INSULIN THERAPY.

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SINCE Sakel (1) introduced treatment by insulin a vast literature has emerged from all countries. This was admirably reviewed by Wilson and Rees-Thomas (2) in 1938, so that consideration is given here to publicalions since that date. Even so, it has not been possible to incorporate all the publications, but a sufficient number has been drawn upon to present the essential position as it is to-day. Whatever may be the final judgment on the efficacy of insulin therapy, there is no doubt that its introduction has been an enormous stimulus to therapeutic endeavours. Its main interest has been to the psychiatrist, but the problems presented have attracted the attention and interest of workers in other branches of medicine. Ebaugh (3) has summarized this interest thus: "The physiologist has become interested in the mechanism which produces the coma; the biochemist is interested in studying the various chemical changes which take place during therapy; the neuropathologist is concerned with the pathologic changes that occur during and after the therapy; the internist is concerned with the problem of 'punishment' that the body is forced to absorb during the actual treatment; the psychologist is absorbed in following the psychological changes which take place under the influence of the treatment; the orthopaedist desires to know the type of fractures occurring during insulin, electrical and metrazol therapy; the neurologist studies the influence of these therapies upon the organic nervous system; and the psychiatrist attempts to explain the manner in which the psychosis is altered."

A relatively brief review of the literature, such as this purports to be, is facilitated by a classification of the different aspects of the treatment. Various contributions will be considered, therefore, in so far as they relate to—

(1) Modifications of the method of administration and general management.
(2) Frequency, type and treatment of complications.
(3) Results of treatment; prognostic factors.
(4) Psychological, biochemical and histopathological aspects.
(5) Conclusions.

MODIFICATIONS OF THE METHOD OF ADMINISTRATION AND GENERAL MANAGEMENT.

In the ten years which have now elapsed since the introduction of insulin therapy much experience has been gained. Problems remain unsolved, but it is now possible to evaluate more clearly the possibilities and advantages of the method. In the light of this additional experience many modifications have been made in the technique. Sakel (4) in 1938 recommended modifications of his original method, and various other workers have elaborated their own

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variations, several of which merit consideration. In an attempt to avoid the severe symptoms Beno (5) suggested a modification whereby the same dose of insulin was administered on successive days. The actual dosage remained small, so that deep coma was not produced. Sargant and Craske (6) gave doses which were described as being just insufficient to produce a slight coma or hypoglycaemic excitement. They aimed at producing a state of drowsiness, and the patient was awakened by the administration of glucose if even a slight coma was suggested. Tomlinson and Ozarin (7) reported favourable results from a similar method in which they employed an average dose of 5 to 50 units of insulin. They experienced only 4 convulsions in over 4,000 treatments and there were no contra-indications to the method. Benefit has been claimed, and is readily possible in the treatment of minor symptoms. If, however, the symptoms are of a psychotic and severe nature then the use of such methods seems doubtful, unless there is some other contra-indication to intensive treatment.

One of the major problems, which has been aggravated by war conditions, is the length of time involved for the course of treatment and the necessity for a large trained staff to be available. It is not surprising to find, therefore, that numerous efforts have been made to modify the technique so that the period of time should be shortened and the degree of nursing supervision reduced. With this end in view insulin has been introduced intravenously instead of intramuscularly, it being hoped that a saving of insulin would result as well as the time involved in treatment. Jones (8) reported that the same amount of insulin was required intravenously as by the intramuscular route, but that coma was produced more rapidly. One patient who was coma-resistant remained so to intravenous insulin. Similar results were reported by Sherman, Mergener and Low (9), and Goldfarb (10). Polatin, Spotnitz and Weisel (11) favour this method of administration. They found that a smaller dose of insulin was necessary to produce coma and that this developed more rapidly. They also reported quite frequent spontaneous recoveries from coma, so that the patient could then drink the solution of sugar. They were of the opinion that the degree of nursing supervision was lessened. Sandison and McGregor (12), after an extensive period of observation, reported that by this method of injection a saving of insulin amounting to 28 per cent. was obtained. They found also that hypoglycaemia occurred earlier and was more profound, and that recovery after termination was more rapid. They were of the opinion that insulin produced its beneficial effect by a stimulation of the nerve centres controlling the autonomic system. Studies of the flow of gastric juice suggested to them that intravenous insulin was a more powerful autonomic stimulant than intramuscular insulin. Mahoney and Herskovitz (13) reported on urticarial complications following intravenous injections, and they advocated giving initial small doses of insulin subcutaneously to determine the degree of sensitivity to the drug. They reported furthermore that there was a tendency to develop secondary coma in spite of an adequate glucose intake. Peterson and Lutz (14) have employed this method of administration as being more likely to induce convulsions during coma.

Various modifications in the type of insulin have been used. Protamine zinc

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insulin has been tried because of its prolonged action in depressing the blood sugar. Neither Goldman (15) nor Sandison and McGregor (12) were impressed by the efficacy of this method. The latter were of opinion that there was no particular danger involved in giving this drug intravenously, and they found no apparent advantage from a combination of protamine zinc with ordinary insulin. The consensus of opinion is against the use of this drug, and Reese and Van der Veer (16) have summarized the objections: (*a*) The effect of equal doses is not the same, and the dose must therefore be constantly varied, as no uniform treatment dose can be established; (*b*) closer co-operation with the laboratory is necessary; (*c*) the danger of after-shock is greater, and (*d*) epileptiform attacks are more frequent. Polatin (17), while agreeing that there was no therapeutic advantage over ordinary insulin, suggested that it might be beneficial if the latter produced allergic symptoms. Goldfarb (18) and Kant, Phillips and Stolzheise (19) have recommended that the administration of insulin in small divided doses was more effective in lowering the blood sugar. The latter suggested that the total dose of insulin be divided and the second half be given one hour after the first. They claimed that the amount of insulin necessary to produce hypoglycaemic coma was reduced and the number of days before the initial coma developed was also shortened.

There are differences of opinion as to the duration of treatment, particularly as to the number of comas which should be given. The general opinion is that if improvement is to be achieved, evidence of this will be apparent relatively early in treatment, and no advantage will be gained by more than 60 comas. Polatin and Spotnitz (20), however, have carried out this method over prolonged periods. They aimed at producing a mild hypoglycaemic state characterized by weakness, excessive perspiration and drowsiness. They have reported that one of their patients had received such treatment over a period of 2½ years; marked clinical improvement was claimed, and they were of the opinion that the beneficial effects were cumulative. Protracted comas which lasted from 3 to 15 hours, with a subsequent state of stupor of from 7 to 72 hours, have been advocated by Billig and Sullivan (21) in those cases of schizophrenia where a satisfactory psychiatric improvement did not occur, or when previous shock therapy had been unsuccessful. They recommended the administration of thiamine hydrochloride and novaldine according to the severity of the symptoms.

The dosage of insulin depends on two factors: (*a*) the sensitivity of the patient, and (*b*) the degree of coma which the physician desires to produce; but neither of these factors alters the sequence of the symptoms.

Considerable variations have been experienced in the reaction of patients to insulin, and it is generally agreed that there is a marked individual sensitivity to the drug. Success in the induction of coma has been reported with doses of 15 units by James, Freudenberg and Cannon (22), and of 18 units by Parfitt (23); others have reported failures after the injection of enormous doses of insulin. Banting (24) was unsuccessful in one case after the administration of 1,000 units, and we have had a similar experience. The consensus of opinion is in favour of a gradual increase from the initial dose of 10 to 15 units. Reese and Sauthoff (25) have advocated giving an initial dose of 60 units so as to shorten the pre-

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paratory phase and increasing the dose daily by 10 to 30 units. The chief criticism of this, however, is the increased degree of risk. To avoid the use of very large doses of insulin in overcoming resistance in insensitive patients von Braunmühl (26) has developed his zigzag method. In this he has recommended alternation on successive days of the maximum and the minimum dose, and on the third day the administration of either half the maximum (delayed alternation) or the maximum dose (direct alternation). Variations of this have been elaborated and facilitate the development of coma on a lower dosage than was formerly required.

The second phase should be reached in the third hour and the patient should lose consciousness. Unless it is desired to produce some particular reaction on the part of the patient, the majority of physicians do not further increase the dose of insulin after the coma stage has been maintained. It cannot be stressed too strongly that the only safe method of assessment as to the dosage is by detailed observation of the development of the clinical picture. Considerable help will be obtained from a study of the tables which have been produced by Frostig (27) and by Ross and Malzberg (28). These tabulate the list of symptoms which may be expected and show their time relationship. Frostig (27) states that the efficiency of the same insulin dose increases from the 1st day of treatment until the 12th to 26th day. A decrease of efficiency is then observed, and another climax of sensitization occurs when the second part of the treatment is reached. In choosing the daily dose to be administered it is necessary to consider (*a*) the individual susceptibility, (*b*) the depth of the preceding coma, and (*c*) the actual change in the patient's sensitization. The progression of the symptoms makes it possible to use them as gauges of the depth of the coma. He divides the reaction into four stages: (1) the cortical phase, (2) the basal ganglial phase, (3) the midbrain phase, and (4) the medullary phase. He defines the absolute time limit as five hours, beyond which treatment should not be extended—though obviously it might have to be terminated earlier. The time at which the medullary phase is reached is dependent to a certain extent on the dose. Large doses may achieve this in three hours, whereas smaller may not achieve the same reaction for six to seven hours. He recommends that the dose employed should be such that the medullary symptoms appear in the last half of the fifth hour. He is of the opinion that the shock seems to be therapeutically adequate if the tonic phase persists for one hour, but his results suggest that this may be more applicable in recent cases. Rossman and Cline (29) favour the induction and prolongation of deep coma in more chronic types of illness. Obviously such a method carries with it a greater degree of risk and necessitates considerable experience.

The termination of the treatment is by the administration of sugar. Most physicians favour the original method by nasal feed except when any dangerous situation develops. Benefit has been achieved by ensuring that the solution of glucose is well diluted and warmed before being passed into the stomach, as recommended by Hunt and Feldman (30). The rate of absorption is thereby increased. Sometimes an intensification of the symptoms of hypoglycaemia has been seen after the administration of glucose, and this is considered to be due to an increased bodily flow of insulin as the result of stimulation by sugar.

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The practical point of this is that it is expedient to keep the patient under observation in bed for at least 30 minutes after feeding. In an effort to conserve sugar Sandison and McGregor (31) report their results from a feed in which sugar is replaced to a large extent by potato. Others who have used this method have not been so impressed by this variation, and have found the frequency of secondary comas to be increased. McGregor and Sandison (31) recommend termination of the coma by intravenous administration of glucose, and within a short period of time the patient should recover sufficiently to drink the potato soup. Many others recommend termination by the intravenous method as a routine procedure, among whom are Olsen (32), Leulier, Le Clercq, Casalis and Capelle (33). This method of termination should always be augmented by additional oral administration of carbohydrates.

Frequency, Type and Treatment of Complications.

Like many other forms of treatment the application of insulin therapy is not without risk; in fact in inexperienced hands the method is definitely dangerous. Isolated instances of complications have been recorded and will be referred to briefly. Freed and Wofford (34) reported a case of sub-arachnoid haemorrhage during insulin therapy, and refer to reports of various types of haemorrhage during treatment. They suggest that there exists a relationship between hypoglycaemia and haemorrhage into various organs. They consider that this is due to damage to the walls of the capillaries by anoxaemia, resulting in an increasing permeability. Pulmonary complications, including broncho-pneumonia, lung abscess and pulmonary oedema have been reported frequently. O'Neil (35) refers to pulmonary oedema as occurring in cardiac failure or as evidence of cardiac insufficiency; its onset may be most alarming. These complications will be referred to later as causes of death. Hinko, Fenton and Balberor (36) draw attention to the occurrence of allergic symptoms. They point out that sensitivity to insulin during treatment may not be limited to a decrease in tolerance and local reactions, but may suddenly show itself as an anaphylactic reaction and demand immediate and appropriate treatment.

Everybody is agreed that the prolonged coma is by far the most serious of the complications that may develop. If the patient does not wake up within 30 minutes after receiving the glucose feed, then intravenous glucose should be given. In most cases recovery of consciousness is rapid, but occasionally no response is obtained; coma becomes prolonged and may persist for hours, days or weeks. Fever, rapid pulse rate, increased respiration and vomiting are common accompaniments, and death may result, often through pulmonary complications. Sherrill (37) has shown that if animals are left too long in coma the administration of glucose will not revive them and they will die. Lester (38) studied 25 cases of prolonged coma and found the mortality-rate in this series to be 16 per cent., while the death-rate due to this complication in the total insulin therapies reported was 0·33 per cent. He was of the opinion that prolonged coma might be expected once in every 1,877 treatments.

An enormous amount of research work has been done in an effort to obtain an understanding of the mechanisms involved and to elaborate a satisfactory method of treatment. The large number of therapeutic methods suggested,

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together with the conflicting views on their efficacy, merely illustrate our inadequate knowledge at the present time. Lumbar puncture was recommended in the earlier stages; now many believe it to be of no benefit. Vitamin B_1 administration has been advocated by Freudenberg (39), Finiefs (40), Fraser and Sargant (41), Muller (42), and by Frostig and his co-workers (43), whereas Gillman and Parfitt (44), Goldman (45), and Cleckley and Templeton (46) have found no benefit from its administration. Adrenaline was recommended by Reese and Van der Veer (16) and by Fraser and Sargant (41), but is now generally accepted as of doubtful value and by some as definitely contra-indicated. Venesection was recommended by Frostig (47), whereas blood transfusion has been advocated by James (22) and his co-workers, Wortis and Lambert (48), Menzies (49), and Procter and Easton (50). The administration of calcium has been advocated by von Braunmühl (51), Finiefs (40), and Fraser and Sargant (41), but little benefit was obtained by Gillman and Parfitt (44) and by Muller (42).

Irreversible coma often develops in the early stages, and Muller (42) is of the opinion that it is avoidable and is due, as a rule, to deficiency in technique. Further administration of glucose by the stomach is valueless. In most cases this is merely retained and very little is absorbed. Binzley and Anderson (52) stress the fact that the reaction continues in the presence of normal or high blood sugar, which is generally agreed. Finkleman (53) is of the opinion that irreversible coma develops in those patients in whom the blood sugar rises to hyperglycaemic levels, but the brain is unable to utilize sugar. He questioned the usefulness of further intravenous glucose unless the blood sugar has been estimated and a low level found. Freudenberg (39) drew attention to the fact that the large doses of glucose given increased the ratio of carbohydrates to the other food metabolized, and to rectify this suggested the administration of vitamin B_1 as stated above. Cleckley and Templeton (46) considered that there was a marked deficiency in oxidation, and consequently advised giving riboflavin and nicotinic acid.

Patients who recover from a state of irreversible coma, not infrequently show definite mental improvement. This has been commented on by, among others, Easton (54) and Rossman, Murray and Cline (55), and because of this improvement Kraulis (56) at one time advocated that one should attempt to produce this reaction. Kant (57) disagreed with this because of the mortality rate, and also the danger of producing permanent organic brain damage. Frostig (58) considered that the danger to life, the possible damage to the brain, and the clinical results made the risks in the induction of protracted coma too great. Its therapeutic use could not be justified unless we were able to predict and control it. In our present stage of knowledge this cannot be done. Frostig (58) was of the opinion that there was no likelihood of protracted coma if treatment was terminated at or shortly after the beginning of the medullary phase. He suggested that the prolonged effects of insulin on the nuclei of the medulla resulted, initially, in suppression, and finally in paresis of their functions. Suppression of these would obviously lead to suppression of the mechanism for the assimilation of carbohydrates. To avoid this complication he suggested (*a*) termination as soon as signs of medullary involvement appeared; (*b*) if, because of the severity of the mental picture, more in-

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tensive treatment was necessary, then coma should be terminated, initially, by the intravenous method; (*c*) patients who showed a tendency to protracted coma should receive the regular administration of vitamin B_1.

The occurrence of epileptiform seizures has attracted considerable attention. They were considered in Sakel's (59) earlier writings, when he described two forms of hypoglycaemic coma—wet and dry; in the latter, convulsive attacks might occur during the third hour of hypoglycaemia. Frostig, Bennett, Schreiber and Thomas (60) have shown that there is no correlation between the degree of perspiration and the insulin convulsion. In a series of cases the percentage of shock without perspiration for the comatose type was 11·2 and for the convulsive type 14·7. As to the frequency of such convulsions Goldman (61) found the incidence to be 3·9 per cent., Frostig (60) 4·2 per cent. Goldman (61) was of the opinion that they were a characteristic of the patient rather than of the method, and that they were evidence of specific and probable individual irritability of the cerebral cortex to hypoglycaemia. There was some evidence that those patients were more susceptible to convulsive attacks whose mental symptoms were of long duration.

It is now recognized that there are two varieties of convulsion—early and late. The former occurs within 45 to 100 minutes after the injection, the latter in the fourth hour. Von Braunmühl (26) considered convulsions to be of the late variety if they occurred after the second hour. Frostig (60) and his co-workers have pointed out that the types of convulsions are not identical; those due to insulin consist of forceful lightning-like jerks, which they refer to as myoclonoid. They drew attention to the accompanying degree of vascular collapse which follows the twitching, even though all the myoclonoid twitchings are not necessarily followed by a seizure. The danger depends on the time of the occurrence of the seizure; the early variety are much less serious than the late. Many considered the early seizure of therapeutic value, but Schulz, Heilbrunn and Sternleib (62), Goldman (61) and Müller (42) disagreed with this opinion. Malzberg (63) reported that the recovery rate in the New York Hospitals was not increased in those patients who had convulsions, and thus threw doubt on the generally accepted belief that convulsions were beneficial. Late seizures, on the other hand, are to be regarded as dangerous, and as an indication to shorten the duration of coma or to reduce the dose. Müller (42) recommended in such cases the administration of luminal in 2- to 3-gr. doses early in the morning; and Frostig (60) has attempted to control the incidence of convulsions by intravenous injections of sodium amytal in doses of 1½ to 2 gr. in the myoclonic prodromal phase. The injections might be repeated if the twitchings should reappear. Compression fractures of the spine have been reported in 20 per cent. of those patients who develop convulsions during treatment by insulin. Various techniques have been elaborated to prevent the incidence of fracture, consideration of which will be found in the chapter on convulsive therapy.

Results of Treatment; Prognostic Factors.

A comparison of the results of treatment as published by different investigators is always difficult. This is due to the selection of cases, the tech-

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nique adopted and the evaluation of the clinical condition after treatment, in all of which there might be wide variations. Each new treatment for schizophrenia has found those readily optimistic, counter-balanced by others more guarded. Now that results are available in a fairly large group of cases, a better assessment may be made of the advantages and disadvantages of this method of treatment.

It is interesting to recall at this stage the previous results of schizophrenics treated by ordinary conservative methods. Stalker (64), in his follow-up study, has tabulated previous similar statistical studies by other physicians since the end of the last war. In his own series of 129 cases, treated between 1932 and 1937, which he was able to trace, 12 per cent. had a complete remission, 8 per cent. a social remission, 9 per cent. were improved, 21 per cent. had relapses and 50 per cent. were not improved. Guttmann, Mayer-Gross and Slater (65) followed up a series of 188 schizophrenics three years after discharge from hospital; initially all had been considered to be of good prognosis. They found that over 33 per cent. had remained well, 41 per cent. were in mental hospitals and over 50 per cent. were invalids at home or in hospital. In an early contribution Sakel (66) claimed 70 per cent. of full remissions among his recent cases treated by insulin. Of the others under treatment, the duration of whose symptoms was over six months, it was found that the result varied in direct relation to the duration of the illness. The results of 1,039 cases treated in the New York Hospitals were reviewed by Malzberg (63) in 1938, and these were compared with the control group of a similar number. In the treated group there were 12·9 per cent. reported as recovered and 27·1 per cent. as much improved. The corresponding figures in the control group were 3·5 per cent. and 11·2 per cent. If one included all degrees of improvement, the corresponding figures were: treated 65 per cent., controls 22 per cent. Ross, Rossman, Cline, Schwoern and Malzberg (67) reviewed this same treated group two years after treatment and found that 12·7 per cent. were considered recovered and 14·2 per cent. much improved. When one included all degrees of improvement the number fell from 65 per cent. to 45·4 per cent. They concluded that the condition of these schizophrenic patients treated with insulin had become practically stabilized with respect to the possibility of further deterioration and approximately 45 per cent. showed some degree of lasting improvement. The recovery-rate remained practically constant. As regards clinical types, the rate of improvement was higher in catatonics and paranoids than hebephrenics.

Bond and Rivers (68) have made a similar review of cases followed over a number of years after treatment. Their series has the advantage that all the patients were treated in one hospital by a group of psychiatrists with the same standards of diagnosis and evaluation of results. The immediate results in 188 patients showed improvement in 55 per cent., which fell off to a level of 33 per cent. in the second, third and fourth years. The immediate recovery-rate was five times that of control cases and the distant recovery-rate twice that of controls. They report an interesting observation. Between 1936 and 1938, 82 patients were treated by different physicians; the aim was to maintain hypoglycaemic stupor with the minimum dose necessary. When this was

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reached a reduction in dosage was made if the coma level could be maintained. Convulsions were regarded as evidence of over-dosage. In 1939–40, 72 patients were treated by one physician. The coma dose was not considered the optimum; deeper and longer stupor was achieved by increasing the dosage, and convulsions were not regarded as a contra-indication to increasing the dose of insulin. Of those treated by the method employed in 1936–38, 44 per cent. were improved at the conclusion of treatment, whereas by the method in 1939–40 the corresponding figure was 63 per cent. The respective figures at the end of 12 months after treatment showed that 34 per cent. of the 1938 group had remained improved and 57 per cent. of the 1940 group.

Menzies (49) reported his findings in 118 patients after treatment. Of these, 85 were able to leave hospital; 12 subsequently relapsed, but 50 per cent. of these made a satisfactory improvement after further treatment. He advocated the use of a standard diet by means of which he had been able to reduce by 30 per cent. the amount of insulin necessary to produce coma. Prolonged treatment he regarded as essential, and did not despair even if improvement had not been achieved after 140 comas.

An analysis of 50 patients treated by Cheney and Clow (69) showed that at the end of treatment by insulin 48 per cent. had improved. A follow-up study at the end of six months to 2½ years after treatment revealed that the number in the improved group had fallen to 36 per cent.

Not all investigators are impressed with the value of this method. Libertson (70) found an initial improvement-rate of 62 per cent. in 165 patients so treated, but that this rate subsequently levelled down to 40 per cent., and corresponded closely to the results achieved in a control group. He concluded that considerable doubt was felt at the Rochester Hospital as to the value of the method. Similarly Gottleib and Huston (71) formed the opinion that insulin therapy given to a group of 66 schizophrenics did not increase the remission-rate over that obtained from more conservative methods. In both their insulin-treated and their control group 44 per cent. of those whose symptoms had been present for less than six months made a complete or social recovery. The method of treatment adopted was that insulin was decreased after coma levels were reached, and they considered that difference in the technique of insulin treatment might yield different rates of remission.

The majority of the results reported are in support of the method, and sufficient evidence is now available to make the following deductions: (*a*) Insulin does materially alter the clinical picture in schizophrenia even up to the complete abolition of symptoms. (*b*) The increased rate of improvement reported in acute cases ranges from 1·5 to 3 times that of ordinary hospital methods. (*c*) Those who respond to the treatment do so in a relatively short time, and the method, therefore, appreciably shortens the course of the illness. (*d*) Apart from those who recover, many others show a marked temporary improvement which they appear unable to maintain. The necessity for further work to determine the nature of this reaction is apparent. (*e*) While the immediate results are higher than in controls, as times goes on the discrepancy, though still apparent, becomes less marked. (*f*) Insulin therapy remains only a method of treatment. Its application is much more effective if combined

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with all other therapeutic facilities, re-educational, psychological, occupational, etc.

With regard to the incidence of relapses various findings have already been enumerated. In those patients whose symptoms had existed for longer than twelve months before treatment Muller (42) found that symptoms recurred in 6·5 per cent.; if the symptoms had existed longer than twelve months relapses developed in 13 per cent. Horwitz, Blalock and Harris (72) collected reports from the literature on 262 cases. They found that 22, or 8·4 per cent., had relapses. Of their own cases 25 per cent. relapsed within twelve months. A high proportion of these patients showed improvement with further treatment.

It is difficult to obtain a true mortality-rate from the small group of patients reported by individual physicians. Bond (68) reported that three patients died in a series of 188. Muller (42) recorded the mortality-rate as 0·5 per cent. in 500 cases. Malzberg (63) in a series of 1,039 cases reported that there were 13 deaths—1·25 per cent. A more recent analysis has been made by Kinsey (73), who circularized a questionnaire throughout a large number of hospitals. He obtained particulars of 12,234 patients, and of these there were 90 deaths associated with the treatment—0·73 per cent. There was a relatively high incidence due to cerebral causes, of which there were 50, 38 being the result of prolonged coma. Twenty-two deaths resulted from pulmonary causes, of which pneumonia accounted for 16. There were 12 deaths from cardiac complications, and the others were included in the miscellaneous group. James (74) and his co-workers in 1937 expressed the opinion that the death-rate would always prove to be in inverse ratio to the care with which a proved technique was adopted and applied. It is reasonable to assume that further reductions in this mortality-rate will yet be made.

Prognostic Factors.

Numerous reports are available as to the favourable prognostic factors in patients treated by ordinary hospital methods. Stalker (64) in the review already referred to found that the favourable factors were (*a*) healthy habits of reaction, (*b*) preponderance of non-constitutional factors, (*c*) acute recent onset, (*d*) well retained affective response, (*e*) acute types of illness which could not be fitted into the four standard sub-groups. It will be readily appreciated from the following opinions that the same factors hold good in cases treated by more active methods.

Practically all are agreed that the main prognostic factor is the duration of symptoms prior to treatment. The type of personality and the circumstances surrounding the onset of the illness was stressed by Ross and Malzberg (28) as next in importance. Menzies (49), however, considered that of greater importance was the fact whether or not the patient had attained satisfaction in his unreal world. If he was still unsuccessful in attaining a satisfactory world of phantasy and delusion he was worth treating, and he suggested that this was the reason why paranoid types responded better than others, in that they were still unsatisfied with the world of phantasy which they had created. Freudenberg (75) reviewed his results in 72 patients with particular reference to the prognostic factors. The favourable factors were (*a*) acute

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onset, (*b*) short duration of illness, (*c*) pyknic or athletic build, (*d*) cyclothymic temperament, (*e*) tendency to remission. In estimating the prognosis he advocated the consideration of all the factors at the one time ; if three or more unfavourable factors were present the prognosis was increasingly serious. Cheney and Clowe (69) expressed the opinion that the best outlook for recovery or improvement was in males under 30 who had had an adequate prepsychotic personality, were suffering from a psychosis with an abrupt onset and a definite external precipitating cause. They had been ill for less than a year before treatment, and the mental picture was that of an excited catatonic state without evidence of deterioration. It is obvious, therefore, that the prognostic factors in schizophrenia are the same, irrespective of the method of treatment.

With regard to the influence of age, Freudenberg (75) considered this to have no decisive influence on the outcome. Ross and Malzberg (28) found that those over 25 years of age responded better than those under. The older group had made a better emotional adjustment, and in most cases there were definite precipitating factors.

An important prognostic factor during treatment is the effect on bodily weight, the consensus of opinion being that clinical improvement is always accompanied by a gain in weight. Von Braunmühl (76) has described four types, classifying each according to the bodily response. Both Muller (42) and Plattner (77) reported that they had never seen clinical improvement associated with loss of weight.

Most of the work in insulin therapy has been carried out in the treatment of schizophrenia. It has been found that of acute cases the paranoid offer a better prognosis than the catatonics, but in the hebephrenics and the simple varieties the outlook is relatively poor. Of the more chronic types of illness the catatonic variety appears to respond better than the paranoid. Skottowe (78) has drawn attention to a group of patients—those showing dys-symbole—who have failed to react to any known form of treatment; all of us have had similar failures. He was of the opinion that it was a waste of time to treat this type of patient, but sufficient evidence is not available in support of this. Most physicians report a better prognosis in atypical cases. This immediately raises the question of diagnosis, especially in the early stages of the illness, and the probable inclusion, by some, of clinical types which would not be readily accepted by others as schizophrenic. As regards the use of insulin in the treatment of other syndromes, success has been claimed in the treatment of manic excitement and also involutional melancholia. Endogenous depressions do not respond favourably to this method. It is recommended also in the treatment of obsessional neurosis—Freudenberg, etc. (75)—and reference has been made earlier to its employment in smaller doses in other types of neuroses. More recently psychological and encephalographic examinations have suggested that they may be of prognostic value ; these will be discussed later.

Psychological, Biochemical and Histopathological Aspects.

Psychological investigations.—Various psychological studies have been made with a view to throwing greater light on certain clinical phenomena associated with the treatment and also their use as a prognostic aid. Orenstein and

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Schilder (79) devoted special attention to a study of Gestalt functions, both during and after treatment. At the same time the attitude of the patients towards their symptoms while under insulin treatment was considered. They found a general retardation in reaction. Difficulty was experienced by the patients during treatment in general perception, and a difficulty in naming objects was particularly noticeable. There was a marked degree of perseveration noted and visuomotor Gestalt patterns were of a primitive type. They also noted the occurrence of what they described as empty, almost playful excitement, which was considered to be due to the hypoglycaemic state. In some patients quite definite schizophrenic symptoms appeared which might be considered as an activation of the psychosis. Those patients who recovered showed objective insight; they appreciated the fact that they were ill and that their behaviour was abnormal. They lacked any appreciation of the psychodynamics of their reactions, and the investigators had the impression that this was better during the psychotic state. Complete objective insight was lacking in partially improved patients. The improvement resulting from insulin therapy is, therefore, very similar to that seen from spontaneous remissions. Piotrowski (80) investigated how much prognostic help might be achieved from psychological performance tests. He employed the Rorschach method and limited examination to six tests, which he selected for their high predictive value and the ease with which their presence could be determined. These tests were of two groups: (1) pertaining to certain fundamental intellectual traits, and (2) pertaining mainly to the patient's sensitivity and responsiveness to environmental changes. He was of the opinion that the Rorschach method enabled one to distinguish with greater precision than was otherwise possible intellectual regression from emotional regression. The results of his investigation showed that the greater the degree of intellectual regression the smaller the chances of improvement, but the greater the degree of emotional regression the better were the chances of improvement from insulin treatment. Piotrowski (80) found that many unimproved schizophrenics showed Rorschach records resembling organic brain disease. Wechsler, Halpern and Jaros (81) employed five tests, (1) Vocational Interest Blank, (2) Counting by 3's Test, (3) Similarities Test, (4) Directions Test, (5) The Word-meaning Test, in an investigation of 20 schizophrenics before and after treatment, and again before discharge. Of these tests, the first—details of which are given—was most effective. They reported that there was a definite falling-off in the scores by some patients after treatment, and suggested that the therapy might have a detrimental effect so that certain patients had been harmed rather than improved. Halpern (82) also investigated the results of the application of the Rorschach tests, and corroborated the findings of Piotrowski that unimproved schizophrenics showed Rorschach records resembling organic brain disease. He quotes evidence in favour of the view that the Rorschach method is an aid in assessing the likelihood of success in insulin therapy for schizophrenic patients.

In discussing these studies Katzenelbogen (83) considered that apart from their usefulness in predicting the outcome of insulin therapy they suggested either of two possibilities: one is that those patients who respond well to the

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tests and benefit subsequently from treatment belong to a special type in the heterogeneous group of schizophrenics; the other is that success or failure of both test performances and treatment depend closely on the degree to which the mental functioning is impaired by the schizophrenic process.

Biochemical investigations.—An enormous number of laboratory investigations have been made in an effort to correlate the clinical symptoms with the biochemical changes recorded. Georgi (84) and others have shown that the fall in blood sugar is rapid, generally within 30 minutes, that it usually attains its minimum level during the second hour and then rises again. Coma ensued only when the blood sugar had remained at a low level for a considerable time; this period varied in different individuals. It was considered that sugar was withdrawn from the blood stream to the cells of the brain, and that symptoms were dependent in large measure on its concentration, intra- or extra-cellular. Jones (85) failed to get any consistent findings in his attempt to correlate blood-sugar readings with changes in the pulse rate and blood pressure. Fortuyn (86) was of the opinion that the biochemical changes in the blood did not explain the variations in the clinical picture of hypoglycaemia, and he suggested a diencephalic mechanism. He considered that stimulation of this mechanism produced a mixed sympathetic-parasympathetic reaction. Mayer-Gross (87) has suggested that the difficulty in explaining the mechanism of hypoglycaemic unconsciousness in the precomatose stage and in coma might be related to two different levels of cerebral integration, i.e. cortical in the early stage and diencephalic in the later.

Most writers have found an increase in the systolic blood pressure during treatment. Robinson and Robinson (88) found a noticeable increase in both systolic and diastolic pressure within the first hour following the administration of insulin. The blood pressure reached its maximum as the blood-sugar concentration reached its minimum. Increased blood pressure was not an absolute indication of impending complications, but should be considered as a warning signal. Such an increase might be indicative of adrenalization, but might also be an indication of central pathological changes which might not be reversible.

Many detailed studies of the changes in the constituents of both the blood and the cerebrospinal fluid are available without throwing much light on the mechanism. Kingsley and Freed (89) showed that during treatment there were alterations in the volume of the cerebrospinal fluid and in the permeability of the blood cerebrospinal fluid barrier. Insulin caused a rise of globulin and a depression of the albumin-globulin ratio. These changes readjusted themselves to their previous level when treatment was discontinued.

Numerous reports are available on the effect of hypoglycaemia on the metabolism of glucose and oxygen in the brain and other tissues. Dameshek and Myerson (90) have demonstrated that brain metabolism is diminished when the brain is deprived of its main food-stuff, such as during insulin hypoglycaemia. Wortis and Goldfarb (91) made metabolic studies in 45 schizophrenics before, during and after treatment by insulin. Before treatment the arteriovenous oxygen differences of the schizophrenic brain did not differ from normal; neither was any change noted in the observations made after treatment was completed. During regular coma, however, the arteriovenous difference was

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found to be reduced, even after allowing for the possible changes in the blood-flow. Within an hour after the injection of insulin the arterial carbon dioxide content was raised, but it returned to normal within 30 minutes after the administration of glucose. It was noted that in those patients who developed seizures a sharp rise in the carbon dioxide level was found before the convulsion developed. They concluded that there was a depression of the respiratory centre during insulin hypoglycaemia which resulted in a decreased sensitivity to the normal stimulus of carbon dioxide.

The consumption by the brain of oxygen and glucose has been investigated by Himwich, Bowman, Wortis and Fazekas (92). There was no diminution of oxygen or glucose utilization when small doses of insulin were employed. With doses of 40 units or over the diminished metabolism was apparent. This diminished utilization of oxygen by the brain supports the view that carbohydrates are the chief energy supply of that organ. They found, also, that there was an increase in the alkali reserve of the blood as it passed through the brain. There was no change in esterase activity as the result of intensive hypoglycaemia.

They considered that the neurological manifestations were dependent on biochemical changes. With the depression of the cerebral mechanism were associated first, symptoms of excitement of the central nervous system and then of depression. Sweating, extensor spasms and motor activity all appeared according to the degree of diminution of cerebral oxygen uptake. Deep coma was constantly associated with greatly diminished utilization of oxygen by the brain.

Their study suggested that mental activities, like the neurological, were dependent on brain metabolism as the effect on the mental functions paralleled those on the reflex changes. Both normal and pathological processes were similarly affected, being simultaneously released at one time and depressed at another. The mechanism by which the pathological process is restored to normal is not disclosed.

An effort was made to correlate the clinical findings, the brain metabolism of glucose and oxygen and the electroencephalographic findings recorded during treatment by Himwich, Frostig, Fazekas and Hadidian (93). Their results confirmed that with the development of symptoms of hypoglycaemia there was a decrease of brain consumption of glucose and oxygen and a diminution of the alpha waves. The regression of these changes was apparent as the degree of coma lessened.

With regard to the possible mechanism of the action of insulin in the treatment of schizophrenia, Hoffman (94) put forward experimental proof that the anoxic and the hypoglycaemic syndromes involved the same physiological mechanism. As the result of his experiments he concluded that hypoglycaemia acted on the central nervous system in a way similar to that of oxygen deficiency and in both, the rate of oxidation was reduced, that the sensitivity of the central nervous system to oxygen deficiency was greatly increased in hypoglycaemia, and that the combination of hypoglycaemia plus oxygen deficiency induced by insulin produced a more effective stimulation of the sympathetic nervous system. He inferred that insulin improved schizophrenic patients by the same

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mechanisms which were called into play in the animal experiments described, firstly by reduction of the oxidation rate of the central nervous system, and secondly by stimulation of the sympathetic centres.

Autonomic activity during insulin therapy has been noted by many other investigators. Gerard (95) noted the autonomic changes without ascribing any specific therapeutic effect. That there is normally a reaction to the injection of insulin tending to antagonize it and restrain its effect is shown by McDonough (96), who found that completely sympathectomized dogs were markedly hypersensitive to insulin, a small dose in the absence of sympathetic reaction producing much more effect.

There are differences of opinion as to whether the sympathetic or the parasympathetic plays the major role. Gellhorn (97) was of the opinion that both asphyxia and hypoglycaemia elicited predominating signs of sympathetic and not of parasympathetic stimulation, and that this phase of hypoglycaemia seemed therapeutically important. Parker (98) has noted a fluctuating change in autonomic activity with parasympathetic predominance in the first stage, sympathetic in the second, followed by parasympathetic during deep coma. Fortuyn (87) concluded that an increase of both the parasympathetic and sympathetic components resulted from hypoglycaemia. Increased gastric motility and secretion were indicative of the stimulation of the former, while the alteration in the blood pressure, acceleration of the pulse rate and the perspiration so frequently seen were the result of the stimulation of the sympathetic.

Repeated examinations have been made to ascertain the presence of pressor substances in the blood so as to determine more accurately the effect of hypoglycaemia on autonomic activity. Tietz (99) observed a rise of blood adrenaline during insulin coma, which supported the view that there was an activation of the sympathetico-adrenal mechanism. His results suggested that there was retention of a fairly high and constant level of adreno-cortical substances in the blood of patients who had recovered after treatment with insulin. Cameron and Jellinek (100) concluded from their observations that prior to treatment there was a degree of adreno-sympathetic impairment, and that this was overcome in large measure in those patients who recovered and relatively unaffected in those who were unimproved. They suggested that the failure of some patients to respond to the treatment might be due to irreversible damage or to constitutional inadequacies in the autonomic mechanism.

Insulin resistance.—Because of the failure on the part of certain patients to develop hypoglycaemia, investigations have been made to determine the possible presence in their blood of substances antagonistic to insulin. Meduna (101) and his co-workers claim that the blood of 60 per cent. of the schizophrenic patients which they tested had an antagonistic effect on the action of insulin. They were of the opinion that there was a biochemical disturbance in schizophrenia, and that this disturbance indicated the presence of an anti-insulin substance in the blood of schizophrenic patients. They put forward the suggestion that the failure of the organism to adjust this disturbance might be one of the aetiological factors in the illness itself. Harris (102) investigated a group of 13 schizophrenics, and tested their sensitivity to test doses of insulin

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according to the method of Csépai and Ernst. Some showed a normal response, others either a decreased or an increased degree of sensitivity. Seven were studied by a method similar to that of de Wesselow and Griffiths with regard to the possible presence of substances in the serum which affected the action of insulin. The serum of some showed a pronounced antagonistic effect, while that of others showed little or no effect.

Himsworth (103) was of the opinion that blood contained a substance necessary for the activation of insulin, and that insulin resistance was due to an inadequate amount of this activating substance. This, as Harris (102) pointed out, does not account for those cases in which an injection of blood or serum has an antagonistic effect on the action of insulin in the experimental animal. It is possible that the amount of substances in the blood which increase or decrease the activity of insulin may vary with different persons. The results of Harris throw doubt on the importance of an anti-insulin mechanism in the pathogenesis of schizophrenia; further investigation is obviously required. No correlation was found between the tests and the subsequent dose of insulin required to produce coma during treatment.

Freeman, Looney, Hoskins and Dyer (104) report the results of their investigations on 32 schizophrenics and 20 normals. They found that 41 per cent. of the patients showed some degree of resistance to insulin, and they were in agreement with the results of Meduna (101). They suggested that the specific factors responsible for insulin sensitivity were of endocrine origin, since resistance to insulin has been recorded by Fraser (105), etc., in endocrinopathies involving the adrenal cortex, the thyroid and the pituitary. It is possible that this insulin insensitivity in schizophrenia may be another example of the general tissue resistance to change recorded by Angyal, Freeman and Hoskins (106).

Electrocardiographic findings.—The most frequent change found in the electro-cardiogram during treatment is a depression and inversion of the T-wave. The observations made by Messinger (107) suggested that this change was reversible, and might be produced by small as well as large doses of insulin. Goldman (108) found that after repeated treatments the abnormality persisted for periods up to six months. Barker, Shrader and Ronzoni (109) found a similar change in alkalosis. Goldfarb and Bowman (110) thought the change might be due to some cause other than insulin. They found that this change was identical with the electrocardiogram obtained from conditions where the causative agent was a vitamin deficiency, and that such could be reversed or prevented by the administration of vitamin B_1. They concluded that the change was due to the repeated consumption of large amounts of glucose, a vitamin-free substance, producing thereby a relative insufficiency.

Electroencephalographic findings.—It is generally accepted that, as has been reported by Finlay and Macfie Campbell (111) and others, there is nothing consistent or diagnostic in the electroencephalographic tracings taken from schizophrenics. A great many variations may be obtained, none of which is specific to this type of illness. Similarly, no special type of tracings have been found in patients treated with insulin. McNeil, Dewan, Meyers, Procter and Goodwin (112) report in a series of patients in whom they made parallel

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psychological, psychiatric and physiological examinations while under treatment by insulin, that they were unable to observe deteriorative changes in the cerebral cortex, as recorded by the electroencephalograph. They report that the quality of the electroencephalographic recordings was consistently lower than normal, but that they were otherwise representative of the population as a whole. The catatonic patients examined, who showed a marked inertia, had a frequency greater than the average. Similar results were reported by Hoagland, Ruben and Cameron (113). They found a progressive decline in frequency which showed a time relationship with the low blood-sugar level, and that sugar injected during treatment restored the frequency. They believed that the alpha frequencies were directly proportionate to the rate of carbohydrate metabolism of the cells of the cerebral cortex.

Histopathology.—Much experimental work has been carried out on animals to ascertain the effects of hypoglycaemia on the central nervous system. These have shown that following severe hypoglycaemia definite pathological changes, especially cellular changes, both focal and diffuse, occur there. Neumann, Cohn and Katzenelbogen (114) carried out experiments on cats, to which insulin was given in doses sufficient to produce coma. Subsequent pathological examination showed acute nerve-cell changes in the form of chromatolysis and swelling, cytolysis or karyolysis being present in almost every case, but not uniformly distributed. In the cerebral cortex the small nerve cells were chiefly involved. In those animals who died of hypoglycaemic shock the nerve-cell destruction was more widespread. Winkelman and Moore (115) found in cats which died as a result of deep coma that there was severe damage to neurones. Involvement of ganglion cells was apparent and there was an increase of glia. In their opinion the changes were more severe than those resulting from convulsive therapy.

Tannenberg (116) exposed rabbits to anoxic shock by slow deprivation of oxygen, and compared the results with those found in another series of rabbits injected with insulin in doses sufficient to produce coma and convulsions. The symptoms which developed were similar except that those seen in the rabbits exposed to anoxia were more rapid in development. The pathological changes were much the same in the central nervous system as well as the heart, skeletal musculature and liver. In the nervous system there were varying degrees of degenerative changes in ganglion cells with reactive glial proliferation. The cerebral cortex, the Purkinjë cells in the cerebellum, the cornu ammonis, the medulla and spinal cord were usually involved. These changes they considered to be best explained by the deprivation of ganglion cells of carbohydrates, which are, according to Himwich, their chief nutritional material. The hydropic changes found in the heart, skeletal musculature and liver were usually reversible. In the brain, however, single ganglion cells of various areas were destroyed, and they put forward the suggestion that this was perhaps a necessary step in the effective therapy of schizophrenia.

Finley and Brenner (117) carried out similar experiments on adult *Macacus rhesus* monkeys, in whom they produced hypoglycaemic coma and allowed this to extend from 3½ to 20 hours. After shorter periods of coma there was acute swelling and vacuolation of the ganglion cells, and they considered that

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these changes were reversible. After more prolonged periods of coma the changes were clearly irreversible, and consisted of marked swelling of the astroyctes and a marked microglial reaction and swelling of the capillary endothelial cells. The changes were more marked in the cerebral cortex. In animals exposed to repeated comas they found severe extensive lesions in the cortex of each. They were of the opinion that there was first a proliferation and hyperplasia of astrocytes, followed by an intense glial reaction with damage to nerve cells. This led to complete disappearance of nerve cells from the affected area, with a subsequent increase in the number of glial cells. It was probable that the lesions represented the cumulative result of minor brain damage.

Reports are now available of numerous pathological examinations of the nervous system of patients who have died following hypoglycaemic treatment. The changes found show a considerable degree of similarity to those already recorded in experimental animals.

The degree of change found by McKeith and Meyer (118) in the ganglion cells was considerably less than has been reported by several others, and there was only slight evidence of typical ischaemic necrosis. The predominant feature was a proliferation of the fibrous glia, most marked in the cerebral and cerebellar white matter and the globus pallidus. The changes found favoured an anoxic process.

Ferraro and Jervis (119) are of the opinion that the striking pathological changes of the blood vessels of the brain indicate the direct damaging action of insulin. They assume that the cellular waste of brain tissue in severe hypoglycaemia is brought about by a mechanism of anoxia involving biochemical facts and vascular changes. The amount of oxygen conveyed to the tissue by the blood vessels is reduced, since high doses of insulin produce proliferative changes in the vessel wall leading to narrowing and obstruction of the lumen.

It would appear that the degree of reversibility of these changes is dependent in large measure on the depth of coma. Whether or not there is any therapeutic value in a certain amount of brain damage, as has been suggested, remains undecided.

Conclusions.

In the ten years which have elapsed since the introduction of insulin therapy an enormous number of variations in the technique have been advocated, and these have been discussed. The necessity for individualization is stressed, and the employment of such degrees of coma as the clinical condition warrants. In this, much benefit may accrue from the regular administration of the treatment by one experienced physician.

Insulin therapy does materially alter the clinical picture in schizophrenia, even up to the complete abolition of the symptoms. It also shortens the duration of the illness.

There is an increased rate of improvement in acute cases as compared with controls. As time passes the discrepancy between these two groups, though still apparent, becomes less marked.

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Apart from those who recover, others show a marked temporary improvement which they are unable to maintain. The reasons for this offer a field for further investigation.

The various clinical factors that may influence the prognosis have been given, and the possibility of additional prognostic help from psychological performance tests has been discussed.

Various views on the mechanism have been considered, particularly in relation to the effect of treatment on the oxygen and glucose consumption of the central nervous system and on the autonomic nervous system. These factors, while relevant, do not in themselves adequately explain how the psychosis is benefited.

Certain dangers are associated with the method and there is the risk of persistent brain damage, but agreement is felt with Jessner and Ryan (120), who state: "In view of the gravity of a schizophrenic psychosis, it would appear that despite the possible occurrence of damage not clinically detectable, the risk involved should not necessarily be regarded as prohibitive if there is a chance for improvement."

Insulin therapy remains only a method of treatment; to be most effective it must be combined with all other therapeutic facilities, re-educational, psychological, occupational, etc.

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