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Development and present status of insulin shock treatment in schizophrenia

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DEVELOPMENT AND PRESENT STATUS OF INSULIN SHOCK TREATMENT IN SCHIZOPHRENIA

By

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I first became interested in the use of insulin for the treatment of schizophrenia while serving as a Junior interne at the Hastings State Hospital during the summer months of 1947.

Many questions came to my mind while watching the physiological changes taking place in the patients during the active treatment and the mental changes which in many instances followed a short period of treatment. This created in me an interest in this therapy, which I wish to set forth to the best of my ability and research in the following paper. The questions to be answered for my interest and for those who read this paper are as follows:

(1) Who was the first to establish the use of insulin and what were the conditions surrounding its initial use?

(2) When, where and by whom was this treatment first accepted and carried out in the United States?

(3) What are the physiological theories of insulin therapy in the treatment of schizophrenia?

(4) What proof is there that insulin is of value in the treatment of schizophrenia?

(5) What complications have resulted from the use

insulin in schizophrenia?

(6) What is the present status of insulin therapy in the United States?

I found in answer to the first question as presented in the introduction an article by J. Wortis (1), in which he states that Manfred Sakel (2), a young Austrian physician, in 1930 reported that the abstinence symptoms in morphine cures could be relieved by large doses of insulin. His working hypothesis was simple. He supposed that the abstinence symptoms were a sign of general nervous hyperactivity, such as he saw in hyperthyroidism. The nervous system in turn, was exposed to the continuous action of circulating hormones, especially of adrenalin. The abstinence symptoms were therefore either due to (a) nervous hypersensitivity or (b) excess of the excitant hormones. In either case, the diminution of adrenalin ought to have a sedative effect, and Sakel used insulin, an antagonist, to paralyze its action. This is the theory reduced to its simplest terms, and Sakel used insulin, an antagonist, to paralyze its action. This is the theory reduced to its simplest terms, and as Wortis stated, it may very well be wrong; but whatever its validity, it has proved fruitful in

practice and the value of insulin in abstinence cures has been confirmed by others.

The similarity of the abstinence symptoms to other types of excitement suggested the possibility of influencing excited states of different origin in the same way. The response of several schizophrenic patients to insulin treatment was favorable enough to encourage further research. The treatment of morphonists and schizophrenics was, however, not the same. Sakel's treatment of morphonists did not go so far as to produce hypoglycemic shock, though it came very near it. From observation of some cases of accidental hypoglycemic coma, however, and from several theoritical considerations, Sakel ventured to produce hypoglycemic shock deliberately in schizophrenic patients.

Principle of the procedure was as follows: Patients were treated by a regular series of hypoglycemic shocks, produced by deep intramuscular injections of insulin, and lasting several hours. The necessary doses are usually, but not necessarily, high and vary from 20 to 200 units and more. Sakel distinguishes four phases in treatment.

(1) Preparatory phase - Gradually increasing doses of 15 to 40 units of insulin given

daily at intervals of four and a half hours; the first injection is given fasting, the others at least two hours after eating. No food is allowed four hours after the first injection and for two hours after the others unless there are special threatening indications. Preliminary treatment varies in length of duration from individual to individual, depending on patient's condition and response. The dose is increased by 5 to 10 units daily for 3 to 10 days, until an apparent physical reaction is attained. Dose is then further increased and maintained to introduce:

(2) Shock phrase - This consists of the production of a series of severe hypoglycemic shocks, usually one a day, by injection of approximately 50 to 150 units as required. Occasionally, a second smaller dose, of 20 units is necessary to calm the patient. If the patient is strong and the response is good, one rest day a week is sufficient.

(3) Rest phase - After the severe shocks, an interval of one to several days follows,

during which the patients receive no insulin, or very little--in any case, no more than is absolutely necessary to keep the patient quiet. If further shocks are then indicated, they are resumed, otherwise treatment is ended with:

(4) Polarization phase - Large insulin doses are again given three times daily until just before obvious hypoglycemic symptoms appear.

The second question as presented in the introduction was answered in a paper by B. Malzberg (3) written in 1938. Dr. Malzberg tells us that Dr. Sakel came to the United States in 1936 and that Dr. Frederick W. Parsons, then Commissioner of the Department of Mental Hygiene, took advantage of the opportunity to have insulin shock treatment introduced into the New York Civil State hospitals under the very eyes of its great exponent. Dr. Sakel was invited to give instructions in such therapy to a group of selected physicians from the several state hospitals, and for six weeks, beginning December 8, 1936, such instruction was given daily at the Harlin Valley State Hospital. Despite the fact that the

patients selected for the treatment were all considered to offer a poor prognosis, Dr. John R. Ross, superintendent, reported the outcome as highly satisfactory. Hypoglycemic therapy was then undertaken in other hospitals. Foreseeing the need of a careful record of the results of treatment, a statistical schedule was prepared in the spring of 1937 with the authorization and advice of Dr. Parsons, and the hospitals were requested to forward to the central statistical bureau of the department a schedule for each patient who had completed the course of treatment.

In answer to the third question concerning the physiological theories J. Wortis (1), states that Dr. Sakel (2), gave the following picture as a tentative theory. Insulin shock stimulates metabolism in general and liver function in particular, so that toxins are eliminated. Further that insulin shock, like any other shock revives strong primitive normal response and eliminates recent abnormal ones and that insulin has a specific vagotropic action. That Dr. Sakel pictures schizophrenia as a state in which nerve impulses travel fast and free and fly, so to speak, off the handle. Insulin inhibits and blockades the nerve cell, so that the nerve pathway

patterns like jurymen locked in a room, finally come to order. The seat of action, he believes, is the vegetative centers.

Dr. Wortis believes that schizophrenia may be a symptom of nutritional disturbance in the brain. He has demonstrated that the respiratory quotient of brain tissue is unity--the brain in other words is normally dependent on carbohydrates for nutrition. Lactic acid, glycogen, and sugar are all utilizable, but the mechanism and the intermediaries of brain metabolism are not yet fully known. There is no doubt, that insulin or insulin-like substances are instinctly involved. He states that high lactic acid findings so common in schizophrenia must be ascribed to some local factor which interferes with oxidation. It has been shown that insulin diminishes lactic acid production by promoting conversion of lactic acid into glycogen. Gray matter in contrast to white matter, is not dependent on lactic acid for nutrition. One can only suggest that insulin shock or insulin may directly or indirectly promote carbohydrate utilization.

H. A. Hoffman (4) in a review of pharmacological aspects of insulin shock therapy tells us that Gellhorn

(5) has put forth experimental proof that the anoxia and hypoglycemic syndromes involve the same physiological mechanisms. He attempted to substantiate the anoxia theory of insulin convulsions and, in accordance with the modern ideals to extend it to the preconclusive or hypoglycemic state by the following experiments: (1) By using blood pressure determination as the indication, he has shown that inhalation of low oxygen and the induction of hypoglycemia both gave the same blood pressure response (probably through the action of the pressor reflexes); (2) he showed that animals subjected to partial anoxia by low inhalation were subject to insulin convulsions both at a lower dosage and with greater intensity; (3) he demonstrated that the blood pressure rise resulting from the inhalation of low oxygen was greatly increased during hypoglycemia. He therefore, concluded that: (1) Hypoglycemia acts in the central nervous system in a way similar to that of oxygen deficiency--in both instances, the rate of oxidation is reduced; (2) the sensitivity of the central nervous system to oxygen deficiency is greatly increased in hypoglycemia; and (3) the combination of hypoglycemia, plus oxygen deficiency induced by insulin

and inhalation of a oxygen deficient gas mixture, produces a more effective stimulation of the sympathetic nervous system, measured by blood pressure response, than even the inhalation of pure nitrogen.

Hoffman has further made several physiological studies before, during and after the insulin treatment of acute schizophrenia. Choline esterase determinations were made on blood serum of twenty two schizophrenic patients. The choline esterase level was initially lower than that of the average control. Following insulin treatment the choline esterase level increased significantly but tended in the second week following medication to decrease toward the initial level. However, it should be noted that these changes occurred irrespective of whether the patients recovered or not. Potassium, calcium and phosphorus levels of the blood were determined four times in two weeks preceding and four times in the two weeks following insulin treatment. Postassium and calcium showed no changes following medication. The phosphorus level of ten patients who recovered dropped significantly after insulin treatment to the physiological level. The not recovered patients, however, showed only an insignificant decrease.

By noting greater pulse and blood pressure variabilities in schizophrenic patients who recovered than in those who did not (bradycardia and hypotension) and by noting that these returned to healthy average after insulin, they concluded that prior to treatment there is some degree of adrenosympathetic impairment and that this is largely overcome by treatment in the recovered patients and relatively uneffected in the not recovered patients.

All the blood lipid values (except free cholesterol) that is, phospholipids, total cholesterols, cholesterol esters and total lipids--were initially significantly lower than the values obtained in the normal controls. Following insulin, the levels of all the lipids except free cholesterol were increased significantly, reaching the normal levels in the recovered as well as in the not recovered patients.

Hoffman (4) in discussing the work of Abramson (6) tells us that peripheral vascular responses were studied, during the injections of massive doses of insulin in schizophrenic patients and it was observed that a marked increase in blood flow through the extremities at the height of the hypoglycemic response took place. He suggests that this probably happens in the brain, too. This would be consistent

with the above allusion to the decrease in the oxidative metabolism of the brain in schizophrenic patients and the improvement of the patients with the restoration of normal metabolism.

Parsons (7) reminds us of the truism that numerous patients with mental disease have been improved after severe physical illness; and he feels that the face of death due to serious physical upset associated with insulin hypoglycemia constitutes an important psychological factor in improvement of the schizophrenic. Although this idea finds much corroberation, the more recent literature is in disagreement with this hypothesis.

Bowman (8) has attacked the problem from a study of brain metabolism. The brain metabolizes carbohydrates. After insulin, blood carbohydrates are greatly reduced. Although the brain is put to rest by a lack of carbohydrates, there is an adequate amount of oxygen in the blood. Thus insulin hypoblycemia depresses cerebral metabolism by deminishing the food supply of the brain (blood sugar), and this seems to favor the amelioration of schizophrenia.

Davidson (9) gives us many improtant facts in regards to the reticulo endothelial system and insulin therapy in schizophrenia. He states that the protective

role of the R.E.S. in disease in general is well established. The beneficial influence is due to stimulation of the system, by one or another agent and the abilities of the system to produce blood, to phagocyte, to retain electro-negative colloids and to form antibodies.

Regarding the status of the R.E.S. in schizophrenia, he has shown that we deal in this psychiatric disorder with a hypofunction of the system.

The possible relationship of the R.E.S. to the hypoglycemia which is considered the most important feature in the therapy, as well as upon certain psychometric aspects of the system of defense of the total personality. We must have in mind, however, that besides hypoglycemia there may be other agents instrumental in the cure, such as other dynamics of insulin, as well as psychological factors. As to hypoglycemia we have to be cognizant of the fact that besides the insulin there may be other factors which participate in the process. For instance, excitement and other psychological states are known to produce hypoglycemia. Again it has been shown that hypoglycemia may be due to a conditioned reflex.

Physiologically hypoglycemia manifests itself clinically from drowsiness through a variety of neurological phenomena, to its climax of coma which may or may not be accompanied by convulsions. The dominent feature in a convulsive state is not the convulsion but the loss of consciousness.

Assuming the above facts to be applicable to our cases it becomes necessary to inquire into the physiology of unconsciousness. Burridge (10) gives us an answer to the question. He recognized three kinds of unconsciousness: (1) When the excitation process, which according to him, is rooted in two sources of energy-colloidal aggregation and electrolytes is of too small intensity because of insufficient ionization of the brain. (2) When the excitation process is of unfavorable composition in relation to colloidal aggregation and electrolytes but which remains within the limits of responsiveness of the brain, and (3) which is the case in a fit, when the excitation process is not only of bad composition but also of an intensity greater than the ability of the brain to respond. Burridge shows further that the composition of the excitation process depends upon the synergy of the double nerve

supply. He shows that the vagus decreases the efficiency of the ionic element, while the sympathetic system increases the part of colloidal aggregation. He states further that considering the preconvulsive state is neurovegetative, it seems justifiable to think that loss of consciousness is the essential element in the seizure. If so, we may further agree that at dawning of consciousness the ionic part of the excitation process may be very small. Consequently, it may be relatively easy to expel, in a way pushing out emotional experiences into the unconsciousness. It is possible that repeated expelling from consciousness of emotional experiences together with improvement in resistance due to improvement in the function of the R.E.S. well ultimately prevent the conflict to break through.

E. B. Kietz and S. M. Birnbaum (11) conclude that it is evident the sympathetic-adrenal mechanism is active during insulin shock therapy. Whether such activity is of importance in the treatment can only be determined if it differs in the recovering cases as compared with the refractory ones.

The retention of a fairly high and a constant

level of adrenocortical substance in the blood seems, from their work, to be a characteristic of the recovered schizophrenic who has undergone insulin therapy. That this may indicate an improved ability to maintain homeostasis seems likely.

That autonomic disorders exist in schizophrenia has been suggested by Kietz and Birnbaum. In fact it is stated that in schizophrenia there is a "loss of that permanent coloring of the background of mood which in normal people influences all chance oscellations of the emotions, equalizing and checking them." It is described by wide and sluggish pupils, wide spread vasomotor disorders, poor blood pressure and pulse responses to cold and pain, increased numbers of white cells in the blood, low basal metabolism and sleep disturbances.

Kietz and Birnbaum have quoted Grinker (12) as stating that "the biological data resulting from studies of schizophrenics suggests strongly a deficiency in some central autonomic coordinating process measured clinically in defective homeostasis."

No one can deny McFarland's (13) statement, as quoted by Kietz and Birnbaum, that schizophrenics lack "the free expression of human personality made possible by the autonomic regulation of the internal

constants." The fact that some patients fail to respond to the therapy furthermore may be due to irreversible damage in these cases or to constitutional inadequacies in the autonomic mechanisms. It has been shown that the retinal vascular bed is smaller in patients who do not improve or who deteriorate. They believe moreover that the failure to obtain a stable high blood adreno-cortical value as a result of shock therapy may be another sign of the constitutional or irreversible defect present in the schizophrenic patients who co not react to this therapy.

The failure to achieve stable high adreno-cortical values in cases showing social improvement sufficient to leave the hospital but who retain some schizophrenic characteristics, agrees well with the psychologic findings before and after insulin therapy which show that even though improvement is gained, schizoid reactions may be shown in responses to the Rorschad test at the end of treatment.

That high blood adreno-cortical levels were present in recurred schizophrenics may seem inconsistent with the observations that few signs of sympathetic excitement are present in the normal person. Gellhorn (5) stated that "epinephrine decreases the reflex responses of the sympathetic

system." Therefore, when the level of adrenalin in the blood is at a steadily high level, we might expect fewer signs of sympathetic overactivity. This fits in well with a few unpublished observations they have made in patients with oculogyric crisis--showing that just before the onset of the crisis the patients have very low blood adreno-cortical values although their pupils are widely dilated. They have "hot flashes" and "feel jittery", and their blood pressure rises. That the inhibiting affect of high blood adreno-cortical value may be on the hypothalamic centers is certainly possible and deserves further study.

It would be of great interest to find whether the dilated pupils, relaxed G. I. tract and other sympathetic symptoms found in schizophrenics are accompanied by low adreno-cortical values as these studies suggest.

Ferraro and Jervis (14) believe that although the biochemical approach is likely to offer the conclusive evidence for the explanation of the mechanism of action of insulin in treatment of schizophrenia, there can be little doubt that pathologic investigations may add significant data.

The most significant histologic alterations in

treated schizophrenics may be summarized under the two headings of neuron cells and blood vessels.

(1) Neuron cells--Nissl's method disclosed that the majority of the nerve cells in the cerebral cortex appeared altered. A large variety of changes was observed ranging from chromatolysis and shrinkage to severe colliquation and formation of cellular shadows. Homoginizing alterations and ischemic nerve change were also frequently seen. Lipoid infiltration of the neuron cells was also found in some instances, particularly marked in the Ammon's horm.

There were marked alterations of the normal cytoarchitecture of the cortex. Areas of almost total loss of nerve cells were observed extending at times over a centimeter in length and their distribution was irregular. Areas of relatively intact lamination were observed near areas of marked cellular destruction, the boundaries between the two zones being often abrupt. In all cases dropping out of cortical neurons was observed, either diffusely throughout the six laminae of the cortex or involving more markedly the superficial layers. The glia showed some hyperplastic reaction and ameboid changes

were occasionally present. There was apparently slight increase of microglia cells while the oligoglia showed acute swelling. There was also complete dropping out of the nerve cells of the lamina pyramidalis of the Ammon's horm.

(2) Ferraro and Jervis also noted that the blood vessels showed striking changes. There were areas in which a large number of proliferated small vessels and capillaries were present either in the whole width of the cortex or in some layers of it. High power examination of the altered vessels showed that the vascular walls were considerably thicker than normal, due to proliferation of cellular elements. Both endothelial and adventitial cells appeared enlarged and actively proliferating. The nuclei were swollen and the granuli of chromatin were numerous and darkly stained. Varying phases of karyokenesis were occasionally noted. It was not infrequent to observe pictures which could be interpreted as budding formation of new capillaries. The proliferative changes of the vessel walls resulted frequently in narrowing and eventually in obliteration of the lumen. In the areas of major vascular proliferation the neuron cells had disappeared,

however productive vascular changes were occasionally noted also in areas of relatively well preserved neuron cells.

The mechanism by which these cellular changes are brought about remains a problem for investigation. Such widespread and severe degenerative changes of the neuron cells as seen in numerous sections are commonly regarded as histologic evidence of a toxic action. However it seems preferable to replace the rather vague notion of toxicity by a more clearly defined concept indicating impairment of some specific cellular function brought about by the toxic substance. As far as insulin is concerned, there is much evidence in favor of the opinion that the respiratory activity of the brain cells is depressed, the effects of glucose deficiency on the nervous system being similar to those of oxygen deficiency.

The fourth question as presented in the introduction, I shall answer by the presentation of reports on large case series, case studies with control series, and follow up studies. I shall demonstrate how scientifically the medical profession has established the value of insulin therapy in schizophrenia.

Manfred Sakel (15) in 1937 reviewed the first one hundred (100) cases ever to be treated with insulin, and reported the following results: In recent cases, eighty eight per cent had good or full remissions, and could go back to their former environment. Of these, seventy per cent were full remission. In all other cases, that is all cases of over six months duration, the results varied in direct relation to the duration of the illness. Forty seven per cent of the cases showed good remissions with capacity to work, of which nineteen per cent were full remissions.

Sakel on examining the statistics for spontaneous remissions in schizophrenia in various countries, found that the figures varied between five and twenty per cent. Even compared with the otpimistic figure of thirty per cent, we still have a large balance in favor of the treatment. It was formerly thought that only recent cases would show a satisfactory response to treatment. However later it was realized that in some chronic cases more or less improvement was possible.

Malzberg (3) gives us the following analysis based upon the histories of 1,039 patients with

schizophrenia who were treated with insulin in the several Civil State Hospitals in New York State.

Of the 1,039 patients, 525, or 50.5 per cent were males, and 514, or 49.5 per cent, females. Of the 1,039 patients, 134, or 12.9 per cent, were reported as recovered after the completion of treatment; 282, or 27.1 per cent, were much improved; and 263, or 25.3 per cent, were improved. A total of 679, or 65.4 per cent, thus showed some degree of improvement after treatment with insulin. Three hundred and forty seven patients, or 33.4 per cent, showed no improvement after treatment with insulin. Thirteen patients died during the treatment with insulin. Sex differences occurred as follows: the recovery rates were 13.5 and 12.3 per cent, for males and females, respectively. Combining all degrees of improvement, they found that 69.0 per cent of the males showed some degree of improvement, compared with 61.7 per cent of the females.

Now, the critical point is the comparison of the outcome of treatment among insulin treated patients with that of a corresponding group of patients who had not received such therapy. The

control group consisted of 1,039 first admissions with schizophrenia to the New York Civil State Hospitals, almost all of whom were admitted during the year July 1, 1935 through June 30, 1936. They were able to trace the institutional histories of these patients up to June 30, 1937. The latter were matched with the insulin-treated group, so as to maintain the same total for each hospital, in the same sex proportion and the same distribution of types of schizophrenia. They found that 3.5 per cent of the control group were discharged as recovered, 11.2 per cent as much improved, and 7.4 per cent as improved. Some degree of improvement was therefore shown by 22.1 per cent of the control group, compared with 65.4 per cent of the insulin treated group. In other words, the rate of improvement in the insulin treated group exceeded that in the control group in the ratio of 2.96 to 1, or by 196 per cent. Considering the individual degrees of improvement: the insulin group included 12.9 per cent of recoveries as against only 3.5 per cent in the control group, a difference of 9.4 ± 0.79. The much improved groups included 27.1 and 11.2 per cent, respectively, a difference of 15.9 ± 1.1.

The groups characterized as improved showed a difference of 17.9 ± 1.2 per cent, in favor of the insulin treated group.

Among the 1,039 patients treated with insulin there were 13 deaths, a rate of 12.5 per 1,000 under treatment. Among the control group there were 48 deaths, a rate of 46.2 per 1,000. The latter rate is in excess in the ratio of 3.7 to 1.

Of the 1,029 patients who received insulin treatment, 24, or 2.3 per cent, were of the simple type; 206, or 19.8 per cent, were hebephrenic; 356, or 34.3 per cent, were catatonic; and 448, or 43.1 per cent, belonged to the paranoid type. Disregarding the simple type because of the small frequency, they found percentages of recovery as follows: hebephrenic, 6.3; catatonic, 17.4; and paranoid, 12.7. Combining all degrees of improvement, they found the following percentages: hebephrenic, 52.9; catatonic, 70.0; and paranoid, 66.5. Clearly the catatonic and paranoid types are more responsive to insulin treatment than the hebephrenic. The catatonic type appears to respond somewhat better than the paranoid, though the difference (3.5 ± 2.4 per cent) was hardly significant. Combined degrees of improvement were as follows: hebephrenic, 15.6;

catatonic, 27.3; and paranoid 19.4. Combined ratio of improvement in the insulin-treated group exceeded those in the control series in the following ratios: hebephrenic, 3.4 to 1; catatonic, 2.6 to 1; paranoid, 3.4 to 1.

In considering the relation of age at beginning of treatment to outcome of treatment they found in both groups of patients the ratio of recovery was relatively high at the younger ages, and showed a tendency to decline with advancing age. This was more marked, however, in the control group. In the insulin-treated group, the combined rates of improvement, which were 67.0 per cent at 15 to 19 years and 68.1 per cent at 20 to 24 years, declined to 62.7 per cent at 35 to 39 years and 63.2 per cent at 40 to 44 years. At corresponding ages in the control group the percentages were 32.8, 28.7, 15.1 and 16.2, respectively. It appears that the age at beginning of treatment is of less significance under insulin treatment than among untreated cases.

More significant than age at beginning of treatment is the duration of the disease before treatment. Among the insulin treated patients there was a progressive decrease in the recovery rate from 42.9 per cent when the disease was less than 1 month old,

and 33.3 per cent when it was of 1 to 3 months duration, to 3.4 per cent in the group with a duration of 11 to 14 years. The downward trend is clearly evident. The combined rate of improvement was 85.8 per cent among those with a duration of 1 to 3 months. The rate of improvement declined steadily with the increasing duration of the disease prior to treatment. The control group showed a similarly declining trend in rate of improvement with a progressive increase in the duration of the disease prior to treatment. Rates of improvement were in excess in the insulin treated group over the corresponding rates in the untreated group in ratios of approximately 3 to 1.

Correlation of outcome of treatment with the duration of insulin therapy shows the recovery rate with a steady decrease as the period devoted to treatment increased. Those receiving treatment for less than a month showed a recovery rate of almost 25 per cent. As the period of treatment increased to over two months the recovery rate fell rapidly to less than 10 per cent. Combining all grades of improvement, they found, on the whole, a similar tendency. Those who had

been treated for sixty days or more showed an improvement rate of approximately 60 per cent, whereas those with shorter periods of treatment had an improvement rate of 70 per cent.

Correlation of outcome of insulin treatment with the number of injections showed the recovery rate increased from 15.0 per cent among those who had received from 10 injections, to 25.5 per cent among those who had received from 10 to 19 injections. In the remaining groups there was clearly a downward trend in the percentage of recoveries as the number of injections increased. The same result was shown when all degrees of improvement were combined.

The conclusion from the above data shows there can be no doubt as to the immediate efficacy of the treatment of schizophrenia. Insulin shock therapy raised the recovery rate from approximately 4 per cent in untreated cases to 13 per cent in treated cases. It brought about a marked improvement in an additional 27 per cent, compared with only 11 per cent in the untreated group. Combining all degrees of improvement, they found that 65 per cent showed some degree of improvement after treatment with

insulin, compared to only 22 per cent in the untreated group. Improvement rates were lowest among the hebephrenics. They were highest in the simple type. Rates of improvement among catatonics and paranoids were significantly higher than those of the hebephrenics. There is a striking correlation between the rate of improvement and the duration of the disease before the beginning of treatment. The earlier in the course of the disease that the patient is submitted to treatment, the better is the prospect of recovery and rehabilitation.

R. A. Savitt (16) in 1938 gave some comparisons between insulin treated and non insulin treated cases of schizophrenia. Contrasting a group of 195 patients diagnosed schizophrenia, who were not treated with insulin, against a group of 45 insulin treated cases, the group was broken up according to the duration of illness as accurately as could be determined. There were 82 patients in this group who were ill about six months, 15 about one year, 25 about two years, and 73 ill for more than two years. Fifty eight of this number had been paroled. Grouped according to duration of illness, the paroles were as follows: 27 from the six months group, 4 from the one year group, 10 from the two year group, and 17 from the

category of chronic cases. Expressed in percentages they are, respectively, 32.7 per cent, 26.6 per cent, 40 per cent and 23.2 per cent. Taking the entire 195 cases as a whole, the percentage of paroled amounted to 29.7 per cent.

In the insulin treated cases of 45 patients, 27 of these showed enough improvement to warrant parole, thus making a parole percentage of 60. According to the duration of illness these 45 may be broken up as follows: 14 ill six months, 8 one year, 9 two years, 14 over two years. Expressed in percentage of improvement, they are, respectively, 78.5 per cent from the six month group, 37.5 per cent from the one year group, 66.6 per cent from the two year group, and 50 per cent from the chronic group. If we compare these figures with those obtained in the control group, we find that in each category of the treated individuals there is a noticeable higher percentage of improvement than in the controls.

Comparison of the Percentage of Paroles In The Noninsulin Treated and Insulin Treated Group, According to Duration of Illness

	Six Months Per Cent	One Year Per Cent	Two Years Per Cent	Over Two Years
Noninsulin treated	32.7	26.6	40	23.2
Insulin treated	78.5	37.5	66.6	50

Of the patients paroled the degree of home adjustment was variable. Five of the 27 paroled failed to adjust and were brought back, thus making 18.5 per cent returned.

In comparing the group of 129 paroled noninsulin treated cases in the identical 8 month period during which they observed the home adjustment of the treated group, they found that 29 were returned to the hospital, a return rate of 22.4 per cent. This was about 4 per cent higher than in the treated group, but it may be explained by the fact that a number of the 129 paroles were really poor parole material and were sent home for custodial care.

In conclusion it can be said that in the above group of patients hypoglycemia shock treatment seemed to offer a greater chance for improvement in schizophrenia than do routine treatment measures. The period of illness and hospitalization is cut short by this treatment, when it is effective. The hypoglycemic therapy does not influence the

parole adjustment of improved patients. Relapses occur about as frequently in the treated group as in the nontreated category. Also that hypoglycemic treatment when effective, is only one step in the process of rehabilitating the schizophrenic. Considerable attention must be directed to psychological and environmental factors.

M. Muller (17) in 1938 collected the following figures from the different clinics and institutions in Switzerland. In these studies there was a total of 495 cases, that had been derived from 22 different institutions.

Patients in which the duration of the illness was less than six months, the percentage of remissions was 59.1 per cent. If the improved cases are included, there is actually obtained a remission rate as high as 83 per cent.

Patients in which the duration of illness was from six months to one year, the percentage of remissions, 52 per cent, was not far behind that of the first group. Susceptability to the curative effect of the insulin treatment reached the peaks in cases of one year's duration of illness.

A compelation of the varied periods of treat-

ment of the two hundred cases listed under Social Remission and Full Remission shows a range from 2 to 161 insulin days. The average is 52 days, and the mean, 54.5 days. The average length of treatment for the recent cases is 50.5 days, and that for older ones (more than six months) is 61.7 days.

When the duration of the treatment was 60 days and over, patients who were ill less than six months gave a remission rate of 44.2 per cent; those who were ill over six months had a remission rate of 68 per cent.

Treatment of insufficient duration does not allow a judgement as to whether or not favorable results might be obtained with a more prolonged treatment. If they eliminate, therefore, all uneffected cases with insufficient length of treatment (less than sixty days) one remission rate for recent cases rises from 59.1 per cent to 65.3 per cent.

Here again Sakels insulin therapy for schizophrenia has stood another practical test.

Duration of Illness = E.D.[3]	No. of cases	SR[1] + FR[2]		Cases influenced by the treatment		Cases not influenced by the treatment	
		Cases	%	Cases	%	Cases	%
Not longer than or up to 6 mos.	210	124	59.1	174	82.9	36	17.1
½ to 1 year	73	38	52.1	48	65.8	25	34.3
Not longer than or up to 1 year	283	162	57.2	222	78.4	61	21.6
1 to 1½ years	39	13	33.3	25	64.1	14	----
1½ to 2 years	49	11	22.4	29	59.2	20	----
1 to 2 years	88	24	27.3	54	61.4	34	38.6
More than 2 years	124	14	11.3	54	43.5	70	56.5
Total	495	200	40.4	330	66.7	165	33.3

[1]SR = social remission
[2]FR = full "

	Remission figures	
	Recent cases	Old cases
60 days	13.8%	21 %
70 days	11.0%	16 %
80 days	6.2%	10.4%
90 days	5.6%	10.4%
100 days	6.4%	9 %
More than 110 days	1.2%	1.2%
	44.2%	68.0%

After Elimination of Cases With Insufficient Duration of Treatment (Less than 60 Days).

Duration of Illness	After elimination cases unaffected with the insufficient treatment			After elimination of unaffected and improved cases with the insufficient treatment		
	Total No.	SR + FR cases	%	Total No.	SR + FR cases	%
Up to 6 mos.	190	124	65.3	168	124	73.8
From ½ to 1 yr.	62	38	61.3	60	38	63.3
Up to 1 yr.	252	162	64.3	228	162	71.1
From 1 to 2 yrs.	76	24	31.6	62	24	38.7
More than 2 yrs.	99	14	14.1	91	14	15.4
Total	427	200	46.8	381	200	52.5

Results Obtained in Cases With Previous Psychotic Attacks (Only cases with duration of illness up to 1 yr.)

No. of attacks	No. of cases (total)	FR + SR		Influenced		Uninfluenced	
		No. of cases	%	No. of cases	%	No. of cases	%
First attack	266	133	59.7	162	78.6	44	21.4
Subsequent attacks	77	40	51.9	59	76.6	18	23.4

Relapses

Duration of illness	No. of relapses in					
	FR + SR		Improved cases		Total	
Up to 6 months (210)	8 (124)	6.4%	4 (50)	8.0%	12 (174)	6.8%
From ½ to 1 year (73)	3 (38)		1 (10)		4 (48)	8.3%
More than 1 year (212)	2 (38)		12 (68)		14 (106)	13.1%

Steinberg, Hulbrunn, Liebert (18) in 1939 reviewed a group of 120 cases of schizophrenic patients treated with insulin; of these 35 had been ill for six months or less, and of this number 29 or 83 per cent recovered; 2 or 6 per cent made a social remission. This gives a total remission rate of 89 per cent for this group.

In the group of patients ill from seven to eighteen months 37 patients were treated with insulin, of these 19 or 51 per cent recovered; 5 or 13 per cent ma e a social remission, giving a total remission rate of 64 per cent for this group. Thus, of 72 patients, ill not over eighteen months, 48 or 67 per cent recovered and 7 or 10 per cent showed a social remission a total of 77 per cent.

In patients ill from 19 months to five years, there were 48 patients treated; only 1 or 2 per cent recovered; 7 or 14 per cent made a social remission.

Three hundred cases of schizophrenia were treated with metrazol. Of these 19 patients were ill less than six months; 8 or 42 per cent made a complete remission; 6 or 31 per cent made a social remission--a total of 73 per cent for this group.

In the group of patients ill from 7 - 18 months

there were 46 patients treated with metrazol; of these 10 or 22 per cent made a complete remission; 7 or 15 per cent showed a social remission, giving a total of 37 per cent.

Combining the groups we have a total of 65 patients, of whom 18 or 27 per cent recovered and 13 or 20 per cent made a social remission, a total rate of 47 per cent.

In the group of metrazol treated patients ill from 19 months to 5 years there were 146 cases; of these 11 or 7.6 per cent made a complete remission; 6 or 4.1 per cent made a social remission, together giving a total of 17 patients and a 11.7 per cent remission rate.

This statistical comparison shows a definite superiority of insulin treatment so far as complete remissions are concerned, while the social remissions are more numerous with metrazol treatment.

In patients ill longer than 19 months the recovery rate is greater with metrazol than with insulin. The complete remission rate in insulin treatment is 2 per cent, while with metrazol treatment it is 7.6 per cent.

A. Coyni (19) reviewed 57 cases treated in

St. Elizabeth's hospital, Washington, D. C. from September 13, 1937 to May 27, 1938. All cases were followed for six months to a year after termination of treatment. The following results were noted.

RESULTS OF THERAPY AT END OF TREATMENT

Sex and color	Unimproved	Improved	Recovered	Out Rolls
White females	8	11	2	4
White males	7	15	3	7
Negro males	3	3	1	1
Negro females	2		2	2
Totals	20 (36%)	29 (50%)	8 (14%)	14 (24.5%)

RESULTS OF THERAPY AT END OF 6-12 MONTHS

Sex and color	Unimproved	Improved	Recovered	Out Rolls
White females	14	3	4	5
White males	16	5	4	7
Negro males	4	2	1	1
Negro females	2		2	2
Totals	36 (63%)	10 (17%)	11 (19%)	15 (26%)

It was also seen that all recovered cases showed a duration of illness of less than two years and the 45 per cent had been ill only six months or less. The percentage of improved cases followed the same curve and there was no sustained improvement noted in those patients ill over five years.

In general it might be said that the patients usually began to improve during the third and fourth weeks of treatment, and a patient who remained unchanged after 40-50 days of intensive therapy did not show much improvement later, although there were exceptional cases.

There was no definite relationship found between the convulsive seizures and the therapeutic results obtained. Of the 57 patients treated 19 had convulsions and of these 19, 7, or 33 per cent, improved or recovered. The remaining 67 per cent were unimproved.

E. D. Bond (20) in 1941, reviewed the results of 125 insulin treated and 153 consecutive control cases from the Pennsylvania Hospital, Philadelphia, Pennsylvania.

In terms of duration before treatment, 58 of the patients had been ill less than 18 months before treatment, 46 had been ill 18 months or more, while in 21 patients either different attacks or conflicting statements made it unwise to set a definite duration.

Cases of less than 18 months duration had recovery much improved percentages of 67 per cent on

discharge, 54 per cent in one year and in two years.

It was curious that cases with a history of attacks and others whose duration was uncertain had a 60 per cent remission rate on discharge but had all relapsed by the end of the second year.

Cases of over 18 months duration had recovered much improved percentages of 30 per cent on discharge and 14½ per cent after one and two years.

Of 156 consecutive control cases they showed a recovered much improved rate at discharge of 3.8 per cent. This rose to 16 per cent by the end of the first year and remissions at that level for the second and also for the fifth years.

In these control cases there were only a slight difference between cases with a duration under and over 18 months in the recovery rate.

The surprise was a comparison of the treated and control cases lying in the difference on discharge between 57 per cent and 4 per cent, at the end of one year the difference between 35 per cent and 16 per cent and at the end of two years between 29 per cent and 16 per cent. As the control cases kept on at 16 per cent for the next three years, it is possible that the downward trend of insulin shock

cases would continue until it met the control figure.

E. D. Bond and T. D. Rivers (21) related that of all comparisons inside of the Pennsylvania Hospital where standards have not varied as far as senior physicians can judge, they found the recovery much improved rate in schizophrenia before the advent of any shock therapy was below 10 per cent. However with the advent of insulin therapy they presented the following results on 188 consecutive cases of schizophrenia.

INSULIN SHOCK RECOVERY RATES

Of 188 cases	55%	were	recovered	or	much	improved	at	the end of treatment
Of 159 cases	42%	"	"	"	"	"	"	"
Of 141 cases	42%	"	"	"	"	"	"	"
Of 108 cases	36%	"	"	"	"	"	"	"
Of 71 cases	31%	"	"	"	"	"	"	"
Of 43 cases	37%	"	"	"	"	"	"	"

CONDITION LAST REPORTED FOR EACH YEAR'S CASES

Year	Cases Which Finished Treatment	Per Cent Recovered and much Improved
1942	16	44
1941	36	44
1940	29	55
1939	25	52
1938	21	24
1937	61	30
	188	

The results of insulin shock therapy, with an immediate recovery rate of 55 per cent, show a tnedency to level off at about 33 per cent in the second, third, and fourth years. With an immediate recovery rate five times that of control cases in the Pennsylvania Hospital and with a long distance recovery rate twice that of controls, the therapy seems justified.

Weinberg and Goldstein (22) in 1942 gave the following results with insulin therapy on those patients failing to improve with metrazol therapy. All failures on metrazol were given a three month rest period, following which they underwent a physical examination and were placed on insulin

treatment.

Out of one hundred patients treated, sixteen were considered to have recovered.

Sixteen patients responded to insulin therapy with a social recovery.

Under the institutionally improved group, of which there were thirty seven, many of these were taken off violent wards and most of them were placed in useful industrial groups.

Thirty patients failed to respond to therapy altogether. Thirty two patients or 32.22 per cent showed definite good improvement; thirty seven patients or 37.37 per cent showed some improvement, while thirty or 30 per cent showed no improvement.

Eleven patients who were placed on insulin therapy within six months from time of their onset showed the following results: 9 or 81.81% resulted in complete recovery, 2 or 18.18% in social recovery. Sixteen patients who were placed on insulin within the first year of illness, resulted in the following: 4 or 25% recovered, 4 or 25% recovered socially, 7 or 43.75% were institutionally improved and 1 or 6.25% were unimproved. Out of the eight patients who were placed on therapy within their

first one half years of their psychosis, one or 12.5% resulted in social recovery, 5 or 62.5% institutionally improved and 2 or 25% were unimproved. Sixty four patients treated with insulin who were ill for a period longer than one and one half years of this group, only 3 or 4.68% recovered, 9 or 14.06% were socially recovered, 25 or 39.06% showed institutional improvement and 27 or 42.18% were unchanged by the therapy.

One can conclude that insulin undeniably has its value in the treatment of psychosis. Also that insulin therapy is indicated in most of the early cases even where other chemotherapeutic agents have failed to alleviate the symptomatology.

E. D. Bond and T. D. Rivers (23) reported the following after seven years of insulin therapy, in the Pennsylvania Hospital.

It was, of course, difficult to make comparisons between different series of cases, but it would appear that their previous rate of recovery before shock treatment was instituted, varied from 10 to 20 per cent. In order to accumulate a new control group of 100 consecutive cases without selection and treated prior to the introduction of shock

therapy, they reviewed their records, starting at 1926, and took in order through that and preceding years all cases which had entered the hospital and were diagnosed by the same staff as schizophrenia. Of these 100 cases, which were followed for 5 to 7 years, 16 were recovered or much improved at the termination of their hospital stay, 16 were recovered or much improved at the end of 5 years, and 14 were reported well at the end of a 6 to 7 year follow up. Of these 11 steadily maintained recovery from the close of hospital treatment to the close of the follow up; in others the condition changed from time to time.

By insulin therapy they have treated a total of 251 schizophrenics. Of this number 138, or 54 per cent, were recovered or much improved at the end of treatment. They have been able to follow up 49 of these cases for 5 years; of these 22, or 41 per cent, maintained their status. In comparison with this insulin treated group, the 100 control cases not under shock treatment showed a 16 per cent recovery rate at the end of 5 years.

A comparative study of cases whose duration of obvious illness was five or more years before

admission. For the insulin group the terms of illness in such long standing cases were as follows: 9 had been ill for 5 years, 10 for 6 to 8 years, 11 for 9 to 16 years, and 3 young patients had been ill all their lives. In seven of these chronic cases there was recovery or great improvement at the end of treatment but only two of these held their gains. The terms of duration of obvious illness before hospital admission in the control cases were as follows: 2 had been ill for five years, 5 had been ill for 6 to 8 years, 2 for 9 to 12 years, while in 2 cases the onset might be placed either at 2 or at 10 years before admission. Of these control cases only one showed favorable response to hospital treatment and the gain was not held.

In all cases duration of illness of 5 years or more made for a poor outcome.

Of the 138 patients who initially were recovered or much improved under shock treatment--

88 were recovered or much improved when last reported

25 relapsed and remained relapsed

3 relapsed and then improved

1 relapsed and then recovered

5 lost part of their gains

16 demonstrated many irregularities of progress

Of the 49 insulin treated cases that could be followed for 5 years, there were two recoveries which occurred long after insulin treatment was discontinued, and four patients were unable to hold their recovered state during the sixth year of the follow up.

The insulin treated patients enjoyed 251 years of health out of the possible 564 years comprising the collective follow up periods. Out of approximately the same number of years, 551, which were amassed in the follow up of the control cases, only 78 years of health were registered. This difference was attributable to the fact that a significantly larger percentage of insulin patients are brought to health as an immediate result of shock treatment. By the same token, the larger percentage of subsequent relapses must in part be a function of the larger absolute number of cases for whom some period of health has won.

J. W. Taylor (24) criticises the results of shock therapy in that the return rate of patients

released from mental hospitals is high.

From the spring of 1937 until June 30, 1939, 214 schizophrenics completed a course of shock therapy. Of these 153 or 71.5 per cent were released. On June 30, 1944 of the 153 released, 125, or 81.7 per cent, were out of the hospital. Of this 81.7 per cent, 105, or 68.6 per cent had not returned; 20 or 13.1 per cent had returned and were released following further shock treatment; 28, or 18.3 per cent, returned to the hospital and to date are still in residence there.

Of the 20 patients who returned and went out again, 16 had one return. Four patients had two returns, remaining out before the first return for periods of eight months, one year, two years and three years; and before the second return, one year, two years, one year, and one year, respectively. Following the second release, they had been out for periods of one year, one year, three years, and two years, respectively.

The 28 patients who returned and are still in the hospital showed that eight were out less than six months, four between six months and one year, six from one to two years, six from two to three

years, and four over three years.

Unquestionably the environment is the principal etiological factor in the return of many of these patients.

A higher percentage of schizophrenics can be released to take their place in the community and remain in an improved or recovered state by the use of shock treatment than can be expected from any other method of treatment at this time.

J. McConnell (25) reports on two years experience with female schizophrenics at St. Ebba's Hospital and presents the following results.

Number of patients completed treatment	86
Number of patients discharged	76
Discharge rate	approx. 88%

	Well	Relapsed	Not traced
Discharged under three months	7	1	0
Discharged over three months and under one year	17	7	0
Discharged over 1 year and under 2 years	28	1	0
Discharged over 2 years and under 3 years	14	0	1

The average length of stay in the hospital after starting treatment was approximately 17 weeks. The

average total stay from admission to discharge was approximately 24 weeks.

Comparable cases admitted to this hospital in 1939 and untreated are as follows:

52 cases; 25 discharged--approximately 48 per cent.

Length of hospitalization--36 weeks.

Of the 25 discharged, 4 are known to be in the hospital again.

Most of the cases treated were those of acute onset, or of a short history and had a relatively better prognosis and quicker recovery than those with a history of previous attack or long onset.

Number of cases under a year and first attack	61; discharged 54; relapsed 3.
Average length of hospitalization after starting treatment.	15.5 weeks.
Average total hospitalization.	21 weeks.
Number of cases over a year, or with previous attack.	25; discharged 22; relapsed 6.
Average length of hospitalization after starting treatment.	22 weeks.
Average total hospitalization.	32 weeks.

Relapses are most likely to occur with the first year.

Those needing lower doses of insulin have a slightly better prognosis but the chief thing is to induce a satisfactory coma.

Number over 120 units, 29; discharged 23; approx. 79%.

Number under 120 units, 57; discharged 53; approx. 93%.

A comparison of results of treated and untreated cases at this hospital showed a recovery rate of 40 per cent higher in treated cases, with a reduction in hospitalization of at least 12 weeks; moreover the relapse rate was lower in treated cases--12 per cent, as against 16 per cent untreated.

R. K. Fruedenberg (26) reports the following results in 112 schizophrenics treated during the past ten years at Moorcroft House. The results were assessed two months after the termination of treatment. Patients relapsing during that period were regarded as unimproved. Amongst the cases with a duration of illness under one year 80.1 per cent were able to leave. Of the patients ill from one to three years 53.6 per cent were fit to return to the community. Where the illness had lasted more than three years only 28.6 per cent could be discharged.

Thirty four of the patients able to leave the hospital have been followed up. The follow up results confirmed those of Chapius and Georgi (27) who found that total recoveries were maintained better than social recoveries and that most relapses occurred within the first three years after discharge.

The follow up revealed the 18 patients who had shown no response to insulin had a subsequent leucotomy performed. Of these 16 were hospital invalids at the end of insulin treatment, 1 was a social defect and 1 a family invalid and both relapsed. After leucotomy, 2, both paranoids, made a total recovery. They had received a full course of 50 comas combined with E.C.T. Two were discharged as social recoveries and two as social defects. Three became invalids. Another five were very much easier to handle inside the hospital and the rest were unimproved.

Amongst their cases total recoveries plus social recoveries amounted to 56 per cent at the end of insulin treatment and 46.4 per cent at the time of the follow up as compared to 34.5 per cent in the control group; 32.1 percent became hospital

invalids in the insulin treated material and 41 per cent in the control group. This is further evidence that insulin treatment, if properly carried out, increases the number and quality of recoveries, assuming the diagnostic criteria of the insulin treated and control group can be considered equal, and the noninsulin treated patients really represent the optimal material for spontaneous recoveries. Insulin is certainly not a panacea for all cases of schizophrenia, and results over a long period are not yet very satisfactory. But so far nothing superior has been evolved, and until better methods are available it should be more generally used.

In answer to the fifth question as presented in the introduction, I find that there has been demonstrated many complications as the result of insulin therapy in the treatment of schizophrenia. I find of particular interest that the complications may be of many different varieties and involving almost any system of the human body.

O. J. McKendrie (28) presented an interesting paper in which he describes the complications that occur preceding coma; during coma; and following coma.

Complications preceding coma--he found only two or three occurring under this heading. The first was explainable on an anaphylactic basis. This could be shown by urticaria or an unusually severe hypoglycemic reaction from which they were revived with difficulty. The second was a convulsive seizure which may occur within an hour after insulin had been injected. The third was the so called "hunger row" wherein the patient vigorously demanded food because of extreme hunger.

Complications during coma--further subdivided as follows: Respiratory: Stertorous breathing due either to an unfavorable position of the tongue or head and sometimes tonicity of the throat musculature. Pulmonary edema may develop in an alarming manner. Laryngeal spasm occasionally occurs and requires termination of the hypoglycemic state. Cheyne-Stokes respiration or even cessation of breathing in the deep comas or following convulsion is not uncommon. Bronchospastic respiration was also encountered as well as irregularities in the respiratory rate and depth. Excessive cyanosis may be due to embarrassed respiration and is an indication for termination.

Cardiovascular--Cardiovascular signs may fluctuate in a most inconsistant manner and bradycardia is of frequent occurrence. Pallor is often a symptom of failing cardiac function. Auricular fibrillation has been experienced by patients in some clinics and extra systoles or dropped beats are not uncommon. Acute cardiac dilatation is prone to occur during the coma stage of hypoglycemia.

Gastrointestinal--Vomiting, a most undesirable gastrointestinal complication because of the danger of aspiration, can be controlled in some cases by the use of atropine and occurs less frequently if breakfast is omitted. Eructations usually are transient and cause no particular difficulty. The appearance of bile in its various forms and other gastrointestinal contents coming from the gavage tubes is of no serious importance.

Central nervous system--Fortunately many of the complications under this heading are only transient, lasting from a few minutes to a few days, Among those lasting for the shortest period of time are hypothermia, hyperthermia, convulsions which may be indicative of cerebral pathology if they occur in late stages of coma, aphasia, strabismus, ciplopia, monoplegea, paresis of the lower extremities and facial

weakness. Those lasting for a longer period of time or causing a fatal termination are: the prolonged coma which may be defined as a state of unconsciousness associated with hypoglycemia induced by the injection of insulin which fails to disappear when carbohydrate is administered intravenously in the usual amounts necessary to awaken the average patient, and possible conditions associated with the prolonged coma, such as cerebral edema, cerebral and meningeal hyperemia.
Muscular--Tonic generalized muscular spasm is undesirable because it embarrasses the cardiorespiratory system and exhausts the patient. Muscular strain sometimes occurs during a convulsion.
Miscellaneous--Severe clonic movements of the extremities develop during which the latter may strike the bed frame, causing contusions. The prevention of tongue biting should receive proper attention and the patient's bed must be properly placed so that he will not come in contact with steam pipes or radiators. Care should be exercised that there be no foreign bodies in the mouth preceding coma.

To the miscellaneous group may be added complica-

tions which are revealed at autopsy. Bryan (29) has reported liver atrophy and degeneration about the central veins on a woman who died several months after her treatment had been discontinued. The Vienna series of cases showed among other things acute pancreatic necrosis, dilatation of the heart, cerebral and meningeal hyperemia, lobar and lobular pneumonia, cerebral edema, coronary sclerosis and thrombosis.

Complications following coma--Perhaps the most common complication under this heading is the relapse which occurs anywhere from a few minutes to several hours following termination of the hypoglycemic state. Some patients will complain of abdominal cramps. In many instances constipation is experienced. Convulsions which fail to disappear with the administration of glucose have been known to occur several hours after termination, ushering in a relapse. Cyanosis with abdominal rigidity developing in the afternoon has been reported and muscular cramps or headaches occasionally annoy patients for several hours. Glucose injected outside the vein may cause considerable swelling and discomfort. Lung abscess and aspiration pneumonia

are not uncommon, but their incidence can be reduced to a minimum by constant and careful supervision. The urine will occasionally show a few red blood cells, finely granular or hyaline casts, a slight trace of albumen or some sugar which has been excreted through the kidneys. Perspiration of a profuse nature occurs when no insulin has been administered.

D. Lester (30) reports the following in a paper on prolonged coma following shock, that coma resulting from severe and prolonged hypoglycemia is ordinarily terminable rapidly by either oral or intravenous administration of a sugar solution.

Occasionally following the administration of glucose (or other sugars) patients may fail to regain consciousness in the ordinary short period of time and the coma may even deepen or death ensue.

Prolonged coma is easily recognized. After the ordinary morning of hypoglycemia and coma or after a hypoglycemia which was marked by unusual reactions on the part of the patient (such as an erythematous rash, severe motor phenomena, respiratory disturbance, cardio vascular failure or a very deep, quiet coma) the administration of the

initial glucose is not followed by the usual return to consciousness. Instead the patient continues in coma.

If unusual reactions have not occurred before the initial glucose administration they usually appear within an hour or two thereafter, and consist usually of fever, diarrhea, vomiting, respiratory disturbances either in the form of "asthmatic type" of dyspnea, apnea, for long periods with resulting cyanosis, or irregular breathing of Cheyne-Stokes type, cardiovascular disturbances, such as weak rapid pulse with or without irregularities, a fall in blood pressure to surgical shock levels, extreme restlessness or deep quiet coma. Gradually failing respiratory or cardiac action may terminate the patients life.

If prolonged coma ends in recovery, this recovery is not sudden as is the recovery from the ordinary hypoglycemia coma but very gradual with the recovery of first one and then another nervous system function. Even after the acute symptoms have passed and the patient has apparently recovered from the coma itself a clouded mental state of the organic type may persist for as long as two or

three weeks.

Of the 25 instances of prolonged coma reported in one study four ended fatally. This suffests that prolonged coma has a mortality rate of 16 per cent while the death rate due to this complication in the total insulin therapys reported is 0.33 per cent. If you assume that 40 shocks per patient is the average extent of an insulin therapy, then this study would represent 46,920 shocks and one may then expect prolonged coma to ensue once in every 1,877 instances of coma. No signigicant conclusions have been drawn from a study of the age, sex, type of illness, or duration of illness of these patients.

The most rational procedure of treatment appears to be to administer intravenous glucose frequently enough to maintain the blood sugar at normal to slightly above normal together with vitamin B_1 by the same route. Other medications will depend upon the predominant symptoms at the time. The extreme restless state requires fairly heavy sedation--to aid the heart digitalis, coramine or caffeine--to stimulate failing respiration, lobeline, metrazol and caffeine. If due to hyperventilation an alkalosis develops, particularly

when associated with tetany, which should be treated with carbon dioxide inhalations. If the coma is prolonged for days suitable nourishment must be given by tube.

There is no agreement as to whether or not prolonged hypoglycemia produces definite demonstrable nervous tissue damage. However it is certain that death will result if hypoglycemia is maintained at a low enough level for a long enough time. From this fact and from the clinical neurologic signs it must be assumed that hypoglycemia impairs the normal function of the nervous tissue as well as other tissues, and that if maintained long enough this disturbance of function is irreversible. That is, death ensues.

There are a degree and duration of hypoglycemia, undoubtedly varying somewhat for each individual, at which the reversible changes in nervous tissue function becomes irreversible. There is a borderline state between the two and the length of time a patient may survive in this state depends on the individual constitution.

Prolonged coma is more apt to occur: (1) When the depth of ordinary coma is profound, (2) the longer the duration of hypoglycemia and/or coma.

(3) When any hypersensitivity to insulin exists. (4) When a deficiency of tissue essentials such as Vitamin B exists. (5) When dosage of insulin is increased too rapidly. (6) Certain number of patients possess a constitution which is unable to stand with average impunity a prolonged period of hypoglycemia.

F. Klein and J. A. Ligterink (31), in an article on insulin and cerebral damage, found that hypoglycemia manifests itself chiefly by symptoms due to disturbances of the autonomic and central nervous system. Given susceptibility of the central nervous system to insulin, it is surprising that fatal damage of the central nervous system so seldom occurs in sufferers from diabetes treated with insulin.

The insulin shock therapy of Sakel has led to the observation of all kinds of cerebral complications. There are numerous cases in which consciousness does not return as soon as expected.

A case history on a male patient, age 25 years was given as follows: In April 1938 insulin shock treatment was started. On the twenty fifth day of treatment, after 90 units had been administered, the

patient did not recover consciousness after oral administration of dextrose. Neither intravenous administration of dextrose nor injection of epinephrine hydrochloride gave a better result, although the level of the blood sugar was raised to 220 mg. per hundred cubic centimeters. Lumbar puncture did not produce improvement either.

The next day, May 26, the condition remained the same.

On May 27th the comatose state was a little less profound, there was a reaction on pain stimulation.

On May 29th ptosis of the left eye appeared, also strabismus and somnolence. Clinically there was a great resemblance to the syndrome of severe encephalitis.

On May 31st the more consciousness returned the greater his restlessness became. The condition showed typical rolling movements along the body axes accompanied by digging of the head into the pillows and swinging movements of the limbs. There was continuous salivation. The patient obviously could not pronounce a single word, but uttered some unintelligible sounds.

On June 8th the patient had fits of crying and

many symptoms of Parkinson's syndrome. Forearms were rigidly flexed and head bent, alternated by ballistic and rolling movements of the body. Salivation continued, ptosis disappeared .

On June 20th the patient pronounced his name and was able to tell time by his watch. There remained persistent incontinence of feces and urine.

On June 23rd the patient had an ataxic gait; he could not write or read, showed paraphasia, motor and sensory aphasia and slept much.

On June 28th the patient had echolalia, no notion of time, and place and disturbed memory. Polyphagia developed. He ate whatever was put before him.

On July 7th psychologic examination revealed motor and sensory aphasia, agraphia, tactile agnosia, ataxia and extreme amnesia. High psychic functions had disappeared.

On August 12th he had persistent alexia; his memory improved and the aphasia disappeared. Motor functions were slightly disturbed. Behavior was infantile with faulty speech and permanent masturbation.

On September 17th, the intellectual level,

approximately ascertained, was that of a child of 8 years of age.

On April 16, 1939 the greater part of the motor functions had been recovered. Alexia had disappeared. The intellectual functions appeared to have for the most part recovered. From February to September 1938 there was total amnesia.

W. Furst (32) in reporting on a death due to pulmonary gangrene due to insulin shock presented the following facts.

The patient was a white male, age 27 years. Physical examination, laboratory studies, roentgen and electro cardiogram studies were normal.

On October 28, 1939 insulin treatment was begun.

On November 16, 1939 the patient began coughing without expectoration but had no other complaints. T.P.R. were normal. Physical examination of heart and lungs were negative at this time.

On November 17, 1939 he received his fourteenth treatment. Shortly after withdrawal of a nasal gavage tube the patient began coughing. The coughing became alarming and production of massive amounts of frothy fluid followed. Physical examination

revealed extreme cyanosis of the face and extremities. Pupils were widely dilated but responsive to light. The respiratory rate was 65/min. Marked dyspnea was present. The percussion note was impaired over the entire chest. Auscultation confirmed the presence of pulmonary edema.

Treatment proved of little avail and the patient succumbed November 22, 1939. At autopsy, incision of the right pleural cavity released foul smelling gas suggestive of hydrogen sulfide. There was a marked yellow fibrinous pleural reaction with about 500 cc of purulent fluid in the pleural cavity. The entire right lung had undergone a compression degeneration and the lower lobe presented marked bronchiectasis with multiple areas of beginning abscess formation and gangrene. Other organs including the brain were essentially negative.

In explaining the pathogenesis of the pulmonary gangrene in this patient, the presence of a subclinical bronchiectasis must be considered as locus monoris resistentiae. Aspiration of infected material from the mouth with plugging of a small peripheral bronchus probably occurred. A fulminating infection of an anaerobic type peripheral to

the block probably resulted in involvement of the interstitial tissue.

Nielsen (33) observed three cases of acute pulmonary edema during insulin shock therapy but gave no explanation as to the possible pathogenesis. Parthon (34) reported the occurrence of acute pulmonary edema in a schizophrenic patient during hypoglycemic coma. They believed the condition followed the injection of adrenalin. Geordono and Zeglio (35) have shown that in normal fasting subjects, blood adrenalin increases 32 to 512 per cent following intravenous injection of 14 units of insulin. It is probable that in an effort to maintain the body hemostisis, the sympathetic nervous system is stimulated following the injection of increasingly large doses of insulin. An excess of adrenalin is poured into the blood stream in order to maintain the blood sugar level. Termination of coma by administration of glucose probably leaves an excess of circulating adrenalin.

According to Bayer, (36) hyperadrenalinemia results in diminished volume output and resultant dilitation of the heart especially the left half. The enormously increased consumption of oxygen by

the heart resulting from the intake of adrenalin can, notwithstanding the dilitation of the coronary vessels, be only partially compensated. Over filling of the left ventricle and auricle with blood may lead to acute pulmonary congestion and acute pulmonary edema which constitutes the precursor of death in acute adrenalin poisoning.

It would appear, therefore, the injection of adrenalin during hypoglycemic coma is contra-indicated.

C. Rupp (37) in an article on the compression fracture of the dorsal vertebrae resulting from convulsion occurring during therapy related the history of a 31 year old male in good physical health.

The first series of treatments progressed uneventfully.

On the seventeenth treatment day, 180 units of insulin were given at 7:30 a.m. At 8:30 the patient was sleeping but could be easily aroused. Suddenly at 9:05 he emitted a cry and immediately a violent anterior flexion of the spine occurred, his body assuming a jack knife like position. With relaxation after about thirty seconds, generalized tonic-clonic movements of the entire body began

continuing for sixty seconds. As the convulsive movements ceased the patient was comatose.

Immediately on regaining consciousness, the patient complained of a severe knife like pain between the shoulder blades, radiating down the spine to the midlumbar region. Pain was severe enough to prevent him from sitting up in bed. Examination disclosed moderate tenderness over the spinous processes from the third to eighth dorsal vertebrae with moderate hyperesthesia to pin prick in the lower extremities. No reflex changes.

Anterior-posterior and lateral x-rays of the dorsal spine revealed a compression fracture of the sixth and seventh dorsal vertebrae with a possible fracture of the fifth.

Roentgenographic examination of the dorsal spine in four other patients having convulsions during the course of insulin shock therapy showed no evidence of compression fractures.

J. W. Klepman and J. Weinberg (38) reported on a case involving cerebral insult following hypoglycemic shock therapy with recovery.

This patient, a female of 23 years of age,

had little reaction until after the sixth hypoglycemic treatment of 50 units. Late in the afternoon following regular insulin hypoglycemia from which she had fully recovered following the usual administration of sugar, the patient became acutely disturbed; combative, resistive and noisy. Later in the same day the patient suffered a generalized convulsion. On the following morning the patient had another generalized convulsion. On the following morning the patient had another generalized convulsion of the grand mal type. Even in the quiescent state it was observed that there were constant myoclonic contractions confined to the left side of the body, conspicuous in the left leg, arm and shoulder. On the same afternoon she became stuporous and had another generalized convulsion, more or less a typical epileptiform seizure of grand mal type. She had five more grand mal convulsions in the evening.

The following morning the patient's condition was greatly improved. She was fully awake and had no more myoclonic twitching or convulsions. There was now no motor paralysis or rigidity, but only a slight weakness of the upper right extremity.

No further convulsions or any other neurological symptoms recurred from then on.

In a detailed case report with follow up studies on anaphylactic response during shock therapy of schizophrenia E. M. Henke, M. M. Fenton and C. H. Balberor (39) contributed the following:

Insulin sensitivity during the course of insulin shock therapy, as denoted by the progressively earlier appearance of coma and necessitating the reduction of the shock dose to one half or one third of its original size, has been frequently noted in patients subjected to repeated deep shocks.

The patient, a thirty year old negro, on January 13, 1941, received his 16th injection consisting of 105 units of insulin at 6 a.m. and almost immediately afterward experienced a generalized pruritis. At 6:20 a.m. he complained of not feeling well, became nauseated, vomited clear fluid and had an involuntary bowel movement. At 6:30 he was semistuporous, skin cold and clammy and impossible to detect a radial pulse. There was considerable edema of face, particularly eyelids and lips. Received 0.5 cc of suprarenin. At 8:30 a.m. he was still semistuporous, his responses were delayed and

his speech slow and thick. Blood pressure and pulse were still unobtainable. At 9:00 a.m. another 0.5 cc of suprarenin was given. At 9:45 a.m. the pulse was readily palpable, strong in quality. Patient was alert, coherent and relevant, but complained of a tired feeling.

The edema of the face gradually subsided and on the following morning was no longer noticeable. The patient was kept in bed another twenty-four hours and then allowed up having no complaints and displaying no unusual symptoms.

About two weeks after the occurrence of this anaphylactic reaction the patient was referred to the allergy clinic for study. The patient was found to be definitely sensitive to insulin. The reactions to crystalline insulin were uniformly larger than to standard or protamine insulin. No sensitivity to animal proteins such as beef, lamb, veal and pork was found.

No skin sensitizing regions could be demonstrated in the circulating blood by repeated passive transfers in seven subjects not sensitive to insulin.

Positive skin sensitivity to insulin in this patient was still present seven weeks after the

anaphylactic reaction.

In a preliminary report on chronic hypoglycemia in psychotic patients following prolonged insulin shock therapy, J. R. S. Mays and Y. H. Yarbrough (40) related that at Milledgeville State Hospital a total of 34 patients have received insulin treatment. Several hundred blood sugar determinations made on fourteen of these patients show the presence of a chronic non-symptomatic hypoglycemia which persists for from three months to two years or more after the termination of therapy. This hypoglycemia is most severe in the first six months after the termination of treatment, but persist in decreasing severity for two years or longer.

Though these patients have continued to perform manual work, this state has not been accompanied by any of the objective or subjective symptoms usually attributed to a low blood sugar level.

All the patients have remained in excellent physical health, have increased appetites and have gained 30 to 60 pounds in weight.

Fasting blood sugar studies on a central group of untreated schizophrenic patients would seem to indicate the presence of a hypoglycemic tendency in

patients suffering with this disease.

No satisfactory explanation of this phenomenon has as yet been found.

A. R. Berger and W. Goldford (41) in an article on complete heart block occurring during shock therapy gave the following case history:

The patient, a male, white and age 21, was negative in the physical examination. Insulin started on March 7, 1940 and the dose steadily increased, since the patient did not go into coma. On April 2nd the patient first became comatose, after receiving a dose of 310 units of insulin. On April 3, at 5:30 a.m., the patient was aroused by severe pain experienced substernally and in the right upper part of the chest and complained of a feeling of being "blown up". The pain radiated to the right side of the neck and lasted about twenty minutes. He claimed to have slight difficulty in breathing and some abdominal cramps. The pulse was very rapid at first, but the patient soon became pale and weak and the pulse rate dropped to 36 per minute. The systolic blood pressure was 110 mm and the diastolic pressure 50 mm of mercury. The heart sounds were normal and no murmurs were

heard.

Reexamination at 8 a.m. revealed that the patient was comfortable and lying flat in bed. Respiration was regular and slow. The apical impulse of the heart was diffuse in the fifth interspace outside the midclavicular line. The aortic sound was greater than the pulmonic and neither was accentuated. The pulse rate was equal to the ventricular rate of 38 per minute. A soft systolic murmur was heard at the apex. There were no thrill, diastolic murmur, gallop or pericardial friction rub. There were no signs of conjestive heart failure. During the next four days a cardiac arrhythmia, which clinically simulated dropped beats or premature contractions persisted. The nature of this rhythmic disturbance was made clear by electrocardiograms and found to be complete heart block.

Physical recovery was complete. On April 26, examination of the heart revealed no abnormalities. Fluoroscopy revealed a normal cardiovascular silhouette.

An unusual complication in protracted shock treatment was presented by Z. Wechsler (42) in the case history of a female patient 45 years of age.

An initial dose of 25 units of insulin was given and this was gradually increased by 15 units daily until a hypoglycemic coma was produced on the eighth day, with a dose of 130 units. It was intended to extend the coma to ten hours if possible.

On the ninth day the procedure was repeated but, to enable the patient to remain in coma longer than on the previous day, the amount of sugar, given hourly, was reduced to half. After three hours and twenty five minutes a hypoglycemic coma was induced, and this was extended to ten hours. To interrupt the coma a large dose of sugar (200 grams) was given, but the patient failed to regain consciousness. In spite of intravenous injection of glucose, Vitamin B_1, sodium chloride, tetrozol, adrenaline given hypodermically and inhalation of "carbogen" the coma became irreversible. During the following days she developed signs of bronchitis and circulatory failure. Her temperature went up to 101.2° F. and her pulse rate to 132. In due course she became increasingly restless; the movements became of a chorea-athetoid type. Abnormal associated movements were particularly marked in the face. The pupils reacted to light and the reflexes were normal. The patient was artificially

fed and developed incontinence of urine and feces.

After fifty seven days she began to take food, and on the following day she appeared to understand questions, but was unable to answer them. Her speech, first distorted beyond recognition, gradually became more normal, though with marked loss of memory for words.

After six months, her physical condition was reasonably good. Her facial expression was somewhat flattened. She was disoriented as to time and her memory was very defective with marked confabulatory tendencies. She was dull and indolent; she had little initiative and did not seem to worry about what was going to happen to her.

Complications of insulin shock therapy, such as a lung abscess, was discussed by H. H. Goldstein, A. P. Bay and J. V. Edlin (43).

Throughout the treatment, it was necessary to tube feed this patient quite frequently. The usual precautions in avoidance of aspirations were judiciously carried out whenever nasal feeding was necessary.

About two weeks after treatment was discontinued the patient began to run a mildly elevated tempera-

ture and seemed uncomfortable. Three weeks after discontinuance of treatment she was transferred to the hospital ward for observation, where her temperature flucuated between 101 and 103 degrees. There was dullness in the left infraclavicular area with rales anteriorly in the upper 2/3 of the chest and at the left base posteriorly. Sputum of thick greenish brown, tenacious and foul smelling, was being expectorated in large quantities and on examination of a smear showed fusiform bacilli and spirochetes. A diagnosis of lung abscess was made, which was confirmed by x-ray which showed an abscess involving the left infraclavicular area and apex with a large central cavity.

The immediate cause of this complication was probably aspiration in the course of nasal tube feeding.

J. W. Klepman (44) reviewed a case of non epidemic parotitis as a complication of insulin shock. The patient was a schizophrenic hebephrenic type. The history showed the patient suffered from the usual childhood diseases, including mumps.

Insulin begun on March 9, 1938. There were 28 treatments during which time the patient had

comas. On April 10, 1938 the patient was found to have an elevation of temperature, and was not given insulin, but treatment was resumed the next day, April 11, 1938 when the temperature was found to be normal.

However, on the afternoon of April 11, 1938 the temperature began to rise again, and by 4 p.m. was 102.5° F. At 8 p.m. the temperature was 103.2° F., and the patient began to complain of sore throat and difficulty in swallowing. She became restless and by noon of the following day there was marked swelling of the right side of the face and neck. This pain on swallowing disappeared in a day or two although the patient continued to run a febrile course and showed a markedly swollen parotid gland. The patient continued the febrile course until about April 23, 1938. The swelling and tenderness in the right parotid gradually became less, until about a week after the disappearance of the fever when it had completely subsided.

It may be deduced, or supposed at any rate, that in prolonged stimulation of the autonomic nervous system that occurs in insulin shock and coma, that the hyperemia of the parotid and the other

salivary glands is conducive to stasis of the secretion with possible partial retention.

The sixth and final question as presented in the introduction can be answered by stating that insulin shock therapy is definitely an accepted method for treatment of schizophrenia, and has scientifically been proven to be beneficial.

There, however, have been minor changes in the technic of insulin administration, which today are used by many in preference, to the original technic of Sakel.

Polatin and Spatnitz (45) presented the following as a newer technic of administration, the so called "ambulatory shock technic in schizophrenia."

The patients treated by this method receive one hypodermic injection of insulin daily at 5 a.m. and when, several hours later, hypoglycemic symptoms have been present for about one half hour, orange juice or sugar water is given and followed by the usual hospital breakfast. The initial dose of insulin is generally five units. This is increased daily until the patients have manifested, within five hours mild hypoglycemic shock, usually characterized by weakness, excessive perspiration and some

drowsiness. As a general rule, 40 units of insulin in one dose was sufficient to produce the desired effect within five hours. The insulin dosage is kept at a minimum and the severity of the hypoglycemic symptoms is controlled by increasing or decreasing the time interval before which food is given.

The aim of this mode of therapy is to treat the patients daily for an indefinite period of time until the manifestations of the mental disorder has subsided.

The usual symptoms associated with hypoglycemia are observed with this type of therapy and coma is avoided. Forty four patients were treated. The duration of psychosis varied from a maximum of ten years to a minimum of a few days. Thirty six patients (82%) showed definite clinical improvement, either slight or marked. Eight patients were considered unimproved. Twenty one (48%) patients showed a marked improvement or were considered recovered.

Eighteen of the forty-four patients treated had had a psychosis of less than one years duration before ambulatory insulin shock treatment was begun. Fourteen (78%) of these patients were either much

improved or recovered. Only four (22%) showed no improvement or only slight improvement. Six patients (33%) were considered to be completely recovered.

In general, it was observed that the time required for treatment was less if the duration of the psychosis was short. On the other hand, patients with a long duration of illness before treatment, required a longer period of treatment before improvement could be observed. The improvement obtained with the ambulatory insulin shock technic was maintained or enhanced, as long as the patient continued to receive the treatment. When therapy was discontinued approximately 33% of the patients who manifested improvement relapsed within two years following cessation of therapy. As a result of these studies, it is suggested that the general concept of prognosis in schizophrenia should perhaps, be revised. The prognosis of patients treated with ambulatory insulin shock technic did not depend upon the duration of the psychosis.

Polatin and Spatnitz (46) also have presented more recently another method of treating schizophrenia, in which combined ambulatory insulin and

electro-shock therapy are combined.

This investigation was undertaken to determine whether the initial rapid clinical improvement obtained with electro-shock therapy in schizophrenia could be maintained and possibly further enhanced by combining the electro-shock therapy with ambulatory insulin treatment. It was considered likely that the strong regressive trends, which follow the temporary improvement obtained with electro-shock therapy, could be checked by ambulatory insulin treatment and that thereafter the patients mental condition might be further improved from the continued application of ambulatory insulin therapy.

Thirty female patients with a definite diagnosis of schizophrenia were treated with combined electro-shock and ambulatory insulin over a period ranging from ten weeks to forty two weeks. The aim of the therapy was to treat the patients with electro-shock until the maximum clinical improvement could be obtained. It was usually found that 20 convulsions were sufficient to produce this effect. Ambulatory insulin was begun at different intervals during the course of the electro-shock treatments. With some patients ambulatory insulin preceded

electro-shock. With other patients both treatments were given concurrently, with still others, ambulatory insulin followed the electro-shock. It was generally found that the best results were obtained if the ambulatory insulin shock therapy was instituted after the sixth electroconvulsion. In this way, the clinical improvement produced by electro-shock therapy was not permitted to lapse but, on the contrary, was maintained and increased. It was found that about eleven weeks of ambulatory insulin therapy were sufficient to produce a comparatively stable improvement.

Combined electro-shock and ambulatory insulin therapy has the advantage of producing rapid clinical improvement with a minimal tendency to relapse over a period of thirteen weeks in patients with schizophrenia.

The efficacy of the combined therapy did not appear in any way related to the duration of the psychosis, to the type of schizophrenia treated or to the prepsychotic personality.

A study of the cases which did not improve with this combined therapy revealed one common characteristic finding which may be of significance

in explaining their failure to improve, during the state of hypoglycemia induced by ambulatory insulin technic, they manifested a peculiar type of rigid, stubborn billigerent behavior. This disappeared with the termination of hypoglycemia. Some form of psychotherapy at the termination of hypoglycemia is considered to be an important factor in maintaining and developing a certain degree of permanence in the improvement.

In summary it can be said that Manfred Sakel, a young Austrian physician in 1936 was the first to establish the use of insulin shock in the treatment of schizophrenia. The similarity of the abstinence symptoms in morphine cure, to other types of excitement suggested the possibility of influencing excited states of different origin in the same way.

Dr. Sakel came to the United States in 1936 and Dr. Frederick W. Parsons, then Commissioner of the Department of Mental Hygiene, took advantage of the opportunity to have insulin shock treatment introduced into the New York Civil State Hospitals.

The true physiological process by which insulin shock therapy is beneficial in schizophrenia

is not known. However there have been many theories in regards to its action in the schizophrenic patient and these theories are as follows:

(1) Insulin inhibits and blockades the nerve cell, so that the nerve pathway pattern, like jury-men locked in a room, finally come to order. The seat of action, believed to be in the vegetative centers.

(2) Insulin diminishes lactic acid production by promoting conversion of lactic acid into glycogen, thus inhibiting any nutritional disturbance in the brain.

(3) Anoxia theory of insulin convulsions.

(4) Adrenosympathetic impairment is largely overcome by insulin therapy.

(5) Face of death due to severe physical upset associated with insulin hypoglycemia constitutes an important physiological factor in improvement.

(6) Stimulation of the reticulo endothelial system and the abilities of the system to produce blood, to phagocyte, to retain electro-negative colloids and to form antibodies.

(7) Histologic alterations brought about by insulin therapy in the neuron cells and blood vessels.

After careful study of the many physiological theories, I believe the following to be the most acceptable, in that the process is associated with brain metabolism. That after insulin, blood carbohydrates are greatly reduced and although the brain is put to rest by a lack of carbohydrates, there is an adequate amount of oxygen in the blood. Thus insulin hypoglycemia depresses cerebral metabolism by diminishing the food supply of the brain, and this seems to favor the amelioration of schizophrenia.

Insulin shock therapy in the treatment of schizophrenia has been scientifically established to be of great value. Through the careful study of many case histories of insulin treated patients and by further comparison with noninsulin treated patients, the following facts have been concluded:

(1) The percentage of total recoveries and improvement is greater in the insulin treated than in the noninsulin treated patients.

(2) Improvement rates are highest in the simple types (catatonic and paranoids) and lowest among the hebephrenics.

(3) There is a striking correlation between the rate of improvement and the duration of the disease

before the beginning of treatment. The earlier in the course of the disease that the patient is submitted to treatment, the better is the prospect of recovery and rehabilitation.

(4) Ratio of recovery is relatively high at the younger ages and shows a tendency to decline with advancing age.

(5) Recovery rate shows a steady decrease as the period devoted to treatment is increased.

(6) The period of illness and hospitalization is cut short by this treatment.

(7) Relapses occur about as frequently in treated patients as in non treated patient.

(8) Hypoglycemic treatment when effective, is only one step in the process of rehabilitating the schizophrenic, and great attention must be directed to psychological and environmental factors.

Insulin hypoglycemic shock is not without its dangers of complications and in some instances ensuing death. Some of the complications seen are:

(1) Prolonged coma following shock.

(2) Cerebral complications.

(3) Lung abscess.

(4) Pulmonary gangrene.

(5) Compression fractures of the vertebrae.

(6) Insulin sensitivity.

(7) Chronic hypoglycemia.

(8) Complete heart block.

Whenever any method of treatment is carried out there will be unforeseen complications and so it is in insulin shock. However many times with utmost care on the part of the Doctor and excellent nursing care while the patient is receiving treatment, many of these complications can be avoided.

Insulin shock therapy is definitely an accepted method for treatment of schizophrenia in the United States today.

There, however, have been minor changes in the technic of insulin administration, such as "ambulatory shock technic" and "combined ambulatory and electro-shock therapy." The value of these methods in comparison with the original Sakel technic is controversial, and until further scientific study has been completed one can not definitely prove or disapprove their true value.

Insulin is certainly not a panacea for all cases of schizophrenia but until better methods are available it should be more generally used.

SELECTIVE BIBLIOGRAPHY

1. Wortis, J.: Response of schizophrenic subjects to hypoglycemic insulin shock, J. Nerv. & Ment. Dis. 84: 497-506, 1936.

2. Sakel, M.: Zeit Neurl, 129: Heft 3 and 4, 1930 and 143: Heft 3 and 4, 1933. (Cited by 1).

3. Malzberg, B.: Outcome of insulin treatment of one thousand patients with dementia praecox, Psychiatric Quart. 12: 528-553, 1938.

4. Hoffman , H. A.: Pharmacologic aspects of shock therapy (with insulin and metrazol), J. Nerv. & Ment. Dis. 95: 18-25, 1942.

5. Gellhorn, E.: The problem of schizophrenia from the physiologic point of view, J. A. M. A. 110: 1433, 1938. (Cited by 4).

6. Abramson, D.: Influence of insulin on peripheral blood flow in man, Am. J. Physiol. 128: 124, 1939. (Cited by 4).

7. Parsons, S.: Treatment of dementia praecox by pharmacologic shock, Mil. Surg. 85: 6, 1939.

8. Bowman, K.: The modern treatment of schizophrenia, Bull. N. Y. Acad. Med. 15: 338, 1939.

9. Davidson, G. M.: Insulin therapy in schizophrenia and reticulo-endothelial system, J. Nerv. & Ment. Dis. 92: 193-201, 1940.

10. Burridge, W.: The excitation process of fits and other convulsive and emotional states, J. Ment. Sc. 75: 396-425, 1929.

11. Kietz, E. B., and Birnbaum, S. M.: Level of adrenocortical substance in the blood during hypoglycemic treatments of schizophrenia, Am. J. Psychiat. 99: 75-83, 1942.

12. Grinker, R. R.: Hypothalamic functions in psychosomatic interrelations, Psychosom. Med. 1: 1-20, 1939. (Cited by 11).

13. McFarland, R. A.: The internal environment and behavior, Part I. Introduction and role of oxygen, Am. J. Psychiat. 97: 4, 1941. (Cited by 11).

14. Ferraro, A., and Jervis, G. A.: Pathologic consideration in insulin treatment of schizophrenia, Am. J. Psychiat. 96: 103-108, 1939.

15. Sakel, M.: The origin and nature of hypoglycemic therapy, Bull. N. Y. Acad. Med. 13: 97-109, 1937.

16. Savitt, R. A.: Some comparisons between insulin treated and non insulin treated cases of schizophrenia, Am. J. Psychiat. 94: 5-23, 1938.

17. Muller, M.: The insulin therapy of schizophrenia, Am. J. Psychiat. 94: 5-23, 1938.

18. Steinberg, L., Hulbrunn, G., and Liebut, E.: Evaluation of the newer treatments of dementia praecox, Illinois Med. J. 75: 405-410, 1939.

19. Coyni, A. R.: Results obtained in hypoglycemic treatment of schizophrenia, J. Nerv. & Ment. Dis. 92: 309-322, 1940.

20. Bond, E. D.: Continued follow up results in insulin shock therapy and in control cases, Am. J. Psychiat. 97: 1024-1028, 1941.

21. Bond, E. D., and Rivers, T. D.: Insulin shock further follow up results, Am. J. Psychiat. 99: 201-202, 1942.

22. Weinberg, J., and Goldstein, H. H.: Insulin treatment of metrazol failures, 100 cases, J. Nerv. & Ment. Dis. 95: 597-609, 1942.

23. Bond, E. D., and Rivera, T. D.: Insulin shock therapy after seven years, Am. J. Psychiat. 101: 62-63, 1944.

24. Taylor, J. W.: Returns of schizophrenics following shock therapy; report on patients released 5 to 7 years ago, Dis. Nerv. System 6: 28-29, 1945.

25. McConnell, J.: Insulin coma therapy; 2 year's experience with female schizophrenics, J. Ment. Sc. 91: 506-510, 1945.

26. Fruedenberg, R. K.: Ten years experience of insulin therapy in schizophrenia, J. Ment. Sc., Lond., 93: No. 390, 9-30, 1947.

27. Chapius, R., and George, F.: Traitements de choc dans les depressions et lea schizophrenics, Arch. Suisse Neur. Psychiat. 1: 55-66, 1945. (Cited by 26).

28. McKendrie, O. J.: Insulin therapy and its complications in the treatment of the psychosis, Psychiatric Quart. 12: 444-454, 1938.

29. Bryan, C.: Effect of dinitrophenol on experimental diebetes, Proc. Soc. Exper. Biol. & Med. 37: 4-8, 1937. (Cited by 28).

30. Lester, D.: Prolonged coma following insulin shock, Am. J. Psychiat. 95: 1083-1093, 1939.

31. Klein, F., and Ligterink, J. A.: Insulin and cerebral damage, Arch. Int. Med. 65: 1085-1096, 1940.

32. Furst, W.: Death due to pulmonary gangrene, Am. J. Psychiat. 97: 380-383, 1940.

33. Nielsen, J.: Pulmonary edema and embolism as complications of insulin shock in the treatment of schizophrenia, J. A. M. A. 111: 24-55, 1938.

34. Parthon, M.: Acute pulmonary edema following injection of epinephrine in schizophrenic patients in hypoglycemic coma, Endocrinol. Genec. Obst. 3: 105, 1938.

35. Geordono, C., and Zeglio, P.: Determination of adrenalin in human arterial plasma before and after insulin injection, Ztachr. F. Klin. Med. 136: 213, 1939. (Cited by 34).

36. Bayer, G.: Anatomy and physiology of the suprarenal glands, Cyclopedia of Medicine, Surgery and Specialties, 1: 165, 1939.

37. Rupp, C.: Compression fractures of dorsal vertebrae resulting from convulsion occurring during course of insulin shock therapy; report of case, J. Nerv. & Mant. Dis. 92: 762-765, 1940.

38. Klepman, J. W., and Weinberg, J.: Cerebral insult following hypoglycemia shock therapy with recovery; case report, Illinois M. J. 79: 236-237, 1941.

39. Henke, E. M., Fenton, M. M., and Balberor, C. H.: Anaphylactic response during insulin shock therapy of schizophrenia; detailed case report with follow up studies, Am. J. Psychiat. 98: 140-145, 1941.

40. Mays, J. R. S., and Yarbrough, Y. H.: Chronic hypoglycemia in psychotic patients following prolonged insulin shock therapy; preliminary report, J. M. A. Georgia 30: 353-356, 1941.

41. Berger, A. R., and Goldforb, W.: Complete heart block occurring during insulin shock therapy, Arch. Neurol. & Psychiat. 48: 476-480, 1942.

42. Wechsler, Z.: Unusual complications in protracted insulin shock treatment, M. J. Australia 2: 616, 1944.

43. Goldstein, H. H., Bay, A. P., and Edlen, J. V.: Complication of insulin shock therapy, Illinois M. J. 74: 175-176, 1938.

44. Klepman, J. W.: Non-epidemic parotitis complication of insulin shock therapy, Illinois M. J. 74: 283-285, 1938.

45. Polatin, P., and Spatnitz, H.: Ambulatory shock technic in schizophrenia; evaluation of effects, J. Nerv. & Ment. Dis. 97: 567-575, 1943.

46. Polatin, P., and Spatnitz, H.: Effects of combined ambulatory insulin and electroshock therapy in treatment of schizophrenia, a preliminary report, N. York State J. M. 46: No. 23, 2648-2650, 1946.