

Controversies  
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## **INSULIN COMA TREATMENT: FACTS & CONTROVERSIES**

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An appetite stimulating effect has been attributed to the hypoglycemic action of insulin and this hormone was commonly employed previously to induce a gain in weight. This appetite stimulating effect was first observed by Pitfield in 1923. His paper was followed by a series of other reports which were more or less confirmatory in nature and showed the usefulness of insulin in malnutrition. These reports on 'fattening cures' were based on clinical trials conducted without controls. Later, however, some researchers struck a discordant note when they working with controls as they could not show any weight gain due to insulin.

Former attempts to restore weight loss in psychiatric patients have included hyperalimentation, where Weir Mitchell (1885) urged the importance of restoration of physique in treatment of neurotic illness by means of an enormous diet, supplemented by rest and heavy massage to promote sweating and appetite. Thereby, he bolstered the neurotic physical constitution and obtained some remarkable psychological improvements.

The Weir Mitchell method suffered eclipse and was gradually forgotten. No one remembered that he picked his cases and the treatment was applied to all and sundry, whether of "good" or "bad" premorbid personality. Attention was switched from the restoration of normal physique to rest, isolation, massage, and diet as treatments in themselves. The results of the Weir Mitchell method that T.A. Ross said, "cured them by the hundred," were attributed to suggestion and to his forceful personality and their effects on patients and followers. Ross (1937) remarked that while he believed in the treatment (he used it with success over a period of five years), he began to doubt its efficacy when relapses occurred and it then seemed to lose its beneficial effects on his patients. Weir Michell's results cannot be attributed entirely to suggestion; there was something more in his method as is shown both

by his case reports and the long period of success it enjoyed. He had grasped the fundamental fact, subsequently forgotten in the energetic development of the psychological approach, that the mental and somatic aspects of an illness can never be entirely disentangled and that physical factors may be the critical in preventing recovery from psychological symptoms.

The hypoglycemic coma technique was developed from use of insulin in symptomatic treatment of patients with various types of psychiatric illnesses. Sakel (1937) began using injections of insulin in sub coma doses while treating symptoms arising from abstinence in morphine addicts, on the theory that insulin might influence the functioning of the nerve cells to relieve the patient's excitement. When such insulin treatment succeeded in decreasing the distressing symptoms of the newly abstinent morphine addict, Sakel decided to try it for treating other forms of excitation in the hope of being able to tone them down as well. Incidentally, when he attempted to determine optimal dosage, some of the schizophrenia patients being treated fell into coma. When they emerged from coma, Sakel found not only had the excitement abated but the psychotic symptoms themselves had lessened and in some cases even disappeared. However, it may be noted that insulin was used in psychiatry before Sakel. The sedative effect of sub coma insulin was first noted by Klemperer (1926) and Steck (1932) introduced it in treatment of narcotic withdrawal. It was also used to overcome refusal of food and to build up rundown patients, but the dosage in these treatments was small and as Sakel rightly claims, "only mild hypoglycemia was produced." The coma which is attained only through marked hypoglycemia was avoided and even considered dangerous and unwarranted. The small dose treatment, the so-called sub coma (ambulatory) insulin method (Kalinowsky and Hoch, 1961) and modified insulin therapy (Sargant and Slater, 1963) have a definite place in therapy, but not insulin shock treatment. Sharp and Baganz (1940), treating psychotic patients by forced-feeding, did find significant weight gain in those given insulin as compared to controls. Sargant and Slater (1940), Sargant and Craske (1941) and Sullivan (1948) contributed much to the revival of insulin shock treatment and used modified sub coma treatment with insulin in mental patients of various symptomatology showing good results. Polatin et al (1940 & 1946) introduced this treatment among patients with schizophrenia and claimed favorable results, in that the patient received increasing doses of insulin until he showed signs of manifest hypoglycemia, but then the insulin dose was not pushed further and shock reactions were avoided.

In insulin coma treatment, initially 10 to 20 units of insulin are given, and up to 1000

units are given subcutaneously. The daily dose of insulin is increased until that point when the patient reaches a semi-comatose stage with facial twitching of muscles. The degree of hypoglycemia can be judged by the extent to which the patient sweats – which can be considerable with rising pulse rate. An accidental occurrence of seizures in the process can be terminated by the intravenous administration of glucose. The treatment is continued daily and patients are given 30 to 40 insulin comas. In this way, insulin coma treatment may be considered similar to Electroconvulsive treatment.

In order to obtain a good response, Polatin et al (1940) treated their patients with schizophrenia for the same period of time as the psychosis had existed prior to treatment, some patients were treated for years. A larger group of 250 patients with schizophrenia treated with sub-coma insulin was reported by Tomlinson (1948), whose results compare favorably with figures obtained by others for insulin coma therapy. In the past, value of sub-coma treatment in many schizophrenia-like syndromes was presented by Greaves et al (1955), but they kept their patients in a state of clouded consciousness for almost an hour, thus, going beyond the usual technique of sub coma recommended for the neuroses, withdrawal symptoms, alcoholics, and so on.

Various combinations have been used with insulin sub coma in treatment of other somatic as well as psychological illnesses; also many other combinations have been tried. It was used with electric convulsive therapy by Polatin et al (1946), though, significant convincing improvements as a result of this combination were not noted. In France, where colloidal gold and other colloidal solutions were used in the therapy of various psychiatric disorders, insulin sub coma was combined with these solutions.

According to Rennie (1943), the administration of insulin in sub coma doses provides an effective method of sedation. Its specific action seems to be alleviation of anxiety, consequently, the psychotic manifestations sometimes disappear rapidly. The method is said to be safe and far superior than that achieved by the usual methods of sedation. Brickner et al (1950) recommended this type of insulin treatment as an office procedure, particularly useful in tension states.

The use of sub-coma insulin treatment in conditions other than schizophrenia is also wide spread. At the International Conference on Insulin in 1958, Bernath (1959) gave an up-to-date account of this treatment. He pointed out that the target symptom is anxiety and although it is not a cure of anxiety, it is a useful adjunct in treatment of patients with different

psychiatric conditions involving anxiety.

Based on his experience with 1000 cases, Sargant (1949) reiterated his favorable impression of the treatment in selected cases but rightly warned against its use as a mere Placebo for many unsuitable cases. In severe depression, it often makes the patient feel worse. Toxic confusional states may be shortened by insulin injections administered twice daily - an application that has proved valuable in treatment of delirium tremens along with glucose. Sargant and Slater (1963) have also found it beneficial in cases of mixed organic and psychogenic nature, especially in post-confusional states. It is also believed that sub coma doses of insulin can be used in anxiety states in order to make the patient more amenable to psychotherapy. Disturbances in the autonomic nervous system quieten under insulin; the patient's appetite improves, sleep is better, and gains weight. According to these authors, "Later smaller doses of insulin were given and they were combined with large doses of tranquillizing drugs such as Chlorpromazine."

The use of insulin coma treatment is gradually becoming less and less popular and many of the staunch supporters of the method, as described by Sakel, "are themselves developing more and more doubt about its efficiency." This can be seen easily by receiving the voices of not only its dissidents, but also of its old supporters like Kelly and Sargant (1965). Libertson (1941) contrasted a group treated with insulin in 1937 with simultaneously admitted controls and found no difference in results. Roberts (1942) found no differences in outcomes after two years, although, temporary improvements were certainly commoner in the insulin group. Rennie (1943) claimed that in modern private hospitals, whether schizophrenia was treated with or without insulin, the results were little different. Gottlieb and Huston (1943) found no significant difference between two groups of patients with schizophrenia, one treated with insulin and other by psychotherapy. In 1951, at the end of four years, they found no important difference, despite segregating early cases of acute onset and studying those separately. Penrose and Murrh (1943), using an elegant actuarial technique in the Ontario State Hospital, found that shock treatment produced few benefits in 1041 patients with schizophrenia, and that in these electroconvulsive therapy was more effective than insulin. Feldman et al (1947) noted a high readmission rate after insulin treatment, with a continuance of social and economic problems. Bourne (1953) found that the evidence for the value of insulin treatment was unconvincing and long term prognosis was not influenced in any way. Boardman et al, (1956) claimed similar results for treatment with chlorpromazine.

Ackner et al (1957) published an important report of a controlled study of 'insulin treatment of schizophrenia,' which they prefaced with a critical review of previous studies, exposing their frequent fallacies and deficiencies. They compared the results of insulin with barbiturate induced coma on a matched pairs of patients. It was concluded that insulin was not the specific therapeutic agent. In fact, prolonged sleep treatment has been extensively used in the erstwhile Soviet Russia and the results, although not as spectacular, compare favorably with those of insulin coma. It is interesting that Ackner's patients gained a lot of weight during treatment, as do insulin-treated and sleep-treated patients.

Kelly and Sargant (1965) reported the most valuable and interesting results of a two-year follow-up on 39 schizophrenia patients treated mainly with insulin coma compared with 84 schizophrenia patients treated with Phenothiazines. Of the 'insulin-treated group', 37 percent were in the hospital and 51 percent were treated as 'psychotics-on-follow-up.' Compared with 26 percent psychotics of 'phenothiazine treated' group, the average length of stay was reduced from 10.7 to 6.7 weeks for the 37 percent in hospital.

The revolution in the treatment of diabetes by oral hypoglycemic agents is now well established and it is appropriate to reflect on their value in the field of psychiatry too, in place of insulin injection. Franke and Fuchs (1955) were the first to demonstrate the hypoglycemic effects of these sulphonyl urea compounds. A new sulfonamide preparation N<sub>1</sub>-sulfanyly – N<sub>2</sub> N butyl carbamide (BZ55) was given a trial in 50 healthy normal persons, in whom it caused pronounced fatigue, sweating, sensation of hunger, tremor and certain euphoria. Blood-sugar determination showed definite hypoglycemic effects. Several years have elapsed since the introduction of the aryl-sulfonyl-ureas as an adjuvant in the therapy of diabetes. After three years of extensive laboratory investigation and comprehensive clinical trials at the hands of thousands of physicians, carbutamide was withdrawn from clinical trials by its producers. This was due to the occurrence of side effects of an allergic character often manifested by sulfonamide therapy. Principally, however, carbutamide was discarded because it was demonstrated that it did not produce increased utilization of glucose in the tissues and was toxic. Tolbutamide on the other hand, has not elicited hepatic toxicity and was earlier available for the treatment of diabetes. Later, this was also discarded. Today, metformin is widely used as an oral substitute for insulin to treat diabetes, but no more for weight gain in psychiatric condition.

*Commentary and Controversy*

In spite of various controversies on the use of insulin coma treatment in schizophrenia, as outlined above, it is pertinent that several lines of evidence suggest that insulin receptor functioning may be abnormal in the brains of patients with schizophrenia. Some authors (Caravaggio F et al, 2015) suggest that (a) insulin receptor expression and or function is reduced in dopamine midbrain neurons in persons with schizophrenia and (b) basal insulin should reduce dopaminergic transmission in the striatum via these receptors and (c) this modulation of dopaminergic transmission by basal insulin is reduced in the brains of persons with schizophrenia. There is a possibility that insulin coma treatment corrects this modulation of dopaminergic transmission.

It has also been observed by researchers (Palomino et al, 2013) that there is some relationship between negative symptoms of schizophrenia and plasma levels of insulin-like growth factor I in first episode of schizophrenia. The evidence for the insulin-like growth factor I (IGFI) deficiency hypothesis in the pathogenesis of schizophrenia has been supported by other researchers (Venkata Subramanian et al, 2007).

Findings further suggest altered levels of circulating insulin and other neuroendocrine hormones associated with the onset of schizophrenia (Guest et al, 2011). Based on these observations, authors suggest function of multiple components of hypothalamic, pituitary, adrenal and gonadal axis may be affected in schizophrenia.

According to Doroshov (2007), most historians of psychiatry regard insulin coma therapy (ICT) either an embarrassing stumble on the path to modern biological psychiatry or as one member of a long line of somatic therapies used to treat mental illness in the mid twentieth century. ICT was perceived by some psychiatrists as an efficacious treatment of schizophrenia. It was not as controversial as ECT, which still is in use with some guidelines, but ICT was discarded without much careful scrutiny after the publication of a few papers (Ackner et al, 1957). I believe insulin has close linkage with the pathophysiology of schizophrenia and its hypoglycemic effects cause mild to moderate seizures like ECT seizures. It was probably for the same reasons that it was considered useful to treat symptoms of schizophrenia, but when the hypoglycemia was mild, as in the case of insulin sub coma treatment, the results were not satisfactory. This might have earned the method its share of negative publicity. Now, with the emergence of modern technology comprising insulin and glucose estimation in plasma, imaging and EEG, renewed scientific efforts must be made to reinvestigate and reestablish the usefulness of insulin coma treatment (ICT) before it is

discarded and forgotten.

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