

# Psychological Bulletin

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## THE INSULIN-SHOCK AND METRAZOL TREATMENTS OF SCHIZOPHRENIA, WITH EMPHASIS ON PSYCHOLOGICAL ASPECTS

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In the past several years two new therapeutic methods have commanded the focus of psychiatric attention—the *insulin-shock* and *metrazol* treatments. The former, through large doses of insulin, effects a reduction in blood sugar and finally gives rise to definite shocks; the latter, through intravenous metrazol injections, produces epileptiform convulsions. Both methods, though leaving us in doubt as regards the actual nature of their therapeutic action, have infused new hope into the treatment of the psychoses, particularly schizophrenia. Both have definitely opened up new fields of research for the psychiatrist, biochemist, physiologist, neurologist, and psychologist. The aim of this paper, which makes no claim to exhaustiveness, is to acquaint the psychologist with these important therapies.<sup>1</sup>

### INSULIN-SHOCK TREATMENT

*History.* The insulin-shock treatment of schizophrenia was discovered by Sakel, who came upon it through the auspicious interplay of observation, deduction, and accident. It evolved from experimentation in the treatment of morphine addiction (44, 45). Sakel, assuming adrenalin to be operative in producing the withdrawal symptoms characteristic of morphine addiction, employed insulin as an adrenalin antagonist. Although careful to limit the doses so as

<sup>1</sup> Both therapies, though employed chiefly in the treatment of schizophrenia, have been tried with other mental abnormalities. This review, however, is limited to the use of these therapies in schizophrenia, covering work up to the spring of 1939.

to produce only mild hypoglycemia, occasionally he was surprised by deeper hypoglycemic reactions than were intended, and the patient slipped into severe shock. Observing beneficial effects from such occurrences, he used hypoglycemic shocks first in treating other excited states, and then in treating actual psychoses. The results obtained were encouraging, especially in cases of schizophrenia. In 1933 he began treating a large series of cases in the psychiatric hospital associated with the University of Vienna. From here the treatment spread rapidly to all parts of the world. In 1933<sup>2</sup> he reported on his new treatment of schizophrenia to the Verein für Neurologie und Psychiatrie in Vienna.

*Technique.* In presenting the technique of administering insulin-shock therapy we will describe the general method outlined by Sakel (47)<sup>3</sup>; this is the prototype from which all others derive. The technique is not rigid; Sakel is explicit on this point, stating that "the method itself is not stereotyped, and allows a wide scope of variation, so that frequent modification may often be necessary for any one patient. Success depends very much on the use of the right modification at the right time, in accordance with the changing behavior of the patient in the various phases" (p. 13).

The essence of the treatment is the repeated production, usually daily, of severe hypoglycemic shocks. These are effected through deep intramuscular injections of insulin, given in bed in the early morning fasting. Several days of cautious preliminary exploration are usually necessary to determine the shock dosage; this dosage may later be decreased in some cases to two-thirds or even a half, as sensitization takes place. Actual shock, which occurs from one to several hours after injection, is preceded by characteristic signs of hypoglycemia. These are weakness, hunger (which may be severe), perspiring, and progressive somnolence. Somnolence may be interrupted from time to time by episodes of excitement. As somnolence deepens, the patient loses contact with the surroundings and passes into shock.<sup>4</sup> Transitory spasms of the extremities, fine muscular twitchings, intense tremors of the entire body, stertorous breathing, and semivocalizations in the nature of grunts and snorts are common.

<sup>2</sup> This report was subsequently published in English (46).

<sup>3</sup> All references to Sakel's writings, unless otherwise specified, will be to his monograph (47).

<sup>4</sup> The term 'shock' has not been rigidly defined. The writers employ it in the sense suggested by Küppers (23), in which lack of ordinary awakability is made the criterion. Müller (31) employs a more concrete criterion, the inability to drink.

The body temperature may drop several degrees. As shock progresses, it may lead to deep coma. In some instances epileptiform convulsions either precede or accompany coma. After such convulsions spontaneous awakening usually takes place.<sup>5</sup> Coma, which is characterized by complete loss of response to any kind of stimulation, tends to occur from three to four hours after injection. It is allowed to continue for from a few minutes to an hour, depending on the psychotic picture and physical condition of the patient. Termination of shock is accomplished in several ways. If the shock is superficial and the patient's cooperation can be obtained, sugar-water is given by mouth; otherwise, a tube-feeding is administered. If a quick arousal is desired, an intravenous injection of glucose is given. This brings immediate awakening. After the patient is fully awake, regardless of method of arousal employed, a regular meal, rich in carbohydrate, is fed to prevent subsequent relapse into shock. The general sequence of events in coming out of shock is just the reverse of that in going in.

Individualization of treatment is important. By varying length, depth, and type of shock a range of reactions may be produced. Sakel strives to evoke, and then fixate, a reaction which is the diametric opposite of the psychotic picture he is trying to combat. Fixation is accomplished through properly timing the termination of shock. He states: "The observation that there is a tendency toward fixation of the clinical picture which happens to dominate at the time of termination, helps to explain the good results of the following modification . . ." (p. 53). The modifications recommended by him are these: Paranoid patients should be subjected to deep comas.<sup>6</sup> Stuporous patients should be aroused from shock at the point of greatest activity; if activity is insufficient, they should be subjected to metrazol convulsions. Excited catatonics should be put into deep somnolence, though not into actual coma, and convulsions should be avoided for them. No patient, other than a stuporous one, should be aroused during a reactivated psychosis (*infra*).

Improvement may be evidenced at first only by abatement of the more gross symptoms, such as hallucinations and delusions. Later, a disappearance of the more subtle emotional abnormalities may fol-

<sup>5</sup> The awakening is probably due to a sudden rise in blood sugar; the muscular activity stimulates adrenalin secretion, which, in turn, mobilizes liver glycogen.

<sup>6</sup> Comas may be encouraged by minimizing external stimulation; if necessary, they can be brought on through administration of luminal.

low. Occasionally a patient will become lucid suddenly and remain so from that time on; but such phenomenally sudden recoveries are rare. Usually lucidity is fleeting in its first appearances, and is confined to the hypoglycemic somnolent periods immediately preceding and following shock. As improvement continues, the lucid periods become progressively longer and extend further and further into the posthypoglycemic state (43). Increasing lucidity and accessibility necessitate more than ever the employment of tact in handling the patient. Sakel describes the situation as follows:

"One got the impression that the patients were so impressionable at this stage that they responded to almost any kind of suggestion from the environment. . . . Probably the most frequent reactions to environmental influences of this kind were paranoid attitudes" (p. 37).

Such periods of lucidity and accessibility afford the physician an opportunity to establish rapport (21) and to initiate psychotherapy (7).

After improvement is well under way, a temporary return of psychotic symptoms is not uncommon. Sakel describes this condition, which he calls "reactivated psychosis," as follows:

"The symptoms which occur during hypoglycemia vary considerably in different phases of treatment. Patients who show a short period of lucidity during hypoglycemia during the early phase of treatment, only to remain psychotic for the entire remainder of the day, later show a complete reversal of reaction and remain symptom-free throughout the day, but may show a certain reactivation of their psychosis during hypoglycemia" (p. 126).

James, Freudenberg, and Cannon (21) explain the reactivated psychosis ". . . as a combination of the insulin psychosis observed in mentally normal diabetics, and the actual psychotic condition for which the patient is being treated." To the writers it appears that the combination of symptoms in hypoglycemia is of the kind found in every organic mental reaction. It consists, first of all, of symptoms which are primarily due to the noxious agent; this may be a brain trauma, an infectious process, or a toxic state such as hypoglycemia. These conditions uniformly give rise to clouded consciousness, delirious symptoms, memory disturbances, etc. In addition, symptoms of a more individual nature may appear; these are especially prominent in psychotics, and seem to account for the so-called reactivated psychosis. We have frequently observed, especially in catatonics, that the same patterns which had previously been present during the severe acute psychosis reappeared in the clouded condition of hypoglycemia. These patterns may continue with remarkable

uniformity, as Palisa (35) points out. In different individuals, however, the shock picture varies widely.

Length of treatment, *i.e.* the number of insulin shocks given, varies according to improvement shown. Treatment should be continued, if possible, until all psychotic symptoms disappear. Two or three months may perhaps be considered a representative course. The question of how long to continue treatment in the absence of improvement is up to the physician. Müller (32) urges a trial of at least three months. Termination of treatment is not brought about abruptly; instead, milder, nonshock doses of insulin are given for a few days to prepare the system for discontinuance of exogenous insulin.

*Dangers.* The dangers of insulin-shock treatment should neither be exaggerated nor ignored. Statistics on fatality rates range between .5 and 1.5% (26, 32). For the most part, fatalities have occurred during unintentional protracted shocks—that is, when glucose or other agents fail to bring awakening. Organic brain syndromes have been reported as sequelae to such protracted shocks (13, 39); most of these, however, proved to be transitory. The dangers of the treatment may be decreased by first giving a thorough physical examination, including an electrocardiogram. Patients showing signs of myocardial damage, tuberculosis, and severe arteriosclerosis should be excluded from therapy.

*Results.* Adequate appraisal of the therapy is as yet impossible. Truly objective indices are not available. Uniform bases of diagnosis and precise criteria of improvement are lacking. Actually comparable control groups have not been used. Finally, the therapy is too new to permit determinations of the permanency of remissions ascribed to it. Despite these limitations to evaluation, the widespread use of the treatment with but few dissenting reports is suggestive of its effectiveness. As Freudenberg states (14): "All authors who have written on the subject, with a few exceptions, regard insulin therapy as an important step forward in the treatment of schizophrenia." In this review we can but cite a few of the more substantial statistics in point, with the hope that they are representative.

Sakel, reporting on his original group of approximately 50 insulin-treated cases, indicates full remissions (apparent cures) in 70% and social remissions in an additional 18%. His figures are considerably larger than those reported by other investigators. The discrepancy is due, in part, to the fact that his cases, being of more recent onset, presented a more favorable prognosis. More representative are the

figures of Müller (32) and Malzberg (26), who have carried out extensive surveys. Müller's figures are based on the combined data from 22 Swiss institutions and comprise 495 treated cases. He reports full or social remissions (patients allowed to return to their occupations in apparent good health), according to duration of psychosis before treatment, as follows: up to six months, 59%; six to twelve months, 52%; one to two years, 27%; over two years, 11%. Malzberg's figures are based on the combined data from 19 New York State hospitals and comprise 1039 insulin-treated cases and 1039 controls. His controls were matched with the treated cases for institution, sex, and type of dementia praecox. He reports 13% recovery and an additional 54% improvement in the treated cases, as compared with 3.5% recovery and 19% improvement in the control group. These data, when presented according to duration of psychosis before treatment, reveal the following percentages of recovery (mere improvement not included): *treated group*—up to one month, 43%; one to three months, 33%; seven to twelve months, 16%; one to two years, 12%; and three to five years, 4%; *control group*—up to one month, 8%; one to three months, 7%; seven to twelve months, 0%; one to two years, .6%; and three to five years, 0%. In comparing these figures with those of Müller it must be borne in mind that Müller's data include social, as well as full, remissions. Both Müller and Malzberg, as well as Humbert and Friedemann (20), report more favorable prognosis under insulin treatment for the catatonic and paranoid types than for the hebephrenic type. Malzberg reports the same trend, though with generally lower remission rates, for untreated cases. Müller finds the more favorable prognosis of paranoids under treatment to hold only for cases of less than a year's standing, and the prognosis of catatonics better in excited than in stuporous cases.

Not all recoveries or improvements are permanent. Relapses are reported by Malzberg in 24.5%, and by Müller in from 6 to 13%, of cases in remission. Müller finds the higher relapse rates in cases of long standing.

*Neurological Aspects.* Abnormal neurological symptoms, of varying degrees of severity, always accompany deep insulin shock. Sakel describes the general neurological change essentially as follows: During mere somnolence the reflexes remain intact, but with deepening shock they become pathological. Babinski, Oppenheim, and Mendel-Bechterew reflexes appear. Brief transitory muscle spasms, myoclonic twitchings, and intense tremors of the entire body may be

observed. If very deep coma ensues, all of the reflexes, including even the corneal and swallowing reflexes, disappear, leaving the patient in an areflexic state, with complete atonia of the entire musculature. Epileptiform convulsions are not infrequent. As the patient gradually awakens from shock following tube-feeding, the reflexes return in the reverse order.

Angyal (1) attributes the sequential nature of the neurological phenomena to a progressive impairment of cerebral function. He conceives this impairment as starting in the frontal poles, proceeding to the motor areas, and finally descending to the brain stem and medulla. His conception is in harmony with the theory that the phylogenetically recent structures of the brain are the more vulnerable and are the first to show disturbances of function. Pap (36), observing choreiform and athetotic movements and decerebrate rigidity, emphasizes the extrapyramidal nature of the shock motor symptoms. Our own observations indicate involvement of both cortical-pyramidal and extrapyramidal structures and suggest less regularity in the sequence of neurological symptoms than the foregoing descriptions might imply. Sakel and others emphasize their observations that the dominant hemisphere is affected first and recovers last in hypoglycemia. We doubt that this is a universal tendency. Orenstein and Schilder (34) cite evidence to the contrary, and our own observations have not indicated such a tendency. Incidentally, the most severe neurological syndrome we have seen, a hemiplegia of two hours duration, contradicted it; this hemiplegia involved the left side of the body in a right-handed individual.

Changes in the activity of the autonomic nervous system are common. These changes consist in shifts of tone from the parasympathetic to the sympathetic division, and vice versa (50, 54). The shifts appear to correlate with emotional state; fear and excitement are accompanied by dominant sympathetic tone. Increased sympathetic tone seems to be a characteristic forerunner of epileptiform convulsions in insulin shock. We regularly observe an increased blood pressure and pulse rate, and maximally dilated pupils a few minutes before seizure. In this latter respect, in our opinion, the insulin convulsion differs from the metrazol, in which maximal dilatation does not occur until the end of the tonic spasm (*infra*).

Electroencephalographic studies have shown both the presence of abnormal brain waves in schizophrenics and the dissolution of these waves with insulin treatment. Lemere (25) and Hoagland, Rubin, and Cameron (19) report the presence of excessive delta waves in

the electroencephalograms of schizophrenics; these waves disappeared after insulin treatment. Lemere also reports a strengthening of alpha rhythm during treatment; the alpha rhythm reverted to its pretreatment level, however, within a few weeks after insulin discontinuance.

*Psychological Aspects.* Interesting psychological abnormalities accompany hypoglycemia, especially the preshock and awakening phases. In some respects they resemble, and in others differ from, abnormal phenomena accompanying surgical anesthesia and other delirious states. Some of these phenomena are externally observable; others can only be arrived at through subjective report. Not all are to be found in any one case, as individual differences in reaction to hypoglycemia are great.

We shall report a few of our own observations. The effect of insulin on the emotional state varies widely from patient to patient. Furthermore, the emotional reaction does not necessarily correlate with emotional state preceding injection. Some patients, showing signs of fear before insulin, may remain apprehensive throughout the whole hypoglycemic period; others, showing the same signs, soon become quiet and relaxed under the effect of insulin; still others, at ease before injection, become almost frantic as hypoglycemia develops. One patient, who always resolved to rest quietly during hypoglycemia, became agitated, sat up in bed, and threw her arms into the air like a drowning person, just before going into shock. This was a daily occurrence with her. She described the experience of going into shock as a feeling of "submerging" or "being overwhelmed." It is apparent that the experience itself of going into shock produces fear in some cases.

The manner of going into shock varies. Some patients simply fall asleep and pass directly into shock from this state. More often, however, a state of clouded consciousness, lasting from a few minutes to an hour or more, precedes the shock. A similar, but shorter, state accompanies awakening. The clouding at times may be so slight as not to be readily apparent. Not infrequently we have conversed with patients in hypoglycemia who seemed completely lucid; yet on returning to them five minutes or so later, and finding them apparently unchanged, we found them oblivious of the previous visit. Such experiences indicate an impairment of retentiveness for new impressions, an anterograde or continuous amnesic state. As clouding progresses, the association processes become sluggish, retardation of speech appears, general reaction time increases, and verbal or motor

perseveration may occur; finally, the patient passes into a severe psychomotor retardation tantamount to a stupor.

It seems characteristic of this clouded, stuporous state that perception and comprehension are impaired earlier than speech and expression in general. Patients showing no indication of comprehending simple questions will later surprise one by accurately reproducing them, explaining that they understood them originally, but had been unable to speak. Such phenomena resemble motor aphasias; we doubt, however, that motor aphasia, unless conceived in a very broad sense, is the correct term for this verbal unresponsiveness. The impairment is not limited to speech, but involves all motor spheres; no attempt is made to substitute either writing or gestures for speech. The experiments of Küppers (24) furnish evidence in point. He induced three assistants to undergo hypoglycemic shocks. The number of shocks for the three totaled 36, several of which were allowed to proceed right up to the point of coma. The subjects reported the following general experiences: sensations of hunger and exhaustion; listlessness and distaste for activity, coupled with irritability in case rest was disturbed; and ideational paucity with impaired conceptual ability. More significant for the question at hand, however, is Küppers' observation that they failed to respond to painful stimulation (pinching) by any sort of defense movement. This is important because, after coming out of coma, the subjects not only remembered the stimulation, but described it as being quite painful. Küppers points out that with respect to pain sensitivity, these findings indicate a dissimilarity between the hypoglycemic stupor and the delirium preceding narcosis.

Perceptual anomalies are common. These embrace spatial, temporal, and motional distortions, and distortions of vividness and intensity. Spatial anomalies are reported by Benedek (6). They include distorted depth perception, in which persons and objects appeared to possess but the two dimensions of height and breadth, and micropsic and macropsic distortions of size. Temporal distortions are reported by Benedek (6) and Pisk (38). Several of Benedek's patients related experiencing a slowing up in the flow of time (present). More commonly, however, they erred in estimating past time. One patient estimated 15 minutes as being several hours, and reported that during this time he had relived all his life experiences. A patient of Pisk, on the other hand, perceived everything in the environment as speeded up; music seemed to her to be played much faster than it actually was, and patients and nurses appeared

to walk more rapidly than usual. Distortions in the perception of motion are mentioned by Benedek (6). The ability to merge the sequence of movements into a meaningful whole was diminished; normal movements seemed jerky, or else the moving object appeared to occupy several positions simultaneously. The patient describing these experiences likened them to some of the earliest movies in which the illusion of motion was imperfect. Anomalies in which sounds seemed louder, colors more vivid, and contours sharper than usual also are reported by Benedek (6). It should be mentioned that patients experiencing these perceptual distortions usually realize that they are due to the insulin. The above-described perceptual anomalies resemble those characteristic of hashish and mescaline.

Aphasic and apraxic phenomena are encountered. They are more common to the awakening than to the preshock phase. Palisa (35) and Sakel describe the gradual return of speech during awakening. The first signs are frequently the utterances of groans and other primitive sounds. Then come inarticulate babblings, which may be followed by a kind of baby talk. This latter has been considered a manifestation of an ontological regression (47); other similar manifestations are thumb-sucking, reporting one's age as of childhood, and mistaking the physician for one's childhood physician. Slightly later, a transitional phase of sensory and motor aphasia may occur; here, ungrammatical speech and literal paraphasia are the prominent features. The truly aphasic nature of these phenomena, which comes out during clinical examination, is also indicated by the patients' awareness of their expressive difficulties. A patient of Palisa (35), a student with medical training, referred to the condition expressly as motor aphasia. Another of his patients reported the experience in these words: "I don't know—I wanted to talk but always swallowed—the letters—the words—I couldn't get them out—I had them, though—talking turned into swallowing." The aphasic disturbances associated with shock, though most interesting from a psychological viewpoint, are difficult to study because of their transitoriness; they change from moment to moment and are usually accompanied by clouded consciousness. Occasionally, however, aphasias, and apraxias too, will continue well into the waking state. In two of our own patients a clear-cut motor aphasia persisted for several hours after consciousness had cleared. Only verbal expression, and not comprehension, was impaired. In addition to the motor symptoms, an amnesic aphasia persisted for some time. One of the patients referred to a pencil as "a thing to write." In a third patient we observed, in

combination with a slight motor aphasia, a condition which might be termed *swallowing apraxia*. This condition persisted for about an hour after she had fully regained consciousness. Several times she tried to drink; but although she tipped her head back and made all sorts of mouth and tongue movements, swallowing did not occur. Since she was not at all resistive, commented on her inability to swallow, and swallowed reflexly when tactually stimulated on the pharynx by a tongue-depressor, it appears that her difficulty lay in the volitional initiation of the swallowing act. We believe that these swallowing apraxias are fairly common, but because of their fleetingness and the clouded condition of the patient when they occur, they usually cannot be demonstrated as apraxias.

Amnesic phenomena, some of which have already been mentioned, occur. They include complete amnesia for deep shock and impaired retentiveness for impressions in the preshock and awakening phases. These are to be expected, of course, because of the clouded condition of the patient at such times. Retrograde amnesias for periods of varying lengths may be present immediately following shock; usually, however, they clear up later.

Various reactions which appear to be manifestations of disinhibition are observed. Some of these resemble phenomena common to alcoholic and other toxic conditions. In three male patients we observed a state of uncontrollable excitement developing in the preshock phase a couple of hours after injection. The state was strikingly similar in all three individuals, and in each individual occurred day after day with almost photographic uniformity. It lasted for about 20 minutes, during which several persons were required to hold the patient in bed. One patient exclaimed to his nurse: "Take off your glasses, I must hit you!"; and another cried in response to the physician's attempt to quiet him: "Doctor, I can't stop it—I can't." These states disappeared when the onset of shock was hastened by increasing the insulin dosage, but returned again in one patient whose dosage had to be decreased to prevent convulsions. They were characterized by clear consciousness; subsequent recollection of happenings was good. Fear symptoms were absent, and there appeared to be no paranoid basis for the states. Rather, they seemed to be simply an enormous, uncontrollable motor discharge. The patients later described their subjective experience as that of having lost control of their actions. The detached, impersonal nature of these excited states, the patient's awareness of the futility and undirectedness of his behavior, differentiates them from epileptic

twilight states and alcoholic and other toxic psychoses. In this respect this type of hypoglycemic excitement more closely resembles the organic 'drivenness' found in certain diseases of the subcortical ganglia, such as epidemic encephalitis. Quite likely temporary changes in the subcortical ganglia are involved in the above-described hypoglycemic episodes.

Other types of impulse release have also been reported. Palisa (35) observed in the awakening phase in a number of cases a sort of frank eroticism which did not, however, extend to gross sexuality; rather, it was a bid for affection. Palisa comments that this was in direct contrast to the patient's usual schizophrenic seclusiveness. Orenstein and Schilder (34) report the appearance of hidden sexual material, *i.e.* homosexual transference. Palisa (35) also mentions, in connection with about this same phase of the awakening period, the sudden appearance and disappearance of aggressive attitudes toward the environment.

A feeling of relaxation, accompanied by hypomanic attitudes, often follows awakening from shock (34). It is our impression that such attitudes are a favorable sign, as we have encountered them especially in cases showing improvement. Furthermore, we have observed a phase of slight elation, lasting from several days to weeks, following termination of treatment in recovered cases.

Recent findings suggest possible prognostic value for certain psychological tests in insulin-shock treatment. Bolles, Rosen, and Landis (8) report indicative results from a battery of performance tests. These tests, designed to measure the capacity for "abstract" behavior, had previously been found to show characteristic differences between normal subjects and schizophrenic patients. After applying the tests to a series of 19 schizophrenic patients prior to insulin therapy, Bolles, Rosen, and Landis compared the test results with the subsequent outcomes of treatment. They summarize their findings as follows: "Those patients whose performances were very poor on these tests tended to show no improvement under insulin therapy. Among those patients whose performances were relatively superior, the number of improvements was larger." Similarly, Piotrowski (37), on the basis of 25 pretreatment records, finds suggestions of prognostic value in some of the Rorschach indices. Among those indices on which a high score seemed suggestive of favorable prognosis were whole responses, human movement interpretations, and color responses; among those indices in which a low score appeared to suggest a favorable prognosis were rare detail responses.

## METRAZOL TREATMENT

*History.* The metrazol<sup>†</sup> convulsion therapy for schizophrenics was discovered by Meduna. The therapy is based on the assumption of a mutual antagonism between the schizophrenic process and epilepsy. Several reports suggested such an antagonism: It had been observed that when epilepsy is complicated with a schizophrenic syndrome, convulsions become rare or cease entirely (33); cases of catatonia had been known to recover after epileptiform convulsions (30); typical epileptiform convulsions are rare in schizophrenics (51). Meduna, reasoning from these reports, deliberately produced epileptiform convulsions in schizophrenics. Originally he employed camphor as a convulsant; soon, however, he abandoned it for metrazol, which produced a more immediate reaction. He first published on the treatment in 1935 (27).

*Technique.* The technique of metrazol treatment is relatively simple (22, 28, 41). The convulsion is evoked in bed. Attendants, in addition to the physician, should be present to protect the patient. Treatment is begun with an initial dose of from 3 to 5 cc.'s of 10% metrazol solution, the dosage depending on the sex and general condition of the patient. Women usually require less than men. Frequently the dosage has to be increased later, as a tolerance for the drug is built up. The metrazol is given rapidly by intravenous injection. Within a few seconds the patient coughs, becomes bewildered, restless, fearful, and confused, and then goes into convulsion. During the convulsion he is unconscious. The seizure, which is of the epileptiform type, lasts from about 30 to 80 seconds. Tongue-bites are prevented by inserting a gag between the teeth; this can easily be done, as wide opening of the mouth invariably occurs during the tonic phase of the seizure. After the convulsion the patient usually remains comatose for several minutes; then, either immediately or after an intermediate twilight state of clouded restlessness, he falls asleep. Convulsions are induced two or three times a week. A course of treatment comprises from 12 to 30 seizures, or, in terms of time, from 4 to 15 weeks. Meduna (28) urges continuing treatment through three additional convulsions after recovery, so as to stabilize the effect.

*Neurological Aspects.* The sequence of neurological events occurring during the metrazol convulsion has been carefully analyzed by Strauss, Landis, and Hunt (52) by means of ultrarapid cinematography and electromyography. They found that the convulsion, last-

<sup>†</sup> Known in Europe as cardiazol, and chemically as pentamethylenetetrazol.

ing from 45 to 60 seconds, consisted of three distinct, though somewhat overlapping, stages: first clonic, tonic, and second clonic. The first stage, with an average duration of 10 seconds, consists in the alternating contraction of agonistic and antagonistic muscle groups at the rate of two to four two-phase movements a second. The tonic stage, with an average duration of 5 to 10 seconds, is characterized by simultaneous high potentials in all muscles. The second clonic stage, with an average duration of 30 to 40 seconds, consisting in the alternation between simultaneous contraction and relaxation of all muscle groups, represents an alternating disappearance and reappearance of the continuous innervation of the tonic stage. The alternation is rapid at the beginning (12 to 14 contractions a second), gradually slowing to one or two a second towards the end, and terminating in complete relaxation. Careful analysis reveals definite differences between the two clonic stages. In the first, adduction and inward rotation of the limbs is associated with flexion of the knee, elbow, and head; in the second, adduction and inward rotation of the limbs is associated with extension of knee, elbow, and head. Furthermore, amplitudes of movement are greater in the first stage. These authors, on the basis of their findings, conclude that the first clonic stage is probably the expression of cortical stimulation, while the second is not. The second appears to be a state of repeated interruption of the decerebrate rigidity which was present in the antecedent tonic stage. The tonic stage seems to be one of continuous decerebrate rigidity. The fact that arm flexion, even up to  $90^\circ$ , sometimes occurs does not contradict this stage; decerebrate rigidity in humans is frequently accompanied by arm flexion.

Angyal (2) regards the first clonic stage as a psychomotor condition. The writers, while in thorough agreement as to the presence of psychomotor agitation after injection, regard this agitation as part of the aura rather than of the convulsion proper. Individual convulsion patterns apparently vary considerably. Meduna (28) reports tonic stages ranging from 7 to 26 seconds, and makes no mention of the first clonic stage. We have observed extremely short first clonic stages, as well as relatively long tonic stages, in certain cases. Sometimes the tonic stage begins with torsion of the head and body to one side.

Smooth, as well as striated, muscles are involved in the convulsion. Emptying of the bladder and ejaculation without erection in the tonic stage, and defecation at the end of the second clonic, are not uncommon (28). Severe blanching of the face, a vasoconstriction

manifestation, is often the first significant sign after injection. Sometimes, however, excessive reddening of the head and trunk, which may be accompanied by the appearance of goose flesh, occurs instead. Later, during the second clonic phase, cyanosis predominates. Meduna (28) attributes the cyanosis to impaired breathing in the preceding tonic stage. Pulse and blood pressure, which can only be measured during certain parts of the seizure, show characteristic changes. Shortly after injection, pulse rate may increase. It becomes still more rapid after the convulsion is over. Blood pressure is raised. Meduna (28) reports rises of from 5 to 15 mm. Hg in diastolic, and from 20 to 30 mm. in systolic, pressure immediately after the seizure. The pupils also undergo changes; in fact, the metrazol seizure affords an unusual opportunity for studying pupillary reactions in the epileptiform type of convulsion. Meduna (28) asserts that the pupils are usually dilated maximally and that the pupillary reflex is invariably absent.

While Meduna's description holds roughly, we agree with Georgi and Strauss (16) that it is not completely adequate. They report wide, fixed dilatation during the tonic and clonic stages, followed immediately by contraction, with continued unresponsiveness to light, after the first inspiration. They also report a hippus, *i.e.* a fluctuation consisting in rapid alternate dilatation and contraction of the pupils, occurring before recovery to normalcy. Our own observations indicate the following general picture, from which, of course, deviations often occur. Often the pupils are dilated before injection, presumably because of fear; however, if they are narrow before injection, they ordinarily dilate slightly before the onset of seizure, usually at the moment of coughing. With the onset of convulsion they suddenly dilate further, but do not reach a maximum until the middle of the tonic stage. From this point on they fail to react to light. With the first deep breath after the convulsion they often contract suddenly, but only for a few seconds; then either a hippus, or successive contractions and dilatations, each lasting several seconds, may occur before normalcy is reached. These observations lead us to the conclusion that the pupillary changes during the metrazol convulsion are the expression of sympathetic-parasympathetic imbalance, and that the so-called fixed pupil is essentially a 'pupillotomy,' as it is in all epileptiform convulsions.

During the recovery period following seizure, changes in the reflexes, both deep and superficial, are present (28, 49, 52). A completely flaccid state usually follows the convulsion. In this state the

Babinski reflex cannot be elicited; it appears later, however, while the patient is still unconscious, and persists for several minutes (49). Foot clonus is established somewhat earlier. In our experience, the most persistent pyramidal sign following the seizure has been the absence of Mayer's reflex (adduction of the thumb as a result of passive flexion of the first phalanx of the fourth finger). Frequently, the abdominal reflexes are missing for several minutes, and during this otherwise flaccid state, the teeth remain tightly clenched. The clenching persists for some minutes, during which the mouth gag cannot be removed except by force.

If the dosage is insufficient, as is sometimes the case since tolerance for metrazol increases during treatment, inadequate reactions result. Angyal and Gyárfás (3) distinguish two degrees of such inadequate reactions, psychic and abortive-motor. The former consists of vasomotor phenomena which are usually accompanied by severe feelings of anxiety; the latter consists of a few clonic twitchings, or, as we have sometimes observed, a short tonic stage, in addition to the vasomotor reactions and anxiety. Both forms are undesirable in our opinion. They tend to augment the fear of treatment and are often followed by extended twilight conditions and extreme agitation. Only in rare instances have we observed improvement, instead of setback, following them.

*Mechanism of the Convulsion.* The mechanism of the metrazol convulsion remains obscure. Speculation concerning it, however, is not wanting. Meduna (28), assuming a practically identical effect for metrazol and camphor, quotes Hildebrand on the effect of the latter drug as follows: "Besides the brain cortex the autonomic centers in the diencephalon are strongly stimulated." Denysen and Watterson (12) consider the chief effect of the metrazol to be vasoconstriction. Experimenting on 32 patients undergoing metrazol treatment, they administered amyl nitrite and histamine in conjunction with the metrazol. These drugs, which had a vasodilatory effect, opposed the action of the metrazol and in some cases prevented the convulsion. On the basis of their findings they conclude that metrazol acts solely through the vasomotor center and that the convulsion is due to a vascular spasm. Their findings and interpretation support the widely entertained view that epileptiform convulsions are the immediate effect of brain anoxemia, the anoxemia resulting from vascular spasm which impedes cerebral circulation. If it be granted that the convulsion is mediated through vasoconstriction, there still remains the problem of how the metrazol reacts on the vasomotor

center. One would suppose that transmission is through the blood stream. Yet, we doubt that this is the actual mechanism of transmission because of the short latency of the convulsion in some cases. We have frequently observed convulsions occurring eight seconds, and in some instances seven seconds, after the beginning of the injection, and Barnacle (4) reports convulsions as soon as five seconds after injection. Such short latencies would hardly allow time for the blood to flow from the vein in the arm to the vasomotor center in the medulla. Mediations through various autonomic reflexes suggest themselves as more likely possibilities. Animal experimentation seems to hold the key to the solution of the problem, an answer to which should cast new light on the complicated question of the epileptiform mechanism, especially in cases of reflex epilepsy.

*Psychological Aspects.* The psychological accompaniments of the metrazol convulsion may be grouped conveniently into those associated with the aura, or preconvulsive state, and those of the post-convulsive state, the patient being unconscious during the convulsion itself. The most commonly reported and most striking feature of the aura is a feeling of alarm, manifest in the facial expressions, spontaneous outcries, and subsequent accounts of the patients. A patient of Schilder (49) always exclaimed: "Mother, mother, help me." Such utterances seem to be more common when the onset of convulsion is delayed. The subsequent descriptions of the aura by patients vary considerably, but many indicate anxiety and a life threat. Schilder's patients described the first signs of the aura as a feeling of "electricity playing all over their bodies," or as an impression that the room was "filled with dazzling white light." Others have described the aura as an "infernal chill," "sinking slowly into a hole," "the anxiety of feeling one's self going" (20). Several of our patients reported vertigo in which the room seemed to revolve, and one of them thought the walls were coming down on her. On the other hand, Gillespie (17), who underwent a single metrazol convulsion for the purpose of self-observation, describes a somewhat milder experience:

"After the injection of 10 c.cm. of a ten per cent solution I felt my body and limbs coming to lie straight in the bed and my head turning to a central position. Then very rapidly something seemed to move in my arms and thorax and to pass up to the base of my neck, where it stopped and increased in intensity. This sensation was not painful, but felt very clear and circumscribed, half-way between thought and sensation like the ideas in delirium. Unconsciousness developed very quickly but otherwise its onset felt like the coming of normal sleep and was not resisted."

Our impression is that fear of treatment increases after several convulsions, and that abortive seizures, in which consciousness is not lost, excite more intense fear than typical epileptiform ones. The intense emotional experience of the aura gives rise, in many instances, to severe fear of injection. In several improving patients we observed a transitory reappearance of psychotic behavior patterns during this preinjection-fear state. With increasing improvement fear still remains, though it may be better controlled. In fact, even after patients fully appreciate the beneficial effect of the treatment, they tend to continue the course only with reluctance. On the other hand, a few emotionally deteriorated schizophrenics do not seem to mind treatment at all. One of our patients of this type actually seemed to look forward to the injections and, although he showed no improvement at all, declared in a stereotyped manner after each treatment that he felt much better. The emotional attitude of patients towards metrazol contrasts with that towards insulin. Many of our improving insulin patients urged continuance of treatment.

The postconvulsive state is characterized by clouded consciousness and retarded psychomotor activity. This state, so far as we can tell, is similar to postconvulsive twilight states following other types of epileptic fit. It does not follow immediately upon termination of the convulsion, but is preceded by a coma of from a fraction of a minute to several minutes in duration, and often by a few minutes of sleep in addition. If sleep follows the coma, the ensuing clouded state tends to be less pronounced. This clouded state presents characteristic symptoms which become apparent on probing. Speech expression and comprehension are impaired. Fully as striking are amnesic aphasias in which difficulty is experienced in naming recognized objects. Schilder (49) maintains that in most cases patients have greater difficulty in naming parts of their own bodies than in naming other objects. Retrograde amnesia for the injection, as well as for events preceding it, is characteristic. This amnesia usually clears up, however, and memory of both the injection and aura returns. Gillespie (17) describes his own experience as follows:

"On awakening I had a mild occipital headache, some aching of the mandibular joints and was conscious of a pungent smell at the back of my nose. At first I could remember almost nothing of the morning's events including the injection, and even the day before seemed indistinct, but otherwise feeling and comprehension seemed normal. Remembrance of the injection returned within a few minutes and of the other happenings of the morning more gradually, but even ten hours afterwards there was

some retrograde amnesia. For the remainder of the day the feeling was distinctly unpleasant, with headache, anorexia and malaise."

Cohen (10) asserts that after the convulsion the cognitive functions return in a definite order, which is as follows: esthesia, prosexia, gnosis, praxia, and mneseia. He finds that immediately after the convulsion pinpricks are not responded to; shortly after this they are responded to, but only by indefinite, mass movement. As time goes on, responses to pinpricks become more localized; they pass progressively through the stages of withdrawal of the pricked limb, scratching of a broad area contiguous to the point stimulated, and, finally, localized scratching of the exact point. During the period of inexact tactual localization he found corresponding inexact localization in the auditory and visual spheres. Addressed by name, patients turned their heads, but not necessarily towards the sound source; presented with objects they appeared to look "through" rather than at them. After the other symptoms had disappeared, amnesia, both retrograde and anterograde, was still evident.

Wittman (56) has studied the course of the metrazol postconvulsive confusion psychometrically. Using a battery of tests of attention, rote memory, retention, substitution, and paired associates available in different forms, she tested each of 30 patients before the convulsion and again at intervals ranging from one-half hour to 48 hours following it. Average scores indicated extreme inefficiency a half hour after the convulsion, with recovery to the preconvulsive level still not complete at the end of four hours. In a second part of the study she tested patients 24 hours after each convulsion with a view to determining rate of improvement during the course of treatment. Individual variations were noted, but average scores indicated a gradual improvement up through the ninth treatment, which improvement she attributes to increased interest, attention, and coöperation. Data beyond the ninth treatment were open to ambiguous interpretation.

*Results.* The metrazol therapy presents the same difficulties of evaluation as the insulin. We can but present a few statistics with the hope that they are representative. Meduna (28), reporting on the first 110 treated schizophrenic cases, indicates remissions in 54 (49%). Analyzed according to duration of psychosis prior to treatment, his data reveal the following percentages of remission: up to six months, 92%; six to twelve months, 86%; one year to one and a half years, 43%; one and a half to two years, 55%; two to three years, 25%; three to five years, 27%; over five years, 0%. Analyzed

according to clinical type, the percentages of remission are: simple type, 51%; paranoids, 55%; catatonics, 30%; hebephrenics, 67%. Beckenstein (5) presents the following results for 218 cases treated at the Brooklyn State Hospital: less than six months duration—13% recovered, 35% much improved, 44% improved, 9% unimproved; six months to two years—1.4% recovered, 15% much improved, 43% improved, 40% unimproved; over two years—.8% recovered, 5% much improved, 29% improved, 65% unimproved. He claims best results in paranoids of recent onset and poorest in hebephrenics regardless of recency of onset. Meduna and Friedman (29) report the combined results from 2937 cases treated in American and European hospitals. The gross American data indicate 19.86% full remissions and 38.43% improvement. Analyzed according to duration they reveal the following: less than six months, 60.95% complete remission and 20% improvement; six months to one year, 36.82% complete remission and 23.13% improvement; over one year, 8.36% complete remission and 37.76% improvement. The gross European data indicate 30.37% full remission. Analyzed according to duration they show 49.66% full remission for cases under, and 13.32% for cases over, 18 months. Mortality for the total 2937 cases is given as .29%.

*Dangers.* Meduna (28) makes the claim that the metrazol treatment is free from danger. He bases his contention on the fact that his data include no deaths, and that out of a thousand convulsions the only deleterious effects, aside from occasional backaches in which no injuries to the ligaments were found, were two arm dislocations and a dislocation of the jaw. Others report more serious consequences. Deaths during treatment are reported in from 0 to 2.2% of cases (3, 22, 28, 29, 42). The reported probable complications leading to deaths include pneumonia, lung abscess, and pulmonary embolism. Other complications include dislocations and fractures (29). A vertebral fracture was detected by Wespi (55), who pointed out the necessity of paying greater attention to complaints of backache. Nevertheless, fractures of spinal vertebrae were considered rare occurrences until very recently, when their incidence was investigated by Polatin, Friedman, Harris, and Horwitz (40). These investigators, through routine X-ray examinations, found a high percentage of compression fractures in the thoracic spine. They report fractures—some of them slight—in 22 out of 51 patients (43.1%) and state that the degree of injury usually bore no relation

to intensity of backache. Such findings may prove a serious objection to the use of metrazol, unless attempts to avoid this complication are successful.

#### COMPARISON OF INSULIN AND METRAZOL THERAPIES

Many workers in the field of shock therapy point out that the metrazol therapy is the easier to manage because the individual treatments are less time-consuming and require less nursing care (53). A metrazol treatment can be completed in half an hour, with little attendant danger of postconvulsive complications. An insulin treatment, on the other hand, not only consumes several hours, during every minute of which the patient must be carefully watched, but also necessitates constant observation throughout the day because of the danger of after-shock. A more important consideration, however, is the question of the respective therapeutic values of the two treatments. At present, no absolute statements can be made on this point. Both are of value. Cases refractory to one may respond to the other, and vice versa (29). For catatonic cases convulsions seem to be especially helpful (47). Our own impression—and this is supported by the two large surveys presenting together results from both therapies (42, 53)—is that, in general, the insulin-shock treatment is the more efficacious.

#### COMBINED TREATMENT

In an effort to retain the desirable features of both treatments, while eliminating some of the undesirable ones, Georgi (15) and Georgi and Strauss (16) have developed a combined insulin-metrazol therapy. The usual dose of insulin is given, and a metrazol convulsion is induced about an hour and a half later. Hypoglycemia is then terminated. Termination can usually be accomplished, in such instances, without tube-feeding, as the patient usually awakens after the convulsion and can be induced to drink the sugar solution. Georgi and Strauss (16) advise either giving insulin and metrazol together two or three times a week or giving insulin daily, with metrazol in addition on alternate days. They recommend the former for cases responding with violent seizures. Braunmühl (9) recommends, for schizophrenics of recent onset, starting out with insulin alone and, later, after about 20 shocks, adding a limited number of metrazol convulsions if necessary. The combination type of therapy offers the following advantages: It obviates the fear reaction so

common in the unmitigated metrazol therapy. Presumably, the somnolent state induced by the insulin tends to eliminate the fear-evoking experiences associated with the metrazol injection. The combined method lowers the threshold for convulsions, thus enabling an appreciably smaller metrazol dosage to be given. Finally, the combination therapy, in employing both insulin and metrazol, reaches cases which might be refractory to either one alone.

We are convinced that in many cases a combination of the two treatments is advisable. Such combined treatment, however, can hardly be prescribed in a blanket manner, as convulsions may have undesirable, as well as desirable, effects. Regulation should be based on the patient's reaction to a trial convulsion.

#### THEORY

Speculation concerning the actual nature of the mechanisms by means of which the pharmacological shock treatments effect cures has not been wanting. Much of it is vague. Each of the hypotheses tends to reflect its author's viewpoint toward the etiology of schizophrenic syndromes. Hypotheses range from the essentially physiological or organic to the essentially psychological. We can but mention a few. Among the physiological theories of insulin effect are those of Sakel, Demole, Georgi, and Freudenberg. Sakel (46) suggests the possibility of a general lowering of neural thresholds in psychotics through adrenal activity, which revives phylogenetically ancient and infantile pathway patterns latent in normal waking thought. Insulin, being an adrenalin antagonist, is supposed to reverse the process. A more definite and experimentally verifiable hypothesis is offered by Demole (11). He points to a disturbance in cerebral respiration preventing the oxygenation of the toxic products of metabolism, which accumulate and give rise to the schizophrenic symptoms. He suggests that insulin stimulates the oxybiotic processes necessary for detoxication. Georgi (15), on the assumption that schizophrenia is characterized by relative impermeability of cell membranes, suggests that insulin stimulates the exchange between the cells and their surroundings. Freudenberg (14) combines the hypotheses of Demole and Georgi into the following:

"In schizophrenia there is probably a primary disturbance in cerebral respiration, perhaps due to some lack of oxygenating substances. This disturbance leads to a collection of toxic products, probably originating from the protein metabolism. Insulin therapy induces the oxybiotic

processes necessary for detoxication and also an irritation of the cell membranes, which results in an increased exchange between the cells and their surroundings."

Among the psychological hypotheses are those of Glueck and Schatner. Glueck (18) considers the various emotional and motor phenomena occurring during hypoglycemia as constituting an emotional catharsis and states that the entire situation might be viewed ". . . as a highly condensed recapitulation of the process by means of which the fate of the ego-dystonic impulses is determined, a process which takes place normally, in the case of ontogenetic development, and artificially, in the course of psychoanalytic therapy." Schatner (48) believes the efficacy of the insulin-shock treatment to lie in its rendering the patient sick, helpless, and dependent. This state predisposes him to a transference in which the physician becomes the mother surrogate and, as such, can take advantage of the relationship to introduce suggestive therapy. We believe that psychological factors are involved in insulin therapy, as in almost every form of medical treatment; however, that the curative effect of such a definitely physical treatment as insulin shock is purely psychological seems *a priori* rather improbable. Furthermore, we question Schatner's explanation, inasmuch as some patients become relaxed and even lucid for short periods after the first small dose, which renders them neither sick nor helpless.

A physiological hypothesis of the effect of metrazol is offered by Meduna and Friedman (29). They suggest that the therapeutic effect may be due, in part, to increased cerebral oxygenation as the result of vasodilation. Schilder (49) offers a somewhat more psychological interpretation; "The victory over the death threat, expressed in the epileptic fit and lingering on in the perceptual and aphasic difficulty, enables the individual to start life and relations to human beings all over again." He characterizes the therapy by stating: "The treatment is an organic treatment reflected in psychological attitudes."

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