INSULIN THERAPY: A REVIEW, WITH SPECIAL REFERENCE TO THE MECHANISM OF CURE.*

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THE insulin treatment of schizophrenia has greatly stimulated investigations, not only into the problem of schizophrenia itself, but also into many aspects of general metabolism. It is difficult to give a detailed account of investigations already made because of their large number. Consideration here will therefore be confined mainly to papers concerning insulin, cardiazol and other recent treatments of schizophrenia read at the eighty-ninth meeting of the Swiss Society for Psychiatry held at Münsingen from May 29 to 31, 1937, together with some references to previous literature.

DIAGNOSIS.

Differences in opinion regarding the diagnosis of schizophrenia are well known. It is therefore of importance to define clearly the criteria of diagnosis, so that results in patients treated with insulin may be accurately compared. In this way we shall ascertain the types of schizophrenia most likely to improve with this therapy. Similarly the relationship between insulin-treated patients and spontaneous remissions will thus be determined. Suggestions of this kind were put forward by Frostig (1937) in his preliminary directions for insulin therapy in schizophrenia and deserve careful consideration.

PROGNOSIS.

Müller found (1937) that paranoid cases of schizophrenia treated with insulin showed the highest percentage of improvement, provided they were of not more than one year's standing. Where the duration of the illness was over one year, cases of catatonic excitement did best. This finding corresponds to that occurring with spontaneous remissions. Bumke, Ederle and Dussik (1936), examining a varying series of unselected cases, found not more than 30% good spontaneous remissions in recent cases (i.e., under six months). The incidence of spontaneous remissions seems to vary in different mental hospitals, partly because of the varying types of cases admitted to different institutions.

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Previous statistics of recovery-rates have been compiled on a basis unsuitable for comparison with the results of insulin and cardiazol therapy. It is therefore of great importance that all centres introducing these new methods should examine both treated and untreated cases under the same conditions.

Dussik (1936) pointed out that the average period in hospital of untreated first-attack schizophrenics of under six months' duration was 202 days, and of insulin-treated cases only 62 days. Kronfeld and Sternberg (Moscow, 1937), who have already treated more than 200 cases, studied all their cases from the standpoint of prognosis. They found cases which did not respond to treatment amongst all the different types of schizophrenia, and therefore state that the prognosis can only be approximate. In common with other workers they regard cases of several years' standing, the so-called terminal states (*Endzustände*) as especially unfavourable. In the experience of these workers, cases of slowly progressing hebephrenia with few symptoms, even if treated early in the disease, have an unfavourable prognosis. Apathetic, slack and hypochondriacal paranoid types are likewise unfavourable. They observe that better results were obtained in patients reacting with some emotional feeling towards their illness. Cases with some tendency to spontaneous remission had better prospects if the attacks showed an acute onset. Even long-standing cases of this type appeared to react favourably. In such cases it is frequently impossible to determine whether a remission might not have been obtained without insulin ; but if the remission begins in close connection with insulin therapy, it is probable that insulin accelerated the remission (Kronfeld and Sternberg). Every author stresses the good results in recent cases, especially those with acute onset, where early treatment is frequently successful after only a small number of comas. The spontaneous recovery-rate in these cases is known to be high, but the remission-rate following insulin seems to be much higher (Sakel, Dussik, Müller, Kronfeld and Sternberg and others). In such cases we cannot say more than that insulin has stimulated a natural tendency to remission. Kronfeld and Sternberg therefore believe that the effect of insulin therapy on chronic cases could perhaps provide us with more evidence of a specific action. But here the situation is still not clear. In their series of 200 cases, catatonics yielded different results, acute forms improving and the chronic stereotyped forms remaining unaffected. Their catatonic stupors generally failed to react. Kronfeld and Sternberg drew the following conclusions :

> " The symptomatic picture and the different types of schizophrenia grouped according to symptoms are of less importance for the final result than the character of the onset, whether acute or gradual, and the course and duration of the illness."

These authors find that the prognosis is better when a patient can easily mobilize his emotional forces. They regard as important the ability of the

patient to remain productive in his psychosis, to react to arguments or otherwise, or to exhibit crystallization of his delusional system. If a personality change predominates, the outlook is unfavourable. Finally, these authors regard a study of the pre-psychotic personality as important. Those patients which, on examination, show temperaments which are found to struggle with their psychosis even if only in a paranoid way usually react well to treatment. Paranoid cases which submit passively to their delusions are found to be resistant to treatment in most cases. All these criteria have been deduced previously to ascertain the probability of spontaneous remissions.

In our experience the constitution shows a certain relationship to prognosis. There was no marked asthenic type among the good remissions, neither was there a case with marked hereditary factors.

All the authors who have written on the subject, with a few exceptions, regard insulin therapy as an important step forward in the treatment of schizophrenia. Judging from reports up to date the number of social remissions after insulin in recent cases varies from 50 to 80%—about double the spontaneous recovery-rate. The reasons for these differences are numerous. Differences in diagnosis may be partly responsible. The selection of cases for treatment must also have some influence. Estimation of the degree of improvement varies in the hands of different examiners.

Müller, looking for the reasons for the variation in results obtained in a total of 495 cases treated in twenty-two different Swiss hospitals, found that an insufficient length of treatment occurred constantly in the less favourable reports. He regards sixty days of treatment as the minimum satisfactory period in refractory cases. Treatment should not be withdrawn as being unsuccessful before the expiration of this period. In his series there were some cases which even began to improve after the ninetieth day of treatment. It is his opinion that treatment should be prolonged up to ninety days, during which time about fifty comas should have been obtained. The fifteen comas tried by some workers have proved quite insufficient (Frostig). It was, of course, the general opinion that if a good remission occurred in less than sixty days of treatment the therapy could be withdrawn with safety. It may be said that even if insulin does prove to have a more specific effect on the process of schizophrenia, previous narcotic treatments (e.g., somnifen), if applied for similar long periods, might have shown better results than were actually achieved. One of the great advantages, however, of insulin over other narcotic treatments is the reliable antidote available, glucose, which makes interruption possible in any case of severe somatic disturbance. The danger of the procedure was everywhere over-estimated at first. In 495 cases treated in Switzerland by the "standard technique", the mortality proved to be only about 0·5%. The bad prognosis of untreated schizophrenic patients and the unsatisfactory results obtained by other treatments applied hitherto render this risk justifiable.

Classification of Remissions and their Maintenance.

Müller proposed to divide remissions into complete, incomplete and partial. The complete remission must show a disappearance of all schizophrenic symptoms, a complete restoration of normal affect, and full insight. Remissions of this kind have been reported from Vienna, Münsingen and elsewhere. Others (Kronfeld and Sternberg, and Press, 1937) believe that all the above conditions are seldom completely fulfilled, and that slight changes in personality frequently remain, especially in affect and will, though " perhaps only some lack of impulse, activity, or initiative " (Kronfeld and Sternberg). These authors regard it as inadvisable to expect complete remissions from a method the effect of which is more or less unknown. They consider success as being more convincing if improvement occurs in chronic cases, such as those suffering from hyperkinesis, stupor, refusal of food, and all those symptoms which render nursing difficult. They regard such results as they obtained with chronic cases as more valuable than the " complete remission " of a recent case liable to show spontaneous recovery in any case. They therefore prefer not to use the term " complete remission ".

The permanence of the remissions by insulin and cardiazol is not yet established. Müller mentions 6·4% relapses out of a total of 124 social remissions, in which treatment had been discontinued for varying periods up to eighteen months. While this preliminary figure seems to be favourable, nothing definite can be said for about ten years (Müller).

Modifications of Technique.

The technique of insulin therapy has been described lately by Frostig (1937). Müller (1937) pointed out that opinions regarding technique seemed to be divided into two schools. One attempts to standardize the methods ; another seeks to treat each case individually according to its nature. Sakel's experience (1936) was, that each of the different phases of hypoglycæmia (euphoria, excitement, somnolence, slight and deep coma, and epileptic fits) has a different therapeutic action. He recommends that stuporose cases be interrupted at the maximum period of excitement and catatonic excitements during the maximum of repose.

Another modification was suggested by Georgi (1937), and called " Summationsverfahren ". He combines Sakel's insulin method with the cardiazol treatment of Meduna (1936), as a result of the discovery that epileptic fits have an important therapeutic effect. The patient is less alarmed if the cardiazol convulsion is given at the time when insulin has induced somnolence or sopor, one to two hours after the injection of the coma dose of insulin. This moment was also chosen because the liability to twitchings and epileptiform attacks is greatest at this stage of hypoglycæmia. It is believed that some

cases which show no improvement with insulin or cardiazol used separately may still show a remission when the two methods are employed in combination. The number of cases treated up to date by the dual method is too small to allow of a final judgment of its therapeutic value.

Many cases, especially old-standing ones, remain unimproved by the usual insulin therapy. An attempt has therefore been made to prolong the period of coma, suggested by Sakel and others. Kraulis (1937) worked out a special method for the purpose. Insufficient cases have been treated hitherto by this further modification for results to be given. Kraulis based his modification on the impossibility of leaving a patient longer than about two hours in coma, since with longer coma irreversible changes in the tissues might occur, produced by deprivation of carbohydrates. He therefore gave only small quantities of sugar, beginning in the fourth hour after injection of the coma dose. The amount of sugar given must be so arranged that the patient does not awake, on the one hand, and that no dangerous somatic signs (such as irregularity of respiration, slow, frequent weak pulse) occur on the other. The nasal tube is introduced at the beginning of the fourth hour, and 10–15 grm. of sugar are given. After one to two hours a further similar amount of sugar is supplied, and such administration repeated until the final interruption. Very pronounced individual differences in the amount of sugar needed are observed. By means of this gradual carbohydrate supply the coma may be prolonged up to twelve hours. The blood-sugar level will be found to be between 40–60 mgrm.%, and must be tested frequently during the prolonged coma. A sudden fall in the blood sugar threatens severe symptoms. The patient may awake after an increase of the blood sugar to over 60 mgrm.

The Mechanism of Cure.

Insulin therapy was first given empirically and the results obtained hitherto seem to justify its application. Possible "rationales" of the cure were developed later. They are at present not much more than working hypotheses, which may prove of some help in further investigations.

(1) *Psycho-pathological.*

In the opinion of Kronfeld and Sternberg, three factors, connected with each other, characterize improvement: (*a*) "Quietening effect on instinctive activities. (*b*) The induction of euphoria, with a change in the habitual mood and decrease of psychotic trends. (*c*) A reappearance of normal somatic sensation. The contents of the individual somatic experiences lose their psychotic significance. From these internal changes a longing for contact with reality results, and is able to break through autistic behaviour." This is similar to Klaesi's view regarding his narcotic treatment of schizophrenia.

Storch wonders whether the psychic happenings in insulin remissions differ from those in spontaneous remissions. He stresses the need to investigate the mechanism of improvement for the reason that all the transitional changes observed during improvement may serve to explain the nature of hallucinations.

(2) *Patho-physiological.*

Investigations along these lines have been made lately by Georgi, Beiglböck, Demole (1937) and others. A short preliminary account regarding some changes of metabolism in schizophrenia may be useful. Pfister (1937), by means of the lævulose tolerance test, observes a rapid rise of the blood sugar in acute schizophrenia, followed by a retarded fall. Chronic cases show a slower rise and a very retarded fall. Similar findings were obtained by Mann (1925–28) in psychotic patients generally. Pfister, in explaining this observation, believes that the ergotropically over-sitmulated organism of the acute schizophrenic aims at keeping large quantities of sugar in the blood ready for use. The chronic cases show, in his opinion, a disturbance of absorption from the intestine, and also of regulation by the vegetative nervous system. On the other hand, the retarded fall of the blood sugar may be due to some disturbance in sugar utilization. In connection with this assumption it is of interest that the oxygen consumption in schizophrenia, as well as in some other forms of mental disorder, is reduced to about 80% of the normal (Hoskins, 1933 ; A. S. Paterson, 1934 ; Topper and Murlier, 1933).

Golla (1928) found a diminished excitability of the respiratory centre to CO_2 in psychotic patients, and Mann (1928) a failure in compensation of the acid-base equilibrium. He believes that these changes may account for the abnormalities in the reaction of the vegetative nervous system and the carbohydrate metabolism.

Adrenaline induces a sudden rise in blood sugar in acute cases and only a very small one in chronic ones (Pfister).

Insulin in the proportion of $\frac{1}{15}$th unit per kilogram of the body-weight induces a lowering of the blood sugar by 20–30% in normal people in thirty minutes. After a further half-hour the normal level is again reached (Pfister). This is supposed to be due to normal adrenaline counter-regulation. If the rise to normal is retarded, it means that there is present a diminished preparedness for reaction on the part of the sympathetic system. In schizophrenia there is often found this retarded rise to normal, and also increased resistance to insulin (Sakel, Niver (1937) and others). Normally, change of posture has little influence on blood-pressure, but in schizophrenia the blood-pressure is said to fall after a change from the lying to the standing position (Pfister). Pfister found that the body temperature of schizophrenics in a cold bath did not fall as far as in normal people. Similarly, a hot bath induces only a slow rise in temperature (Pfister).

From these investigations Pfister concludes that in schizophrenia there is a disturbance of the vegetative nervous system involving the whole organism, including the cerebral cortex. In acute cases there is an initial increased stimulation of the apparatus of regulation, which later, in chronic cases, decreases and finally becomes reversed, with ultimately a complete failure in the activities of the vegetative nervous system. Different conclusions, however, were arrived at by R. Jung and E. H. Carmichael (1937), who investigated the vasomotor reactions and the heat regulation in catatonic stupors and were unable to detect any morbid changes. According to their view the cold hands and œdema seen in catatonic stupor are sufficiently explained by the patients' akinesia, and they believe that disturbances in the vegetative nervous system cannot represent the primary cause of schizophrenia. Wespi (1937) found that during insulin therapy the vegetative nervous system was stimulated, the stimulation alternating between parasympathetic and sympathetic. Demole (1937) suggested as another hypothesis a primary disturbance in cerebral respiration ; this inhibits the oxygenation of the toxic products of metabolism, the importance of which has been stressed by Gjessing (1937) and others. Insulin, then, induces the oxybiotic processes necessary for detoxication.

The investigations of Gjessing (1937), Jahn (1935) and Greving (1935) are of great interest. These authors attribute an important role to products probably originating from protein metabolism, which are retained and exert a toxic action. Gjessing stresses the importance of his discovery of nitrogen retention.

M. Forstmayer and Nicolayev (1937) investigated the permeability of the blood-C.S.F barrier in schizophrenia. They came to similar preliminary conclusions, finding a diminished permeability, which may occur at the onset of schizophrenia or later in the illness. The " toxic products " which induce schizophrenia can only very rarely be retained in the brain-cells by this diminished permeability. Nicolayev found an interesting relationship between the decreased permeability of the blood C.S.F. barrier and the globulins in the cerebro-spinal fluid. When permeability is diminished, the C.S.F. globulins are increased, but in the unsuccessful cases in which permeability is only temporarily increased by treatment, no increase in the C.S.F. globulins is found. Nicolayev regards the increase in C.S.F. globulins as an expression of a parenchymatous damage to the brain-cells at first reversible, later irreversible. He states that in successful cases of insulin therapy the diminished permeability is usually lessened and a fall in C.S.F. globulins occurs, because the parenchymatous damage to the brain-cells has disappeared. If the permeability remains diminished insulin therapy seems to be unsuccessful. In rare cases, with normal or augmented permeability, insulin has no point of attack. Georgi's investigations suggest the same conclusion, and he believes that insulin and cardiazol induce an irritation of

the cell membrane which results in an increased exchange between the cells and their surroundings. He compares his conception with the opening of " sluices " connected with various intracellular processes, and thus considers it as an important factor in the therapy.

Georgi divides the physiology of hypoglycæmia into three stages :

Stage 1.—This lasts from the injection of insulin to a hypothetical " turning-point ", about one to two hours after injection. Georgi states that up to this turning-point the cell sugar probably remains normal, or augmented in spite of the lowering of the blood sugar. He believes that an augmented " potential " (gradient) is then formed between the cell and the blood sugar. An alkalosis is also present. He assumes that in consequence of these changes a special liability to twitchings and epileptiform attacks exists at this " turning-point " (one to two hours after the injection).

Stage 2.—With the " turning-point " the cell sugar is thought to diminish, including the sugar of the brain-cells. The permeability of the cells is therefore increased. At the same time the ionic balance is altered (see later). Stage 2, then, lasts from the " turning-point " till the interruption of hypoglycæmia with glucose. During this stage both the blood sugar and the sugar of the brain-cells are probably greatly diminished, and coma is present until interruption takes place.

Stage 3.—This stage commences after interruption with glucose, and compensating processes occur in the opposite direction to those described in Stages 1 and 2, with, again, an increased liability to epileptic fits.

Georgi's hypothesis concerning the carbohydrate metabolism is based on blood-sugar investigations. The blood sugar does not invariably correspond to the severity of hypoglycæmic symptoms. It is often found to be slightly increased during coma in comparison with the earlier stages of hypoglycæmia (Sakel, Heilbrunn, Zeghauser, 1937). The C.S.F. sugar, however, is decreasing corresponding to the severity of hypoglycæmia symptoms (Day, Niver, 1937, Zeghauser, E. C., 1937) ; this may be connected with the carbohydrate content of the brain-cells, but only investigations on the real carbohydrate content of the brain could provide us with more evidence for Georgi's hypothesis. This hypothesis may be compared with previous theories concerning the action of insulin. The theory of Bürger (1937) assumes that insulin stimulates the burning of glucose and the glycogen formation in the muscles, and that by these means the blood sugar falls. (No lowering of the blood sugar is found after experimentally cutting the blood-supply to the muscles.) The liver serves as a source of sugar by the transformation of its glycogen into glucose, which passes into the blood-stream and so to the muscles. When the glycogen depots in the muscles are filled, glycogen formation in the liver again follows. Collazo (1924) and his co-workers consider the muscles to be the seat of insulin activity. With high doses of insulin, such as are given in insulin therapy, the burning of sugar is so augmented over a long period

(respiratory quotient raised) and the blood sugar becomes so low that the carbohydrate depots in other organs as well as the liver (Cramer, 1924) and including the muscles are drawn upon, and their carbohydrate stores are decreased (" turning-point ", Georgi ; compare Hawley and Murlin, 1925). The respiratory quotient again falls in the later stages of hypoglycæmia. Kerr (1936) has recently examined the glycogen and free sugar content of the brain, following an overdosage of insulin. His results do not completely confirm Georgi's hypothesis. It seems that the turning-point is really the time of onset of the clinical symptoms of hypoglycæmia. It does not coincide with the initial decrease of the brain carbohydrates (experiments of Kerr with cats, which have, on the average, a normal blood sugar of 183 mgrm.%). The free sugar content of the brain is already greatly diminished before the occurrence of hypoglycæmic symptoms. No augmented " potential " between cell and blood sugar exists. The difference between the blood sugar and the free sugar of the brain steadily decreases in accordance with the increasing severity of hypoglycæmic symptoms (Kerr, 1936).

Kerr's experimental results with reference to these points are tabulated below :

TABLE I*.—*Difference between Blood Sugar and Free Sugar Content of the Brain.*

	Following an overdose of insulin.		
Normal mgrm.%.	Two hours after injection; no hypoglycæmic symptoms.	Depressed, prostrated.	Twitchings.
86	26	20·75	2·33

The proportion of blood sugar to the total carbohydrate content of the brain seems to have some direct relation to the severity of the hypoglycæmic symptoms.

TABLE II.*—*Ratio of Blood Sugar to Free Brain Sugar plus Glycogen of the Brain.*

	Following an overdose of insulin.		
Normal.	Two hours after injection; no hypoglycæmic symptoms.	Depressed, prostrated.	Twitchings.
1·00	0·57	0·50	0·26

* Average figures each from three to five experiments. The brain carbohydrates appear in mgrm. per 100 grm. brain.

Low blood-sugar levels, under 30 mgrm.%, must be maintained for about one hour (Georgi, Heilbrunn, R. Freudenberg, 1937) before coma occurs, and during which time they are presumably followed by a decrease in the brain

carbohydrates. The duration of hypoglycæmia is therefore an important factor in the production of coma. The condition of diminution of transference of sugar from the blood to the cells exists similarly in both hypoglycæmic and hyperglycæmic comas in diabetics (Brentano).

Georgi and Strauss (1937) believe that a surprising parallel exists between the patho-physiological changes in the second hour following the injection of the insulin coma dose, and the change which induces a cardiazol fit. The only difference between the changes is that after cardiazol they take place in a few seconds, but after insulin are extended over hours. The same shifting of the ions is found. For example, there is a fall in the potassium content of the blood during the first few hours following the injection of insulin, and the same fall follows the cardiazol injection in a few seconds. There is the same slight increase in blood calcium in both procedures. These changes are supposed to be connected with an increased permeability of the cell membranes. Beiglböck confirms the findings of Georgi, and also finds a decreased potassium content of the blood following insulin. Banting, Best, Collip (1922), and, more recently, Beiglböck, Accorneo, L. Bini (1937), have found an alkalosis of the blood after insulin. A. E. Kulkow, W. J. Weiland and B. E. Kakusina (1937) investigated the narcotic treatments of schizophrenia, and found similar changes in the blood potassium and calcium after barbiturates. Armstrong (1929) found a decrease in the corpuscular acid chloride following somnifen narcosis. Insulin often increases the chlorine content of the serum. There is also an increased loss of chlorine by sweat and gastric juice (Beiglböck). Beiglböck explains all these changes by the electrostatic theory of Keller (see H. Eppinger, H. Kaunitz, H. Popper, *Die seröse Entzündung*, Vienna, Julius Springer, 1935), according to which blood-serum is negatively charged and the apparent parenchymatous cells positively charged. Certain ions, or non-ionized substances, have a tendency to wander to the plasma, and others to the cells. For example, the blood-corpuscles have a small sodium and a high potassium content, the opposite conditions existing in the plasma. Sugar, urea, phosphates, potassium and the non-ionized component of calcium are attracted to the cells, while sodium, chlorine, the ionized calcium, magnesium and some amino-acids are attracted to the plasma. In hypoglycæmia these ionic shifts are accelerated in the normal direction. Its mode of action may be similar to that suggested for previous methods of treatment of schizophrenia by Rudolf (1931). He regards the alteration in the ratio between corpuscular bicarbonate and the corpuscular chloride as the common mechanism of cure in previous treatments. Some increase the (alkaline) bicarbonate, others diminish the (acid) chloride, and thus by altering the ratio in a more alkaline direction they compensate for the failure in the acid-base equilibrium, which Mann (1928) found to exist in psychotics.

In other pathological conditions the direction of attraction of the ions is altered. For example, in anaphylactic shock (in this condition it is to be

noted that there is an absence of eosinophils) there is a sudden increase in the tissue sodium, and potassium migrates from the cells and travels into the serum. The same process occurs in " serous inflammation " (Eppinger, 1935). Recently histamine has come to be regarded as playing an important part in the establishment of anaphylactic shock (Holtz, 1937). According to Zipf (1937) it is only formed in acid conditions. Jahn and Greving (1935) believe that the somatic changes in schizophrenia to some extent resemble those described in connection with anaphylactic shock. Therefore Beiglböck's conclusions that the changes in hypoglycæmia (with augmented eosinophils) are the converse of those found in anaphylactic shock becomes of greater importance.

Although the metabolic findings in schizophrenia are not absolutely specific, the following hypotheses concerning its basis and the mechanism of cure can be regarded as established. 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. Similar but more sudden changes take place in cardiazol therapy. Golla (1928) states : " Intoxication might be attributed to abnormal products of metabolism or to tissue acidification from deficient oxidation . . . ." On the other hand, a permanent ionic disturbance consequent on a failure of respiratory compensation could of itself produce a general disturbance of cerebral physiology (Golla).

Improved brain oxidation and the alkalosis occurring during hypoglycæmic coma may be two factors of great importance in the recoveries seen after insulin therapy.

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