5-1-1937

Insulin shock therapy for schizophrenia medicinal therapy

Charles G. Ingham
University of Nebraska Medical Center

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INSULIN SHOCK THERAPY FOR SCHIZOPHRENIA

MEDICINAL THERAPY

by

CHARLES G. INGHAM

SENIOR THESIS

presented to

THE COLLEGE OF MEDICINE,

UNIVERSITY OF NEBRASKA

Omaha, Nebraska
1937

INTRODUCTION

Schizophrenia, or Dementia Praecox, constitutes a large percentage of all admissions to state hospitals, and therefore has always demanded an unusual degree of attention. Perhaps there is no such type of mental disease about which there is more written. This bulk of discourse in itself is evidence of confusion and uncertainty relative to an accepted understanding. Since the disease most frequently afflicts individuals just as they reach adolescence and adulthood, and too, since the prognosis as a whole is so unfavorable, it is not surprising then, that any new approach which seems to throw additional light on the subject is eagerly discussed.

Ignorance of the pathobiologic processes underlying schizophrenia renders therapy directly of the etiologic factors impossible. There are, however, accidentally discovered correlations which have formed a starting point of therapeutic efforts. As, for example, in the case of dementia paralytica, it was noted that remissions coincided with accidental fevers which led to the establishment of a biologic antagonism between the disease process and the febrile condition and thus to malarial therapy.

Psychiatrists and others interested in searching for a more specific therapy for schizophrenia have endeavored to find such coinciding biologic antagonists which might exist in this disease. However, without having an established etiological basis upon which to work, those making observations in this direction have not systematized or utilized them for conclusions regarding therapy.

In this paper I propose to discuss the insulin hypoglycemic shock therapy for schizophrenia. The methods and principles of procedure as well as the treatment of the shock itself, I quote almost entirely from Wortis (54) and Glueck (19 and 20). These are the only two sources in the literature of this country that discuss this phase to any length. Of more interest than this are the results obtained by this therapy and the mechanism whereby these results are brought about.

The methods are those of Dr. Manfred Sakel of Vienna who introduced this method of treatment. Wortis, who visited Sakel's clinic, and Glueck, who reported the work of Dr. M. Muller of Munsingen, Switzerland, (a coworker of Sakel's) describe the procedure to great detail. Rather than quote them to great length, I shall limit myself to generalizations and devote more time to

statistics of results, and a review of the literature in
regard to the mechanism of hypoglycemia, emphasizing its
action on nervous tissue.

At the same time, I shall discuss to a limit, other
methods of medicinal therapy, which, in my opinion, dis-
play similar action and results as that of hypoglycemia,
either directly or indirectly.

INSULIN THERAPY

Appel, Farr and Marshall (1), in 1929, used small amounts of insulin in undernourished patients with psychoses and reported its usefulness to increase weight and improve gastro-intestinal function in these individuals. At the same time, they listed nine distinct accidental insulin shocks in the course of thirty-one cases, six of which were in three patients, each having two. One of the patients with dementia praecox that they treated, who had for the previous year refused weighing, all medicines and physiotherapy, became agreeable and cooperative and so remained. They failed to state whether or not this patient was one which had suffered accidental shock.

During this same year, Meduna (37) states that Nyiro and Jablonszky in Budapest observed an existence of a biologic antagonism between schizophrenia and epilepsy. They were impressed by the fact that in cases of long-standing epilepsy in which schizophrenia developed, the epiliptic convulsions ceased or became rare. Meduna states further that Steiner and Strauss in a re- on six thousand cases of schizophrenia were convinced that "typical epileptic convulsions are so rare in schizophrenia, if they occur at all, as to throw doubt

upon the correctness of the psychatric diagnosis". In this same article, it is revealed that in 1930, Muller published reports of two cases of catatonia in which recovery ensued after spontaneous epileptic convulsions.

Wortis (54) in introducing his review of recent work of Manfred Sakel states that the latter, in 1930, reported that the abstinence symptoms in morphine cures could be relieved by large doses of insulin. His hypothesis was that abstinence symptoms were a sign of general nervous hyperactivity either due to "(a) nervous hypersensitivity, or (b) excess of the excitant hormones", chiefly adrenalin. Sakel used insulin as an antagonist to paralyze adrenalin action. Whether or not this theory is valid, it has proved fruitful in abstinence cures, and has been confirmed by several other observers.

"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. From the observation of some cases of accidental hypoglycemic coma and from several theoretical considerations, Sakel ventured to produce

hypoglycemic shock deliberately in schizophrenic patients." (Wortis, 54)

Glueck (19) and Wortis (54) give Sakel the sole credit for introducing this method of treatment. Hypoglycemic shock is the essence of his method---it distinguishes his procedure from all previous attempts to use insulin in schizophrenia.

The <u>Method</u>:

The principle of the procedure consists of treating the patients by a regular series of hypoglycemic shocks which are produced by deep intramuscular injections of insulin, and lasting several hours. The necessary doses are usually, but not necessarily high, and they vary from 20 to 200 units, and even more. The response to any one dose varies greatly from individual to individual, and in the same individual at different times. Wortis (54) states that twenty units may produce convulsions in one patient, and "I have seen another (patient) walk around for hours after an injection of 130 units."

Sakel distinguishes four phases in the treatment, as outlined by Wortis (54) and Glueck (19); also, Paskind (40).

In phase 1, (preparatory phase), insulin is given one to three times daily, usually but once a day, 15 to 30 units per dose. Since the object is to produce a hypoglycemia, this is started on an empty stomach, and carbohydrates are withheld for four hours. This dose is increased daily by 5 to 10 units. (Depending on the physical condition of the patient, Glueck suggests in some cases of increasing dosage only every second or

third day.) This is continued until a hypoglycemic
state with coma is reached. Thus begins phase 2, in
which one daily dose is given in the morning and consists
of the same amount as that which produced the first
shock. (This may be varied according to the reaction.)

In phase 2, (shock phase) a series of daily, severe
hypoglycemic shocks is produced. The dose given is that
which produced the first shock. This is alterable, but
as a general rule the minimum dosage for producing shock
is preferable. The patient is then kept at this dose,
receiving as many shocks as are required to bring about
recovery. Every seventh day is a rest day, but feeble
patients may require more rest days (without any insulin).
Some patients have received as high as 60 or 70 shocks
before favorable response was obtained. The effects in
this stage are noticed three-quarters of an hour to five
hours after the injection. Carbohydrates are fed as be-
fore, and treatment to be terminated consists of glucose
given by stomach tube or intravenously. Treatment is
terminated after a convulsion.

Phase 3 (rest phase) is a transition stage between
2 and 4 and consists of one to several days during which
the patient receives very little or no insulin. Such
interruptions may be called for because of intercurrent

febrile and other somatic disorders, or after an epilep-
tic seizure when the patient is usually allowed two or
three days freedom from treatment.

Phase 4 (polarization phase) is referable only to
the cases in which the preceding treatment led to the
desired result. It serves as a means of consolidating
and stabilizing the gains acheived. Much smaller doses
of insulin are administered than in phase 2. Ten to
thirty units of insulin are the ordinary limits, and the
carbohydrates are administered no later than two hours
after the insulinization. The patient is not permitted
to reach a deep state of shock, and the treatment is con-
tinued until the patient's discharge.

The Management of Hypoglycemic Shock Treatment:

Glueck (20) stresses the point that the duration and intensity of each phase be strictly graduated in accordance with the requirements of the individual case. "The most difficult aspect of the entire procedure is the total unpredictability of the reactions to the hypoglycemic state in different patients." He states also that experience alone with a "thorough-going acquaintance with the somatic and psychic characteristics of the individual patient are the most dependable guides in this connection".

In phase 1, one is concerned chiefly in watching for the development of shock. In the course of this phase the hypoglycemia manifestations begin to appear, usually with increasing severity. They consist of profuse sweating, increased salivation and yawning with tremor. Later, clonic twitchings of the arm and leg musculature, or the face may develop. The patient may complain of varying symptoms from sedative feelings and slight paresthesias to oppression and pounding of the heart and double vision. The amounts of insulin required to produce shock are extremely variable. Twelve units have produced epileptic seizures in one patient while another has remained symptomless with amounts up to 240

units. Whether or not the patient shows any reactions indicating shock, Glueck says, "the individual treatment must always be followed by the introduction of the appropriate amount of carbohydrates." Patients are allowed to have fluids during phase 1 and during shock. Also, during this period, they may prophylactically digitalize for 6 to 8 days.

Phase 2 is the most critical and most important stage of the treatment. The patient is in a degree of stupor or coma with other manifestations of a deep hypoglycemic state and he is threatened with a convulsive seizure. Sakel designates the ordinary shock as "wet-shock" because of the profuse sweating which accompanies it, and those patients, according to him, are most likely to develop epileptic seizure who do not display these customary evidences. One must be ready in this phase to administer emergency intervention of shock. This is accomplished through intravenous administration of 30 to 50 per cent glucose solution in amounts of from 100 to 200 cubic centimeters. Hypodermic injection of adrenalin and at times, of cardiac and respiratory stimulants is called for. Glueck (20) states that "the nasal administration of an adequate amount of sugar must also be carried out".

It is desirable to maintain the condition of shock as long as possible since it seems to be the profundity and duration of the coma and the intensity of the affective reaction that determines the therapeutic progress. On the other hand, the patient's physical condition may demand the immediate neutralization of the hypoglycemic state irrespective of the requirements of the therapy of the mental condition. The intravenous administration of glucose usually produces the desired effect immediately, while Glueck states that the oral or stomach tube administration of sugar milk brings about the same results in from five to fifteen minutes. In three cases that I observed at Douglas County Hospital who were under the care of Dr. G. A. Young, it appeared to me that the stomach tube administration brought about a return to consciousness of the patient almost before the tube was withdrawn.

There is no general rule as to the number of shocks the individual patient should receive. Here again one should be guided by the progress of the improvement.

Phases 3 and 4 do not need discussion of treatment because they embody a portion of the management of phase 2.

In discussing the management of the various types of schizophrenic patients in regard to shock therapy, I shall demonstrate variations in handling them later.

Hypoglycemia is ordinarily not prolonged beyond six hours, or at the very most, eight hours, since protracted hypoglycemia produces irreversible changes, as will be discussed later.

Wortis (54) generalizes this by saying that shock should be prolonged until the patient is comatose or at least somnolent. "It should not be terminated during excitement" unless a patient grows literally wild with hunger. Such patients should be fed at once. He lists the following indications for termination of shock: (1) collapse, irregular pulse or bradycardia under 35 to 40 beats per minute; (2) sudden marked fluctuations in pulse rate up to 180 and down to 90 beats per minute for example; (3) laryngospasm; (4) tonic cramps or contractions; (5) epileptic seizures; (6) respiratory disturbances, such as Cheyne-Stokes, stertorous, or brochspastic breathing." Simple psychomotor excitement, cyanosis of arms and legs, or myoclonic twitchings are not indications for termination, in his estimation.

The Cause and Mechanism of Hypoglycemic Shock:

The signs of hypoglycemic shock have been frequently described. Early observations drew attention from time to time to chemical substances which were thought to accumulate and be responsible for these signs. Best (4) is convinced that there is no evidence that a toxic chemical substance accumulates when the blood sugar is maintained at low levels.

I shall enumerate the theories for the mechanism of the neurologic symptoms as I have found them in the literature, as follows:

Anoxemia theory;

Holmes (25) reveals that the various types of tissue that compose the central nervous system in mammals have a different rate of oxygen consumption, and that the activity of gray matter is in this respect far greater than that of white matter. "The term 'gray matter' necessarily includes without discrimination both nerve cells and synaptic junctions." He continues with "the greatly increased oxygen uptake which gray matter displays in the presence of glucose is dependent upon the conversion of the glucose to lactic acid, and disappears if this conversion is prevented by flouride." He feels that carbohydrate is probably not responsible for any considerable

part of the oxygen uptake of nerve, "but this statement
must carry the reservation that little or nothing is
known of the part played by carbohydrate fraction of the
cerebrosides".

Dameshek and Meyerson (11) compared the contents
of dextrose and oxygen in the vessels supplying the
brain before and after the administration of insulin.
They found that "the chemical changes in the blood
usually varied directly with the severity of the reac-
tion,---and that the uptake of oxygen by the brain varied
indirectly with the severity of the insulin reaction,
becoming much reduced during the most severe reactions".
From this evidence they concluded that if the diminution
in the arteriovenous difference in the content of oxygen
during the insulin reaction may signify actual diminution
in oxygen uptake by the brain, then the meurologic
symptoms of the severe hypoglycemia may be due to the
effects of a lack of oxygen on the brain tissue. These
authors agree with Holmes in that oxygen consumed by the
brains of insulin-treated animals is less than that
consumed by normals. However, they make it plain that
there is a very definite oxygen consumption still taking
place even though there is very little lactic acid
available.

Dameshek and Meyerson (11) in quoting Olmstead and
Logan said that the latter found that "decerebration and
decapitation experiments on cats might indicate the ori-
gin of the insulin convulsion was probably in the medul-
la, more specifically in the respiratory center". These
observers were impressed with the possibility that
through the lowering of the blood sugar certain oxida-
tive processes become depressed to such a degree that
the brain cells are affected in much the same manner as
asphyxia. Also, "Kleitman and Magnus, in experiments
on rabbits found that hypoglycemia led in some way to
an irritation of the medulla and thus to convulsions",
even though they noted "arterialization of the blood.
This, together with the well-known sensitivity of the
brain to diminution in its oxygen supply, may account
for such phenomenon as tremor, twitchings and convulsions,
the end result of the lack of oxygen being coma."

Lennox (32), in reporting his data on the average
respiratory quotients of the various portions of body
represented, found that they differed widely. His re-
sults were: (1) Brain, 0.95; (2) Arm, 0.86; (3) Leg,
0.72.

Rudy (44) in speaking of Dudley and Laufberger and
their work on mammals said that these observers showed

a marked decrease in oxygen consumption during severe
and prolonged hypoglycemia which is derived from the
fact that the venous blood is bright red during the in-
sulin reaction. Rudy, however, feels that "diminished
oxygen consumption does not necessarily mean anoxemia,
but may be explained by the decrease in oxidation of
carbohydrates because of the lack in glucose, and by
the hypersecretion of epinephrine."

Epinephrine and sympathetic nervous control theory;

Best (4) states the "epinephrine causes a prompt
mobilization of liver glycogen and probably later the
conversion of muscular glycogen to lactic acid which is
in turn converted to dextrose or glycogen, or both, in
the liver."

Cannon, McIver and Bliss (7) demonstrated that
excitation of the sympathetic nervous system occurred
with marked hypoglycemia. They state that if the blood
sugar falls below a critical point in consequence of a
deficiency, the splanchnic neurons of the sympathetic
system are set in action as indicated by increased
suprarenal secretion. Both the nerve impulses and the
increased secretion of epinephrine have the effect of
liberating sugar from the liver into the circulation,
thus tending to restore the equilibrium.

Brooks (6) found that surviving spinal cats with
the cord transected in the cervical region have a di-
minished resistence to insulin. Hypoglycemia activates
the sympathetic system of a spinal cat to such an ex-
tent that, while 0.5 unit of insulin per kilogram is
never fatal to a normal cat, and usually one can recover
from 1.0 unit per kilogram, the "spinal animals in which
the adrenals have been inactivated cannot recover spon-
taneously from 0.5 unit of insulin per kilogram". He
concludes that "hypoglycemia causes strong sympathetico-
adrenal activity in normal cats can likewise induce
activity of this system in a spinal cat". His results,
he feels, afford further evidence for the existence of
a spinal mechanism which is capable of exerting some
influence upon the peripheral adrenal system because
even though convulsions are eliminated by cervical tran-
section of the cord, other hypoglycemia symptoms occur.

Rudy (44) believes that "the low blood sugar ac-
tivates the sympathetic nervous system and causes a
hypersecretion of adrenalin. The increased epinephrine
secretion promotes a glycogenolysis which causes a
gradual elevation of the blood sugar and relieves the
symptoms. If, however, the blood sugar continues to
remain low because of the overdose of insulin, its

effect continues and additional symptoms develop, such as convulsions and other neurological as well as mental symptoms". From this evidence, he concluded that the early signs of shock were due to epinephrine response, but that the coma and later signs were due to the drop in blood sugar, and he failed to state why this caused symptoms.

Dameshek and Meyerson (11) are opposed to the epinephrine theory. The data brought out in their experiments showed: (1) the diminution of the tremor and perspiration of the insulin reaction after the injection of epinephrine; (2) lack of dilation of the pupil during the insulin reaction; (3) the striking difference between the type of effect produced by insulin and that by epinephrine on the chemical constituents of the blood."

Dworkin (13) showed that "bilateral extirpation of the sympathetic nerve chains render cats permanently hypersensitive to injected insulin." In these animals, the blood sugar curves after insulin injection show a rapid and precipitous decline, with no evidence of a spontaneous recovery. Restitution to normal was brought about with the use of epinephrine or glucose.

Disturbed water balance theory;

Dameshek and Meyerson (11), although they do not consider this phase as a very likely cause for symptoms in hypoglycemia, mention its possibilities. They state that Olmstead and Taylor concluded from studies of the oxygen capacity of the blood that the blood became concentrated when the blood sugar reached its lowest level, while Rathery and Sigwald found a constant elevation of the plasma chlorides and a decrease in the spinal pressure in dogs with insulin hypoglycemia. However, Drabkin and Ravdin disagreed when they found that the cerebrospinal fluid pressure in dogs rose with the fall in blood sugar. "On the basis of these and previous experiments they found that insulin convulsions were caused by an increased cerebrospinal fluid pressure resulting from anhydremia. It is conceivable that the edema of the brain described by Schereschewsky in animals, and by Bowen and Beck in a human case, might be secondary to a disturbance in oxidative mechanisms in the brain and not a primary manifestation."
Cerebral malnutrition theory;

Rudy (44) believes that "in hypoglycemia, the brain cells suffer a lack in nutrition because of the low blood sugar." He feels that the neurological and

symptoms which occur in the first stage of the insulin
reaction are due to the effect of epinephrine on the
vascular system. If no organ damage occurs, the recov-
ery is rapid and complete. The drop in the blood sugar
with its by-effects is the chief factor in the produc-
tion of the symptoms of the insulin reaction. There are
two stages in the hypoglycemias of any origin. They are
both brought about by the drop in the blood sugar."

Dameshek and Meyerson (11) found that the uptake of
dextrose by the brain became materially reduced during
the severe hypoglycemic reaction, although that of the
arm usually became increased, and that the blood lactic
acid became increased during the reaction, no differ-
ences between vessels being noted. "There was no essen-
tial change in the dextrose content of the spinal fluid
during the period of observation."

Ravid (43) proposed that the action of transient
insulin hypoglycemia "may be initiated directly by
insulin itself or by the still unknown intermediary pro-
ducts of carbohydrate metabolism that it produces, as
by creating, as it were, a 'vacuum' for glucose in the
nerve tissues or by a process similar to this. The re-
sulting effect, then, may manifest itself by alteration

of function of either the nerve elements themselves, or the blood vessels supplying them."

Rudy (44) mentions that MacLeod "presented good evidence in favor of nervous control. He demonstrated that convulsions did not occur in a denervated muscle, even when the blood sugar dropped and convulsions were present in other muscles with intact innervation."

There is evidence that animals that are anesthetized, or who have cervical transections of the cord, do not show convulsions.

Powell (41) is also of the opinion that the symptoms are due to cerebral malnutrition.

Effects of Hypoglycemia Shock:

Ravid (43) described a transient hemiplegia as a result of insulin hypoglycemia. "The symptoms seen are shivering, perspiration, loss of consciousness, convulsions with conjugate deviations of eyes and head to right, contraction of muscle of lips, cyanosis of face--- symptoms and signs which are indicative of a definite cerebral involvement." He says that these are classical features of those seen in a lesion of the internal capsule and also involving the retrolecticular portion of the posterior limb.

Carr (8) states that "no matter what the cause, hypoglycemia may be manifested by stupor, amnesia, muscular twitching or convulsions and a number of other less striking symptoms such as restlessness, weakness, anxiety and fatigability."

The first signs of hypoglycemia appear to be due to an epinephrine response. Harrop (22), in discussing the toxic effects of insulin differentiates between mild reactions and severe reactions. The former are subjectively typified by a sense of weakness that is generalized and referred to the abdomen, feeling of trembling, and a sensation of coldness in the extremities and a numbness of the lips. Objectively, they display

pallor, sweating, moderate rise in systolic blood pressure, and the pupils are dilated. The severe reactions, he states, may simulate alcoholic intoxication by showing weakness and dizziness, sweating, mania or excitement, and delusions, obsessions and hallucinations; or there may be loss of consciousness with semi-stupor or stupor, and coma. "A characteristic feature of these attacks is the complete amnesia which the patient exhibits after recovery. His recollection is usually retained up to the moment when symptoms appear, and then it is lost completely."

Ernstene (14) noted that the "pulse rate and pulse pressure increased during hypoglycemia (the systolic pressure rises, and the diastolic falls) and the minute volume output of the heart increased during this state.

Rudy (44) is of the opinion that "the pallor, profuse sweat, increased pulse rate, elevation of blood pressure, vascular spasms and dilatations are brought about by the activation of the sympathetic nervous system and the hypersecretion of adrenalin". Furthermore, "the neurological and mental symptoms, which occur in the first stage of the insulin reaction, namely in the stage of the hypersecretion of epinephrine, are due to the effect of epinephrine on the vascular system."

He states that in Addison's Disease, the patients do not
develop the first stage due to epinephrine, but immerse
directly into the stage of central nervous system, hyper-
irritability with convusive seizures and unconsciousness
because of no compensatory epinephrine action.

Wauchope (50) in reviewing the effects of hypo-
glycemia states that "gross symptoms are headache and
fatigue. The bulbopontine system gives rise to disorders
of speech such as stammering, difficulty in forming words
and slow articulation" when it is affected by disturbed
function. "Ocular disturbance such as double vision,
nystagmus, inequality of pupils, but rarely deafness"
are also manifestations of hypoglycemia. "The cortico-
spinal group comprises paralysis, Babinski sign, aphasia,
perseveration, apraxia, motor irritability, incoordina-
tion, trismus, twitchings and convulsions which may be
tonic or clonic (localized or general) and may resemble
an attack of epilepsy. There may also be disturbances
of smell and taste or paresthesia of the tongue, but very
rarely incontinence of urine or feces." Tremor, chorei-
form movements, fibrillary twitchings, grimacing and
rigor of muscles belong to the strio-thalamic system
when it is disturbed.

Grayzell (21) showed that in rabbits which had been
subjected to severe convulsions one or more times showed
lesions in the cortex, particularly in the pyramical
cells of the third and fifth cortical layers. The milder
reactions consisted of zones containing shrunken, hyper-
chromactic cells with cork-screw processes, while the
more severe lesions showed, in addition, zones of necro-
biosis. The greater the number and the more prolonged
the convulsions, the more severe were the lesions. He
also states that "Speilmeyer showed that focal anatomic
lesions of necrobiotic type in the brain can result from
a purely functional circulatory disturbance." Convul-
sions associated with a variety of intoxications with-
out any organic occlusion of a cerebral artery can well
be regarded as due to vasomotor disturbances.

In a report of the meeting of the Societe medicl-
psychologique (39), Schmid of Munchenbuchsee spoke on
the histopathology of insulin shock and reported on ex-
perimental work on rabbits, and found that the changes
in the nerve tissue were much less marked than antici-
pated. Even though the eleven rabbits received daily
injections of insulin at the rate of 2 cubic centimeters
per kilogram of body weight, there were "no destructive
lesions, hemorrhage or edema found, only tumifaction.

The changes were those of a capillary hyperemia due to the epinephrine response to the insulin treatment." Bersot of Neuchatel described the neurologic syndrome of insulin shock. "Following injection, the patient, before becoming more or less deeply comatose, can present all sorts of cortical, pyramidal, extrapyramidal and vago-sympathetic symptoms. One most commonly observes tonic rigidity, clonic twitchings, more or less uncoordinated movements of the face and trunk, catatonic attitudes, stereotyped gestures, attacks of convulsive epilepsy, abolition of one or all reflexes, excessive perspiration and salivation, vasomotor disturbances, and a bradycardia down to 50."

Glueck (20): "When the patient reaches this shock phase the somnolence passes into a coma of greater or less depth, the normal reflexes become abolished, pathological reflexes take their place (Babinski, Oppenheim, etc.) and finally there sets in a total abolition of all reflex activity. Occasionally one observes a transitory hemiplegia, which, like the asphasia that may develop on awakening, disappears after a short time."

Paskind (40), in a synopsis of Finkleman and Ste-phans' observations says that they concluded, because of the abnormal reactions of schizophrenic patients to cold

and heat, that there is a similarity of these findings
with those in animals with a lesion in the hypothalamus.

Effect of insulin shock therapy:

Freeman (15) and Kasanin (30) agree that schizo-
phrenia is characterized by normal fasting blood sugar
levels, and that the average curve falls well within
normal limits, but the individual variability and the
percentage of abnormal sugar curves are greater than in
normal subjects.

Appel, Farr and Marshall (1) say that there is no
difference in the blood sugar reactions to insulin be-
tween those patients with affective and those with
schizophrenic psychoses.

Rapheal and Parsons (42) are of the opinion that
among the cases of dementia praecox, tolerance curves
vary according to the phase of the clinical course, the
older cases tending to show a more nearly normal curve.
The blood sugar tolerance curves of 28 schizophrenic cases
studied, showed 60.7 per cent abnormal curves when they
were evaluated by the climax of the hyperglycemia. When
estimated by the hyperglycemic area, the value was 72.7
per cent.

Glueck (20) states that apart from the well-known
fact of the individual differences in sensitivity to
insulin, the differences in the symptoms which appear in
the hypoglycemic state seem to determine the degree of

reactivity of the insulin antagonists (adrenalin, pituitrin) which affects in turn the progress of the hypoglycemic state. (Best (4), mentions that thyroxine, adrenal cortex, and anterior pituitary substance are also antagonists to insulin). In cases with considerable muscular irritability and excitement the tendency towards adrenalin neutralization of the effects of insulin is greater. "Muller is of the opinion that the patients are able to exercise considerable volition in the matter of permitting themselves to sink into the deeper phases of the hypoglycemic state," and "according to Sakel, old cases of schizophrenia seem to be more resistive to the influence of insulin than recent cases."

Glueck (20) continues by drawing attention to Sakel's hypothesis that the hypoglycemia supresses the momentarily most active part of the psyche, and thus makes possible the emergence of the latent aspects thereof, which then supplants to a greater or less extent the acute existing manifestations which have already been repressed by the insulin. "Before the stage of complete coma is reached, the hypoglycemia inhibits and delimits the existing (psychotic) state and converts it into its opposite (insofar as one might speak at all of opposites)." Sakel has observed in many patients that if one is delusional

or hallucinated, he would often manifest a brief period
of complete ludicity just before falling in a deep coma,
but the same patient later on, after there had been a
progress far enough to enable him to behave quite normal-
ly when not in hypoglycemia, would, during the shock,
become acutely psychotic again for a brief period before
sinking into deep coma. He calls this "the activated
psychosis." There appears to be a strong tendency to
the fixation of the condition which exists at the time
of the interruption of the hypoglycemia. "The interven-
tion of the shock in the case of an excited catatonic dur-
ing a state of calm and passivity would tend to estab-
lish a similar condition, also, for the non-hypoglycemic
phases. Conversely, in the case of a stupor, the inter-
ruption of the shock during a state of activity and ex-
citement, would tend to continue to activate the patient
outside of his hypoglycemic state." Therefore, Sakel
advocates that the original technic holds good for para-
noid types of schizophrenia, while stuporous patients
receive the most benefit when the hypoglycemia is inter-
rupted at a suitable time during the second phase of the
therapy, when there are indications of activation.
Roughly, excited catatonic types should be allowed to
progress to coma that is more deep. However, the latter

type of patient responds the least favorably to treatment, while the paranoid patients show the best progress, repeatedly.

Glueck (20) continues by saying that Sakel adheres strictly to a biochemical hypothesis with which he endeavors to sum up the explanation of the dynamics and modus operandi of this therapy. 1. The insulin puts a barrier between the cell and external stimuli, thus putting the cell at rest and enabling it to recuperate. He assumes that by keeping the pathologically conditioned cell-pathways in abeyance, the original, normally conditioned pathways have a chance to re-establish themselves. 2. The profound, almost annihilating assault which the cell experiences during the insulin shock perhaps actually eliminates the recently established pathological pathways, and in the course of recovery from the shock, only the older, well-established pre-psychotic pathways become re-animated. A general detoxication of the entire organism through the effect of the insulin on the entire metabolic status." Sakel assumes a progressive development in the cell of pathways which are specific to certain stimuli, and in time there develops a sort of "hierarchy of pathways" the older in time of origin naturally being the more resistive to insult. "Through

the elimination of the existing contemporary patologi-
cal pathways, the older, normal ones have a chance to
reassert themselves and adaptation to reality becomes
normal again."

Wortis (54) in explaining this further suggests
that "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
(Sakel) believes, is the vegetative centers." Wortis'
own view is that schizophrenia may be a symptom of
nutritional disturbance in the brain.

Marquart (35) concludes that "patients with acute
schizophrenia show greater inability to maintain the
steady physiological state than do patients with quies-
cent and chronic schizophrenia," and "it would seem that
the best explanation of this variety of organic disorder
is neither of a primary somatic nor of a psychogenic
cause, but of an intimate interaction of both so that
the total organism reacts in a thoroughly, disorganized
and incoherent manner, intellectually, emotionally and
physiologically."

Results of Insulin Hypoglycemia Therapy:

Since Sakel first introduced this new form of
therapy at Professor Potzl's Clinic in Vienna, it has
been employed in private and public mental hospitals in
Switzerland, in the Netherlands, in Poland, in isolated
German clinics, in Russia and in Japan. Wilson (51)
has suggested that Great Britian investigate and consi-
der the treatment very seriously. There are very few
reports available in the literature of this country, but
it is quite evident that many institutions and clinics,
as well as private clinicians are using this method
of therapy. At the present time, Sakel is in New York
State demonstrating his methods and technic, and has
patients under active treatment.

From time to time, there have appeared articles in
the journals with results quoted by various observers.
Wortis (54), and Glueck (19 and 20), who have been visit-
ing the clinics of Sakel, Dussik, and Muller in Vienna
and Munsingen, have reported earlier on the results of
the latter's work, and their own observations.

By November 23, 1936, at the meeting of the Societe
medicl-psychologique of Paris (29), the time was devoted
to a symposium by visiting and local alienists on the
insulin treatment of schizophrenia. "Muller of Munsingen

reported the experience in 300 cases in Vienna and Switzerland. There were only four deaths, and these were due to organic disease associated with the mental disorder. The results are grouped according to the duration of the disease: Group 1, disease of less than six months' duration; 89.8 per cent improved, including 73 per cent completely cured. Group 2, disease of more than six months' duration; 82 per cent improved, including 50 per cent completely cured. Group 3, disease of more than eighteen months' duration: 45 per cent improved, but including only 0.5 per cent complete cures."

These later reports are improvement over earlier ones as stated by Glueck (19), who quoted Dussik and Sakel's first available statistics on 104 cases. These agree with Paskind (40). These cases consisted of fifty-eight recent ones (duration of under one-half year) and forty-six older ones. In the group of fifty-eight recent cases, a good recovery was made in 88 per cent, enabling these patients to resume former occupations in the community, while 70.7 per cent attained a complete recovery. In the group of forty-six older cases (duration of illness more than one-half year) a good social recovery was made in 47.8 per cent, whereas a complete remission was attained in 19.6 per cent of the cases.

Wortis (54 and 55) quotes results in Sakel's clinic on ninety-five cases. His reports are very similar to those aforementioned.

Dr. G. A. Young, and Dr. R. H. Young of Omaha have over thirty cases treated or under treatment. The reports of their work are forthcoming. At the present, they believe that the therapy has merit.

Dr. F. G. Ebaugh of the Colorado Psychopathic Hospital has five cases under treatment, and four cases have been discharged with favorable results. He plans to continue very careful follow up studies on these cases.

Dr. Steinfeld (46) reported on three "old" cases and reports favorable results on them.

Wilson (51) in gathering statistics for the Board of Control for England and Wales reports that Lichter of Lugoi reported 9 cases, all of which showed no favorable response to treatment. Ederle, of Giessen, treated 15 cases and reported quick remission on new patients, and the old cases were "favorably" influenced. From Tagreb, five patients were discharged out of twenty cases. Kubo, of Keijo, Japan, reported good results with 17 cases, while Rose, of Vilna, Poland had "good" results on 19 cases. Anderson of Antwerp, had a "few" cases with "favorable" results.

Wilson continues with "all researches taken together, spontaneous remissions are found at most in 20 to 30 per cent of cases (with schizophrenia). Natural remissions in acute cases rise over 50 per cent, and in old ones are under 10 per cent." Among the complications of insulin treatment are mentioned bradycardia, tachacardia, pancreatic damage, alterations in sugar metabolism after shock, urticaria, laryngeal spasm, low temperature, aspiration of saliva and other material, and mental sluggishness.

There is no accurate report of the death rate other than that of Sakel and that of Muller, and these are carried only up until December, 1936. Those of the latter have already been mentioned (four in number). Sakel, in his first 104 cases, reported three deaths. (J. A. M. A. 26)

Some comment in the Journal of The American Medical Association (J. A. M. A. 27) issued warning that premature enthusiasm in relationship to this method should not be released.

Strecker (47) in defense of insulin therapy has this to say: "The methods of treatment for schizophrenia have been so numerous as to invoke scepticism against any new method, however well supported, but it is equally

true that malarial treatment of G. P. I. was greeted with the same misgivings. The fact that early cases do so well with insulin therapy does not imply that the same patients would have made an equally good recovery without such treatment."

The therapy is more efficient if administered soon after the illness begins. Sakel believes that the percentage of perfect remissions appears proportional to the duration of the illness. If the illness is present a long time, it seems that insulin shock therapy is unable to waken the physiologically inactivated and atrophied intellect. In full remission, recovery is effected and the patient is restored to society. When a good remission is obtained, it appears that the process is at least arrested.

Sakel, as stated by Paskind (40), has followed a number of patients for over a year who responded to the insulin therapy. "Of those with complete remission, 15 remained well over a year; and 34 over a half year. In the new cases, three cases of full remission, five of good remission and one of social remission have been followed by recurrence. In the others, 42 of the new cases show a good unchanging condition. Among patients with recurrences, five were retreated, three of whom

gained good remissions, one showed no results and one
is still being retreated. Of those of the old cases
with recurrence, six were retreated, one of whom gained
a good remission, one a full remission, two social re-
missions, one showed no results and one is still being
treated."

From the figures for remissions after this treat-
ment, it appears that they are in marked contrast to any
published statistics on spontaneous remissions, that
there is no doubt that insulin shock therapy for
schizophrenia has superior worth, at least for acute
cases. Just how long these remissions will last can be
revealed only by observation in time.

THE VALUE OF SMALL AMOUNTS OF INSULIN IN SCHIZOPHRENIA

In surveying the literature for statistics concern-
ing insulin therapy for schizophrenia, I found several
articles which indicated that insulin in small doses
played a part in the treatment of this disorder, three
of which I will review here.

Appel, Farr and Marshall (1) in their series of
treatments, show that small amounts of insulin are very
useful to increase weight, appetite, and to improve gas-
tro-intestinal function in all the psychoses.

Munn (39) states that "Bulatao and Carlson noted
that the injection of insulin increased the motility of
the stomach in the normal fasting dog. Campbell wrote:
'In intractable anorexia from various causes, hunger may
still be induced with insulin when other measures com-
pletely fail.' It has been proved that insulin stimu-
lates the gastric, biliary and pancreatic secretions."
Munn administered to five patients with catatonic stupor
an average of thirty units of insulin per day for forty
days without variation of the routine diet or the en-
vironment. As a result, "two patients showed no change
in the clinical condition, either mentally or physically.
The remaining three, whose psychoses were all of relative-
ly acute onset, of short duration and associated with

definite emotional precipitating agents, showed the improvement that is commonly observed in persons with this type of condition, with insulin treatment or without it." He concluded that it was impossible to estimate the influence of insulin therapy on the patients.

Bennett and Semrad (2) placed 25 Psychatric patients on high caloric diets and gave them small doses of insulin for malnutrition, and compared them with 25 cases not receiving insulin therapy, other conditions being equal. They found "an average of .423 pounds per week excess gain was found in the cases that had received insulin treatment."

And Wortis (53) describes the rapid disappearance of the schizophrenic patient's facial acne lesions who had under-gone insulin shock treatment (six cases). "The improvement appeared long before shock doses were reached. A relapse of the patient's skin condition occurred coincidentally with a relapse in the patient's mental state in the course of treatment. In the more marked hypoglycemic reactions, the skin is probably benefited by a cutaneous hyperemia and profuse sweating that insulin coma provokes. --- It is possible that both schizophrenia and acne are associated with some common disturbance of carbohydrate metabolism, which is in turn,

benefited by protracted insulin hypoglycemia. It is
also possible that the compensatory production of epine-
phrine which insulin hypoglycemia provokes may be an-
other factor involved."

NEW METHODS OF MEDICAL TREATMENT OF SCHIZOPHRENIA

Method by induced epileptiform convulsions:

Meduna (37), using a 25 per cent oily solution of camphor in intramuscular injections, raising the dose from 8 to 30 cubic centimeters, and later using metrazol in 10 per cent solution, intravenously in doses of from 3 to 7 cubic centimeters, deliberately produced epileptiform convulsions in patients. After administration of camphor, the reaction occurred in from one to two hours, while after introduction of metrazol, the convulsions appeared immediately. The convulsions produced by the two substances were similar, but metrazol, he thought, was more suitable. Of forty-three male patients treated, "nineteen patients were cured, seven showed improvement and the condition of seventeen remained unchanged. In the wards for female patients similar experiments have been carried out with camphor. Of thirty-one patients there, ten were cured, four showed improvement and the condition of seventeen remained unchanged. Summing up, Dr. Rath and I have treated altogether seventy-four patients, of whom twenty-nine (39 per cent) were cured, eleven (15 per cent) showed improvement and the condition of thirty-four (46 per cent) remained unchanged."

Meduna observed that the likelihood of cure is proportionate to the patients' liability to convulsions. He states further that "the percentage of cures far exceeds the number of spontaneous remissions recorded in the literature. There were relapses in which the prompt application of convulsive therapy led to a remission on the day following the convulsion." He feels that "the effect of the epileptic convulsions changes the chemical constitution of the organism in the way suitable for the cure of schizophrenia. Similar remissions of schizophrenia are not unknown, e.g. remissions preceding death, explainable by nothing but a preagonal change in the chemical milieu of the organism at the beginning of dissolution."

Carbon dioxide and oxygen therapy in Schizophrenia:

Henry (23) demonstrated that "practically all of the motor phenomena characteristic of human catatonic can be duplicated in the higher animals by means of injections of bulbocapnine in doses varying from 5 to 10 per cent of body weight. The extent to which catatonic manifestations may be produced is directly related to the degree of development of the neocortex." Dr. Langenstrass, in commenting on these results said that inhalations of mixtures of carbon dioxide and oxygen produced regularly a transient disappearance of the catatonic symptoms.

Loevenhart, Lorenz and Waters (33) found that sodium cyanide administered intravenously in proper dosage caused a cerebral stimulation in the stuporous phase of certain psychoses, and that a mixture of carbon dioxide and oxygen inhaled in a described manner is a far better agent for producing such cerebral stimulation. "By these simple chemical procedures, the mental processes in certain psychotic patients are restored toward normal for a period of from two to twenty-five minutes." These observers offer the following as symptoms of various levels of oxygen fixation:

1. Increased oxygen fixation: depression.

2. Normal oxygen fixation: normal activity.

3. Decreased oxygen fixation: increased psychic activity.

4. Further decreased oxygen fixation: stimulation, principally of motor cortex, often with maniac-like stimulation of psychic activity.

5. Greater decreased oxygen fixation: depression, anesthesia, paralysis (reversible).

6. More severe decreased oxygen fixation: death (irreversible).

Solomon, Kaufman and D'Elseaux (45) acknowledge the fact that bulbo-capnine produces cataleptic-like effects in animals, and they supposed this chemical substance to affect the cortical areas. Carbon dioxide administered showed results analogous to carbon dioxide in patients with cataleptic psychoses. "The cortex must be implicated." From the experiences with the carbon dioxide and oxygen mixture, "one cannot avoid a consideration of a possible direct stimulation of the cellular structure by carbon dioxide, because carbon dioxide is reputed to act as a specific stimulant to the cells of the respiratory centers, and therefore may likewise act as a specific stimulant to cerebral cells." They are prone to consider the possibility of stuporous disorder being in the subcortical or extra-pyramidal system.

D'Elseaux and Solomon (12) arrived at no definite conclusions concerning the effects of carbon dioxide administration to schizophrenic patients, but they believe that the remissions, if any, are due to stimulation of body economy and psychic changes not estimatable.

Bennett (3) states that "periods of lucidity have been reported by several experimenters ranging from five minutes to four hours immediately following the treatment of carbon dioxide administered. The amounts given

vary from 5 per cent to 50 per cent, and administration time from 30 seconds to 30 minutes."

Loevenhart (33) believes that a "true cerebral stimulation is brought about by reduced oxygen fixation in cerebral cells."

Leake, Guidel and Botsford (31) state that: 1. Carbon dioxide depresses the oxygen dissociation curve making oxygen in blood more available to tissues. 2. Cells use more oxygen in the presence of carbon dioxide. 3. Cortical cells in dementia praecox may be depressed by a relative asphyxia. 4. Carbon dioxide temporarily facilitates the restoration of functional oxidation in cortical cells, leading to anesthesis, so when it is withdrawn and the relative asphyxia returns, there is temporary stimulation of those cells due to oxygen want. Prolonged sleep treatment in Schizophrenia:

At the Second All-Union Conference of Psychiatrists, February 2, 1937, (29), Professor Ostankov of Moscow noted that Schizophrenia is far from being as common as it is now diagnosed. "This diagnosis has been made too easily by neurologists and psychiatrists without enough justification." The sleeping treatment of schizophrenia "introduced by the late I. P. Pavlov was discussed by Prof. A. S. Ivanov-Smolensky of Leningrad. If cortical

nerve cells are strongly stimulated for a prolonged per-
iod, they go into a state of inhibition. Pavlov concluded
that in cases of stupor there exists a diffusely spread
stimulation in the central nervous system. This inhibi-
tion preserves nerve cells from destruction. Thus the
sleep method was elaborated. It consists of putting the
patient to sleep for from five to twelve and a half days
by narcosis."

Bleckwenn (5) used sodium isoamylethylbarbiturate
intravenously in over 50 cases of all types of psychoses.
The dosage varied from 7 to 15 grains. "Normal lucid
intervals with spontaneous speech and the taking of
nourishment are seen in protracted cases of catatonic
dementia praecox lasting from 7 to 18 hours." He also
thought that sodium amytal is extremely valuable in pro-
ducing sleep associated with the excited mental states.

Gildea, Himwich, Hubbard and Fazikas (17 and 18)
in two contributions have reviewed the changes produced
by various types of drugs in Schizophrenic patients.
They state that there is "indirect evidence advanced by
Reichardt, Kleist, Loewy and others to indicate that the
syndrome schizophrenia is due in large part to some
dysfunction of the brain stem." Other observers lean
heavily on the possibility of a disturbance of the

function in the centers in the mid-brain which control
the vegetatibe system, and the low basal metabolic rate
found in most schizophrenic patients may be determined
by this defective regulating mechanism. However, there
is no evaluation of these hypotheses from any positive
findings from histopathological studies. The writers of
this article used drugs that are most effective in di-
lating the superficial cerebral vessels (carbon dioxide
and histamine) but found that the results were not as
effective in producing lucid intervals as did sodium
amytal. They concluded that: "The favorable changes in
behavior of catatonic schizophrenia patients to intra-
venous sodium amytal are not dependent on the dilation
of cerebral vessels, on the rise in the carbon dioxide
content or a fall in the pH in the arterial blood."
They found that sodium amytal had a "different and more
favorable effect, and longer duration than treatment by
anoxemia, high carbon dioxide concentration, or painful
stimuli. Since sodium amytal is a drug which acts pri-
marily in the brain stem, it is suggested that its effect-
iveness in rousing catatonic schizophrenic patients from
stupor lends some support to the hypothesis that the
symptoms of this disease are due in part to a dysfunc-
tion of the brain stem."

Dameshek, Meyerson and Loman (10) found that large doses of sodium amytal intravenously caused deep sleep, fall in systolic pressure, fall in temperature averaging 1 degree F., marked diminution in B. M. R. averaging 26 per cent, and slight though definite diminution in "uptake" of oxygen and dextrose by the brain. Small doses caused the same effects, less in degree, with variable effects on B. M. R. They thought that the extreme diminution in B. M. R. was "due probably to a combined effect of sleep and a more specific effect of the drug on brain (hypothalamic?) tissue."

Thorner (48 and 49) is of the opinion that "sodium amytal acts partly by inhibiting the activity of nerve cells. The various divisions of the nervous system are affected in the order of their phylogenetic appearance, i.e. the latest are most easily affected. The 'release phenomena' observed may be explained by the inhibition of higher inhibitory centers." He explained that the effects of intravenous sodium amytal are transcient. As far as mutism was concerned, only one out of eighteen persisted in talking when sodium amytal was discontinued, but ten of these would talk for several days after daily doses of 6 grains. "Flexibilities cerea was nearly always relieved under the influence of sodium amytal, but

as the effects decrease, the symptoms return. Delusions
and hallucinations were seldom helped."

Hoch(34) advocates the employment of prolonged con-
tinuous sleep by using mixtures of barbital compounds,
and maintaining the patient in a desired state of somno-
lence. The patients are kept under the influence of the
drugs for an average duration of twenty days. Signs of
barbital poisoning are watched for, and the patient is
tube fed with high caloric, non-residue diet two or three
times daily. Fecal impactions are guarded against by
soap suds enemas, magnesium sulphate once per week, and
occasional feeding of two or three ounces of vegetable
oil. "After this type of therapy, manic and depressed
patients awake, refreshed and rested, and with a con-
siderable gain in weight. Schizophrenic patients fre-
quently show the same type of improvement for from three
to ten days."

The use of dinitrophenol in Schizophrenia:

Looney and Hoskins (34) stated that McFarland had
suggested "that partial deprivation of oxygen tends to
produce in normal subjects a number of the abnormali-
ties of behavior that are seen also in the schizophrenia
picture. These include defective judgment, depression of
the autocritical ability, retarded perception, perseveration,

restriction in the field of attention, and deficiency of ethical inhibitions. Other schizophrenic traits occasionally seen are silly laughter, anger without adequate cause, destructiveness and mental confusion. Psychological tests under higher degrees of oxygen deficiency have shown lack of skill in motor performance, increase of discrimination time and slowness of association; hallucinations, delusions and stupor have also been observed under these conditions." They were interested to make a study of a drug, the essential effects of which might stimulate oxidative processes. They accordingly subjected a group of ten patients to treatment using dinitrophenol and later dinitro-ortho-cresol. Their results were not made known at the time, because the patients were still under active therapy.

Finkleman and Stephans (16) used dinitrophenol treatment on 12 patients with dementia praecox. The average increase in oxygen consumption rate was 37.16. The average loss of weight was 1.44 lbs. per week. "Two patients with a hypopituitary type of fat distribution did not respond to dinitrophenol with either a loss of weight or increased oxygen consumption. The oxygen consumption rates returned to the pre-treatment values after the administration of the drug was

discontinued. The non-protein nitrogen and icteric index increased and blood cholesterol decreased during treatment. The icteric index and the cholesterol showed a tendency to return to pre-treatment values, but the non-protein nitrogen remained increased. Five patients improved mentally. The increased attention given the patients during treatment cannot be ruled out as having seen the chief agent in causing the mental improvement. The reactions of dementia praecox patients to the administration of dinitrophenol together with oxygen should be studied."

Wishnofsky, Kane, Shlevin and Byron (52) showed that dinitrophenol "causes a significant increase in the concentration of the blood sugar. The elevation of the blood sugar level in hypersuprarenalism and other conditions in which there is an augumentation in heat production must in part be attributed to an increase in oxidative metabolism."

Cutting, Mehrtens, and Tainter (9) found that the "outstanding actions of dinitrophenol are sustained increases in metabolism and body temperature, with enormous activity of all metabolic functions. Doses within therapeutic range cause in man significant increases in metabolism without fever, which is useful in depressed metabolic states."

Statistics are wanting in this method of treatment and its therapeutic value in schizophrenia.

Masserman and Goldsmith (36) believe that the drug undoubtedly stimulates body metabolism, and, by inference, that of the central nervous system. He states that the best results were obtained in young individuals suffering from first occurrences of retarded-apathetic states.

There is reason to believe that the fever produced by dinitrophenol is not the principle by which it produces its effects, if any. Menzies (38) compared treated and untreated cases of schizophrenia over a period of six years with the use of induced hyperpyrexia by use of milk injections and other methods and showed that no increase in the recovery rate can be expected from this treatment alone.

SUMMARY

Dr. Manfred Sakel of Vienna first reported favorable
results of insulin hypoglycemia shock therapy in Schizo-
phrenia in 1933. Since then, he has instigated his
methods in Prof. Potzl's clinic, and his coworkers, Dr.
Karl Dussik and Dr. M. Muller, have approved them, and
the therapy has been adopted in private and public mental
hospitals in several nations.

The therapy consists in a progressive insulinization
of the patient through daily intramuscular injection of
increasing doses of insulin until the so-called shock
dose is neutralized after the lapse of a period of time
required by the individual case through the administration
of an adequate amount of carbohydrates.

The method is divided into four phases. In phase 1,
insulin is given one to three times daily, 15 to 30 units
per dose, started on an empty stomach, and carbohydrates
are withheld for 4 hours. According to the reaction at-
tained, the dose is increased each day by 5 to 10 units
until a hypoglycemia state with coma is reached. This
begins phase 2, in which a daily dose is given in the
morning and consists of the same amount as that which
produced the first shock. This may be varied according
to the reaction. Usually doses of from 20 to 250 units

daily are used. The effect is noticed three-quarters of an hour to five hours after the injection. Carbohydrates are fed as before. If treatment is to be terminated, glucose may be given with a stomach tube or intravenously. After a convulsion, the treatment is interrupted. The number of shocks depends on the amount of amelioration of the psychosis obtained. In phase 3, no insulin is given for varying periods of time. This rest interval may be increased after severe shock. During phase 4, the dose of insulin is decreased or the carbohydrates are given sooner after the injection of insulin.

During the insulin shock, the blood sugar level is lowered. Epinephrine and other antagonists to insulin are brought into play due to body response in an effort to restore the equilibrium. Oxygen up-take in the brain appears to be reduced, and at the same time, dextrose metabolism in the brain is reduced. (Whether or not this is cause or effect is disputable). Plasma chlorides are reduced during hypoglycemia, and in dogs there is possibly increased spinal fluid pressure. The various theories concerning the cause of shock symptoms embody anoxemia of the brain tissue, hypersuperrenalism, disturbed water balance, and disturbed carbohydrate metabolism in the brain. Evidence has been shown that

decerebration or cervical section of the cord, as well as section of a nerve will not produce motor symptoms of the affected areas.

Hypoglycemic shock is characterized by a variety of symptoms, both objectively and subjectively, ranging from slight feelings of uncomfortableness with sweating and pallor, to stuporous condition, convulsions and coma. Complete amnesia accompanies deep shock. There is dispute concerning the histopathologic effects of repeated or prolonged hyperinsulinism, but it is agreed that there are some deleterious and permanent changes. All sorts of cortical, pyramidal, extrapyramidal and vagosympathetic symptoms accompany the advanced hypoglycemic state before deep coma ensues.

Insulin shock therapy appears to suppress the abnormal psyche of the schizophrenic patient and tends to restore the normal intellect. Then, too, there appears to be a strong tendency to the fixation of the mental condition which exists at the time of the interruption of the hypoglycemia. Catatonic types of schizophrenia respond least favorably to this therapy, while the paranoid patients repeatedly show the best progress.

The reports of Sakel, Muller and Dussik, which are the most complete in the literature tend to show that cases of less than six months' duration treated with his

method were 89.8 per cent improved, including 73 per cent
completely cured. In the cases of more than six months'
duration, 82 per cent were improved and 50 per cent com-
pletely cured. In the cases of more than eighteen months'
duration, 45 per cent were improved but only 0.5 per cent
completely cured. These statistics covered over three
hundred patients, These compared favorably with other
more incomplete reports of other observers. Of these
104 cases, 15 remained well over a year and 34 over a
half year. In the new cases, 3 of full remission, 5 of
good remission and 1 of social remission, have been fol-
lowed by recurrence. In the others, 42 of the new cases
show a good unchanging condition. Among patients with
recurrences, five were retreated, three of whom gained
good remissions, one showed no results and one is still
being retreated. Of those of the old cases with recur-
rence, 6 were retreated, 1 of whom gained a good remis-
sion, 1 a full remission, 2 social remissions, 1 showed
no results and 1 is still being treated.

Small amounts of insulin have proven of some value
in improving the appetite, increasing weight, and im-
proving gastro-intestinal function in all psychoses.

Some evidence has been presented to indicate that
there is anbiologic antagonism between schizophrenia and

epilepsy, and there are some very limited statistics to indicate that intramuscular injections of camphor, and metrazol intravenously will produce epileptiform convulsions in schizophrenia and produce remissions in excess to spontaneous recovery.

Administration of carbon dioxide and other substances which cause cerebral stimulation have produced periods of lucid intervals in schizophrenia. This disorder appears to be characterized by low oxygen consumption in the brain, and low basal metabolic rates. Carbon dioxide appears to stimulate oxygen consumption in the cells and reduces oxygen fixation in blood and plasma.

Prolonged narcosis in schizophrenia appears to have favorable but transient effects. Of the sedatives and narcotics used, barbiturates, and especially, sodium amytal seem to be of the most value in producing the desired effects. Sodium amytal is alleged by some authors to act on the brain stem, where, by indirect evidence, the schizophrenic syndrome may be due to a dysfunction of this structure. Sodium amytal causes a diminution of B. M. R. and a diminution in oxygen and dextrose uptake in the brain. The lucid intervals produced by prolonged sleep therapy rarely extend over a period of several days. Flexibilitas cerea and other catatonic symptoms

are relieved more specifically by sodium amytal than other types of schizophrenic reactions.

Dinitrophenol administered to patients with this syndrome are aided transciently. This drug increases oxygen consumption rate, increase in concentration of blood sugar, and increases metabolism, which is useful in depressed metabolic states. Here again, cases of short standing are aided the most.

Pyretotherapy appears to have no value in schizophrenia.

SUMMARY

1. The purpose of the insulin shock therapy is to place the schizophrenic patient into a state of hypoglycemia by a regular series of insulin injections.

2. Convulsions and coma is regulated by introduction of glucose, orally or intravenously.

3. Insulin in large doses decreases the blood sugar level, decreases oxygen and dextrose up-take in the brain, and results in a variety of cortical, pyramidal, extrapyramidal and vagosympathetic symptoms.

4. Insulin shock therapy appears to suppress the abnormal psyche of the schizophrenic patient and tends to restore his normal intellect. The mechanism whereby these results are brought about are not known. The weight of evidence in the literature to date leans toward the theory that it is due to a change of metabolism in the brain, especially of carbohydrates.

5. Remission of the symptoms of schizophrenia following insulin hypoglycemia therapy are in marked excess to spontaneous remissions, and the latter are prolonged. Recent cases respond best to this therapy, the paranoid types receiving the most benefit, and the catatonic types the least.

6. Small doses of insulin are valuable in depressed
   metabolic states.

7. Of the other types of medicinal therapy, the barbitu-
   rates, and especially, sodium amytal, have the most
   value but the desired results are very transcient.

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