentage would have been higher if deep coma had been uniform. In such a comparison as is being made here, only the most exceptional differences can be seriously considered.

## Mortality

The first unmistakably significant difference is shown by the deaths. Taking the figures of Howard *et al.*, which include those of Crain and Thorn, of 264 *functioning* islet-cell cases, 45 were discovered or confirmed at post-mortem and 15 more died of hypoglycaemic effects, i.e. not from the operation as such or from any other cause, so that there was a death rate of 26 per cent. Two of their own nine cases died. There were no deaths in my 290 cases, although one patient was readmitted to another hospital after discharge and died during the second coma of a new course of treatment. Sargant and Slater (1948) reported no deaths in 400 cases. There have been plenty of deaths during insulin treatment because tens of thousands of patients have been treated, but the death rate is always extremely low as compared with the very high death rate associated with functioning islet-cell adenoma. The death rate for the adenomata is all the more striking when one recalls the 58 per cent. only who became unconscious and the 40 per cent. who reached deep coma, as reported by Crain and Thorn.

Most of the deaths in the islet-cell adenoma cases paralleled the age distribution in general and occurred between 30 and 60, but there were plenty of deaths among young people including children and the enormous difference is clearly due to the difficulty of diagnosis and the perils experienced and damage suffered before hospitalization in the case of islet-cell adenoma as compared with the tremendous care in the use of a known instrument, together with the promptitude of interruption for threatening symptoms associated with therapeutic hypoglycaemia.

## Paresis and Paralysis

Various forms of transient paresis and paralysis have been recorded as sequels to insulin treatment (Sakel, etc.) but they are uncommon and there were no such sequelae in my 290 cases which averaged 30 or so comas.

Of Crain and Thorn's 193 cases with satisfactory clinical histories 10 per cent. developed hemiplegia, transient in terms of hours or days as a rule although 2 of the Crain and Thorn cases had permanent palsies. These figures are worth

stressing, 19 hemiplegias with 2 permanent palsies compared with none. This is very much in line with the deaths. The original smaller series of islet-cell adenomata strengthen the picture. The 9 cases of Howard *et al.*, some of those in their 398 cases considered which were additional to Crain and Thorn's 258, showed 1 permanent hemiplegic and 1 transient paraplegia. Of 6 cases of Bowen and Beck (1933) of which brief clinical descriptions are given, there was a case of transient right sided hemiplegia but *with some residual damage*. Moersch and Kernohan (1938) describe a transient hemiplegia *with permanent weakness of the right hand*, Roxburgh's (1954) young patient had *persisting ataxia*. Tom and Richardson (1951) reported paralysis of all four limbs and wasting of the distal limb muscles. Blau *et al.* (1936) described Parkinsonism with pyramidal signs, ataxia and muscular weakness and Lidz *et al.* (1949) wrote of muscular atrophy and scanning speech. Several patients who died from islet-cell adenoma had obvious paralysis before death, all of which points to the conclusion that even the convincing evidence provided by the hemiplegias reported in Crain and Thorn's series does not fully represent the enormous amount of brain damage suffered by islet-cell adenoma cases as compared with schizophrenics under treatment.

Goodman (1954) has recently described severe hypoglycaemic reactions in 3 diabetics, one of whom suffered a transient hemiplegia four times and one of whom died. Labbé and Boulin (1937) wrote an informative article on hemiplegia occurring in diabetics associated with hypoglycaemia, which is extraneous to the comparison being made, as are Goodman's cases, but which help to throw light on the situation being considered. They described two types of hemiplegia, a transient and a permanent which is possibly fatal. The side paralysed is generally contracted and shows exaggerated tendon reflexes, ankle clonus and a positive Babinski, and if right-sided there is added aphasia; hemianaesthesia is sometimes present. Following intravenous glucose the hemiplegia may disappear in minutes or hours or take several days, the hemiplegia may be repeated and there may be permanent residuals.

Labbé and Boulin draw a further distinction between cases developing as a complication of severe hypoglycaemia and others which are not so important in the connection being examined here which develop more commonly in older people, whose routine has been upset possibly by an infection necessitating more insulin. They doubt whether this kind of hemiplegia, most commonly found in elderly diabetics, can be attributed to the degree of arteriosclerosis but they make the point, an important one in brain pathology, that damaged brain is more susceptible to noxious influences, in this case to hypoglycaemia, quoting Goldstein for their support. Reference to this principle will be made later. Even this surprising type of hemiplegia can occur in young people, Labbé and Boulin describe it in a man of 33 with a history of 4 hypoglycaemic comas who developed right-sided hemiplegia and aphasia which left permanent weakness in the hand and leg, and they refer to other severe hypoglycaemic hemiplegias developing in youths and even young children. Taken by and large, the brain damage occurring as a complication of hypoglycaemia associated with diabetes is more severe than in islet-cell adenoma, if deaths are excluded, because the possibility of repeated incidents cannot be avoided whereas operation for islet-cell adenoma often leads to a cure. One can sum up the situation by stating that there is an overwhelming preponderance of hemiplegic and like phenomena associated with both islet-cell adenomata and with accidental hypoglycaemia in diabetes, as compared with therapeutic hypoglycaemia.

## Mental Changes

The crucial and most difficult stage of the comparison is now reached.

First of all dementia will be considered. Marble (1952) describes striking cases and others have been reported by Malamud and Grosh, by Wilder, and by Tom and Richardson (1951) of a catastrophic and permanent dementia, a pitiful mindlessness often associated with double incontinence, occurring as a permanent sequel to hypoglycaemia associated with islet-cell adenoma. The incidence would be about 2 per cent. Most of these cases would be included presumably in the series reviewed by Crain and Thorn and by Howard *et al.* Speaking generally such a phenomenon is unknown following therapeutic hypoglycaemia, certainly nothing like it occurred in the 290 cases considered here; the nearest approach to such a picture will be described in some detail, (Case 2), when the differences will become apparent. Crain and Thorn state that of their well-documented series of 193, twelve patients were thought to have irreversible personality changes but seven of them made a complete recovery. The remaining five, again presumably include the cases of Marble, of Malamud and Grosh, and of Wilder, but not of Tom and Richardson, to which reference has just been made. Lidz *et al.* describe a young man who was admitted to hospital five times in two years for fits and comas and who developed a mental state resembling pseudologia phantastica with speech defect, severe muscular atrophy and ataxia. Fifteen months after operation for islet-cell adenoma he recovered completely except for residual muscular atrophy. Black *et al.* and Smith and Cochran describe other striking recoveries in islet-cell cases and Jetter and Sheflen describe relatively mild neurone damage in a case which came to autopsy, but unusually marked gliosis and fibrosis had developed owing to prolonged survival. It is this extraordinary power of recovery which makes death a greater risk than permanent brain damage in islet-cell adenoma.

The position concerning the sequels of functioning islet-cell adenomata can be summed up as follows. If death or catastrophic damage to the brain can be avoided the potential for recovery is extraordinary; after a reasonable interval of time there is nothing between severe damage and none at all.

(The position concerning children is doubtful and is therefore noted in parenthesis. Wickes (1954) has put forward evidence suggesting that the foetus *in utero* is decreasingly susceptible to severe maternal hypoglycaemia up to the tenth week, thereafter there appears to be little danger to the child before birth. Jelliffe and Stuart (1954) have shown the extraordinary capacity of children to recover from severe hypoglycaemia if death is avoided, but there are many examples of mental defect produced by hypoglycaemia in children (Layne and Baker; Graham and Hartmann, 1934; Greenlees *et al.*, 1952) and this may be an expression of sensitivity to damage or the catastrophic dementia to which reference has been made showing improvement in resilient youth and the evidence I think favours the latter view.)

## Mental Changes in Schizophrenia

It should be noted that as opposed to the conditions before coma, one is dealing in the coma and its sequels with as near a standard situation for both islet-cell adenoma and schizophrenia as is possible. Time after time after such a crisis in the treatment of schizophrenia, there is a very dramatic, permanent, easily-observable change in the mental condition of the patient, always called an improvement, a word unknown in discussions on islet-cell adenoma cases. This improvement is directly related to the severity and duration of the

irreversible coma: thus in sixteen cases reported by Wortis and Lambert (1939), two died, two showed no change after an average irreversible coma of eighteen hours, five were much improved after an average irreversible coma of thirty-two hours and a further week of stupor, and seven were "cured" after an average of forty-eight hours irreversible coma and four weeks of stupor. In other words, the greater the brain damage, the greater the improvement. Wortis and Lambert commented that if a safe method of producing irreversible coma could be discovered, a kind of reversible irreversible coma, it would increase the value of shock treatment. It is a change which has no connection with the gradual improvement which insulin coma often brings about or with the quiet deterioration which sometimes represents a failure of treatment. It is as if a picture of stormy uncertainty is suddenly replaced by a miraculous calm, a state of smiling peace in which it is easy to forget the broken boughs and the flattened flowers. The change is one in the condition of a schizophrenic patient and it can be said therefore that such a change could not be expected in normal patients and this is fully agreed. It is a change peculiar to schizophrenics.

As long ago as 1938 Kraulis was so impressed with the improvement in four out of five of his prolonged coma patients that he advocated pushing up the coma period to twelve hours, a procedure which proved too hazardous for general adoption. The same phenomenon was noted by Parfitt in 1937 and it has been stressed again by Revitch (1954) and Biskupski (1954). Almost uniformly the severity of the event has led to further treatment being abandoned so that, as Revitch has pointed out, there can be no doubt that the striking effect is an outcome of the prolonged coma. There is an abrupt production of sociability, even euphoria, a striking reduction of tension and hostility and an indifference to insane ideas where these persist, a picture, as Revitch again points out, which is very reminiscent of a post-leucotomy state in a schizophrenic. I would go further and say that without the possibility of palpating the skull the two conditions would be clinically indistinguishable. Even the first recovery from the critical condition, to the extent that life is no longer threatened, strongly resembles the immediate post-leucotomy state, with clouding, raised temperature and pulse rate, restlessness and incontinence giving way to drowsiness and apathy.

In my series of 290 cases there were 19 prolonged or irreversible comas of varying degrees of severity and roughly in proportion to the severity, the "prefrontal" picture was produced. It is difficult to draw a hard and fast line, but at least eight of the nineteen exhibited the phenomenon which is now being described, a sudden change of mental state which remains permanent in the sense that the residual palsies of the adenoma cases are permanent, over periods of months or years covering the observation. This peculiar group is confined to schizophrenia; it finds no counterpart in the islet-cell adenoma cases. In the same series of 290 cases there were no other notable sequelae other than five cases of persistent tingling and numbness in the fingers lasting for some months, similar to that described in one of Goodman's cases, occasional complaints of stiffness of the face which was usually more transient, and one permanent anosmia.

Putting aside the possible significance of an unusual sensitivity in schizophrenics under certain conditions, one is left with the fact that severe hypoglycaemic episodes have death, paralysis and dementia as their most prominent sequels in cases of islet-cell adenoma, whereas in schizophrenics these are comparatively almost absent; but a sudden and striking mental change, clinically

for the better, is often seen as a sequel in about 3 per cent. of patients, a permanent change of personality of a kind unknown in normal people. (The condition might be suggested occasionally by such cases as Black *et al.*'s second case, the diabetic alcoholic reported by Bowen and Beck and one of Goodman's cases, but the picture is quickly lost in a steady recovery.) It does not matter how this is viewed, as a sensitivity of schizophrenics as compared with normals, or as a sudden shift in the disease itself, in either case an organic phenomenon peculiar to schizophrenia is evident.

There is, of course, no proof of its nature, but since the change produced is clinically identical with that produced by a prefrontal leucotomy in the same disease, it is permissible to speculate as to whether disease of the prefrontal lobes is important in schizophrenia. This is not a new idea, Schaffer and Miskolczy stated in 1938 that "The schizophrenic process destroys the most human parts of the brain", the frontal, inferior parietal and temporal lobes. Parfitt (1954) has marshalled evidence supporting the view that schizophrenia is incident chiefly in the frontal and temporal lobes and should be renamed phylogenetically and ontogenetically determined encephalopathy.

It might be asked whether this adds anything to the proposition that schizophrenics are often improved by prefrontal leucotomy, in which the improvement may be due to an opportunity for a somewhat simplified and fresh integration of function of the whole brain, and the answer is yes, because the change is brought about under circumstances which do not affect normal people in the same way and which suggest very strongly indeed that at certain stages of the schizophrenic process there is an extreme sensitivity to hypoglycaemia or to an excess of insulin.

No excuse is made for the absence of visible histopathology after the recent articles by Adrian (1954) and Murray (1954), although it might be pointed out parenthetically that Schaffer and Miskolczy based their opinion on microscopic examinations and claimed to have discovered lesions particularly in cortical layers 3 and 5, layers specifically mentioned by Malamud and Grosh.

The following two cases will serve better than further theorizing to indicate the effect of assuming that in fully developed schizophrenia a destructive process is at work in the frontal lobes and to a less extent in the temporal lobes.

*Case 1.* A highly intelligent girl who found little difficulty at first with her work as a librarian, but who at seventeen began to make errors and to suffer from periods of clouding, inexplicable impulsiveness and visual hallucinations which intrigued and frightened her and for which she sought an explanation. The disease from which she suffered was progressive, and at twenty-two she had thirty-two insulin comas in a mental hospital and sixty more a year later, each time with improvement. It is important to note that when she was able to seek guidance on visual hallucinations (and at this time her intelligence and ability as a poet was causing considerable interest), the patient survived without damage, in fact with apparent benefit, a total of ninety-two comas, a good many of them lasting a full hour after the corneal reflexes had disappeared. Two years later there was a further intensification of symptoms, the hallucinations became auditory and involved ideas of sex and guilt, she became crazily argumentative and easily excited and she was unable to maintain her employment. She was readmitted to hospital and on the very first occasion that she reached coma she suffered a delayed recovery and thereafter presented the picture of a severe physiological leucotomy, becoming quiet, bland and easy in manner. During the following two years she has fitted easily into her home, undertaken light household tasks and toyed with insignificant literature, and during the last month has got back to simplified library work. She has become careful of her appearance, is not hallucinated, has the peculiarity of sleeping very little without apparent discomfort, but she is a very inferior person compared with herself five years before. The events in this case become intelligible if one assumes that the disease process was at first mainly incident in the temporal lobes and that a state of frontal instability had developed when her last coma was induced.

The next case illustrates in more detail the physiological leucotomy which is being suggested.

*Case 2.* A young lady, now aged 29. Intelligent parents. Family eccentricity. One of three brothers had depression. Matriculated, good at games, kindergarten teaching from sixteen to nineteen before starting as a medical student. She gave this up after one year and was a nurse in training from twenty-one to twenty-five, completing her S.R.N. qualification and doing a further year as a staff nurse.

Schizophrenic symptoms began insidiously at twenty-four or earlier with increasing difficulty in coping with her work and withdrawal from friends and interests; she became perplexed, indecisive and unhappy, was inevitably slack at her job and later felt that the ward sister had a "down" on her, finally refusing to go on duty because people were talking about her and because references were being made to her in newspapers and magazines. At the same time she was assuming that a deep love affair existed between her and a houseman who did not know her very well.

She was admitted to hospital as a patient early in 1950 at the age of twenty-six, deluded and hallucinated and showing periods of restlessness, elation and noisiness. It proved difficult to induce coma but she had her third with 460 units on 27 April when the procedure for termination began after ten minutes, but the coma proved irreversible and she was never really conscious again for forty-eight hours and in the meantime was extremely near death. Three days after that she was still unresponsive, incontinent and being tube-fed, she did not speak until nine days after the injection of insulin.

During the remainder of 1950 she maintained a picture of bovine indifference, with tremendous loss of memory and concentration, she wrote simple letters as if her mother, who had died seven years before, was still alive and thought she had been in hospital for only a few days. She was quite unrousable to any sense of personal or communal responsibility, appeared colossally lazy and remained occasionally incontinent. She took reasonable care of her appearance and tended to moon after male patients.

Throughout 1951 and 1952 she improved very slowly, exhibited almost cyclothymic mood swings, varying from brightness and a superficial show of alertness to sulky aggression and resistiveness, at times doing simple work in a casual, unrelated way. Appropriate tears of bewilderment appeared occasionally. Tried at a local nursery she was reported as useful but not worth payment. Her nursing knowledge was considerably reduced but she was able to give useful if limited assistance as a ward help. In January, 1953 she did fifty-five out of sixty of Raven's progressive matrices in fifty minutes, which graded her "Intellectually Superior", her Conceptual Quotient was reported as 106 (over 90 is normal) and Mill Hill Vocabulary Grade 3+. "She was co-operative, cheerful and tackled the tests with interest and without fuss." She could play a good but casual game of hockey almost from the time of recovery from her coma. Eventually, early in 1954 she became a Deputy Assistant Matron in a preparatory school working under an understanding senior for sympathetic employers and she has moved into her second term successfully. Here is a girl who is now usefully active, has become pleasantly socialized, with a persisting weakness for assuming possession of a man, who goes out to films, plays games and does well with quite a variety of intelligence tests but who is yet pitifully different from what she once was. On close acquaintance she is found to be defective in original thought, has little insight into or interest in religious or ethical demands on herself as a person or in relation to her environment, the continuity of her personal memory is disorganized, she can only just manage to arrange her considerable knowledge well enough to become self-supporting under kindly and favourable conditions. Her ability to acquire new knowledge is considerably impaired.

As a description of a successful leucotomy this could hardly be bettered, so much so that one is tempted to speculate that the value of insulin coma treatment lies in the slow putting out of action of cells or circuits in functional disorder, that it helps to produce more smoothly a condition of stability in a disease which tends to produce its own leucotomy, and sometimes a very extensive leucotomy, that this is another example of the principle that damaged brain tissue is most susceptible to noxious agents, which was mentioned by Labbé and Boulin. This point is important, a physiological rather than an anatomical leucotomy represents a better procedure if it can be managed. Observe the complete absence of hallucinations in both cases cited.

## Conclusions

A comparison has been made of the effects and after-effects of severe hypoglycaemia due to islet-cell adenoma and of the same condition occurring in schizophrenia as a complication of insulin coma treatment.

The general picture, the clinical and chemical details of irreversible coma, the post-mortem findings and the fits show no certain difference, but death, paralysis and a dementia approaching mindlessness are tragically common in islet-cell adenoma and almost absent in schizophrenia, because of the safer conditions under which treatment takes place.

On the other hand, a peculiar, permanent post-irreversible coma state which is clinically an improvement and is indistinguishable from a "perfect"

leucotomy occurs occasionally in schizophrenia. The irreversible coma which leads to this improvement usually develops with astonishing ease.

It is suggested that this is indicative of an organic peculiarity in schizophrenia.

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