DANGERS AND EMERGENCIES OF INSULIN THERAPY OF THE PSYCHOSES.*

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THE insulin therapy of the psychoses as evolved by Sakel (1) was introduced to Three Counties Hospital 16 months ago. The total number of patients treated and under treatment is 74; 56 have had a full course of the treatment in addition to psychotherapy, and of these, 29 have been discharged and 4 will leave the hospital in the near future. A total number of 3,205 hypoglycæmic comas have been induced up to the present in 4,379 patient insulin days. Serious emergencies arose in only 6 comas. One patient had severe laryngeal spasm, another acute œdema of the lungs, and four delayed return to consciousness. No fatality occurred. Twenty-eight patients had 81 fits in the same number of comas. I shall outline briefly the circumstances which led up to the emergencies met with by myself and some published by other workers in this country, and give the treatment applied.

PREMATURE INCIDENCE OF COMA.

In some instances hypoglycæmic coma commenced prematurely between 1 and 1½ hours after the injection of insulin. This was due to the sensitivity many patients develop towards insulin, and which may have the same effects as an excessive dose (2 and 3). In one instance the patient at his ninth coma became unconscious, 1 hour and 10 minutes after injection of his usual coma dose of 115 units, which was repeated without decrease. He was unable to respond to external stimuli such as calling or touching him and his plantar responses were extensor. Within half an hour he had his first tonic spasm, which, however, was of short duration. Pulse and respirations were satisfactory, and he was allowed to remain in coma approximately an hour, during which two further tonic spasms occurred, the second being somewhat intense with dypsnœa and unobtainable pulse; he was given glucose nasally.† He had a fit 15 minutes

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† The quantities and strength of glucose solutions used are: For oral and nasal administration, 100 to 400 c.c. of 40%. For intravenous use, 20 to 150 c.c. or more of 33% in sterile ampoules of 20 and 50 c.c.

later, and glucose was injected intravenously but without effect. He remained unconscious for a further 9 hours and thus became a case of delayed return to consciousness. However he recovered. After two weeks rest the treatment was resumed, and satisfactory comas were induced with only 60 units. In all the other instances, premature coma was interrupted as soon as it showed signs of deepening, without any complications. The insulin dose was subsequently reduced.

Recent investigations attribute this undue sensitivity to insulin to insufficient glycogen reserve in the liver and other organs. It is a danger to be borne in mind during this treatment and an attempt should always be made to diminish the amount of insulin, once the coma dose has been reached (4).

Cardio-vascular Collapse.

Insulin therapy is doubtless a severe test for the heart and circulation. In severe hypoglycæmia, as it is induced in this treatment, the heart muscle, like all the muscles of the body, is gradually depleted of glycogen, and at the same time is subjected to the effects on the circulation of the hypersecretion of adrenaline which takes place. Hadorn (5), after exhaustive electrocardiographic examinations, reports that in two-thirds of the cases examined during insulin therapy the changes recorded (lowering of the S-T interval and lowering or inversion of the T-wave) were those observed in myocardial disease. These changes, however, were reversible. He concludes that a healthy heart soon recovers by administration of glucose at the termination of the coma for therapeutic purposes, and in emergencies. In pre-existing definite or latent heart disease this reversion to the normal takes place with difficulty, or may not in complications, especially when the coronary circulation is at fault. James, Freudenberg, and Cannon (6) reported a typical attack of cardio-vascular collapse following a comparatively common complication of insulin therapy, such as a fit. Their patient suffered from cardiac disease, and insulin treatment was undertaken with reluctance. Twenty-eight comas were given without serious incident, except that irregularity of the pulse was frequent and was accompanied at times by cyanosis. At the onset of the twenty-eighth coma he had a fit, which was followed by an unusual pallor. The patient suddenly became pulseless and his veins were so collapsed that intravenous glucose proved impossible. 0·5 c.c. of adrenaline solution 1 in 1,000 was given subcutaneously, followed at once by 2 c.c. of 33% of glucose solution intracardially. Restoration of the circulation was immediate, and intravenous glucose made possible. There were no subsequent ill-effects, but insulin treatment was discontinued.

The great handicap in this severe complication is, that owing to the collapse of the vessels, it is technically impossible to give the needed glucose by the intravenous route, and if immediate subcutaneous injection of adrenaline does not relieve the condition, an intracardial injection of 1–2 c.c. of glucose solution

should be given. This should be followed by a larger amount of glucose intravenously. In the event of the circulation not being restored sufficiently to allow of the use of the intravenous route, and also in cases with very small and difficult veins, the glucose should be given intramuscularly and nasally.

Laryngeal Spasm.

My personal experience of this complication has been in two cases. The first, a female, approximately an hour after the onset of the third coma, developed very noisy stertorous respiration with inspiratory stridor lasting for a few minutes. She was becoming somewhat cyanosed when the stridor ceased and her breathing became satisfactory again. A few minutes later the same signs occurred with some intensity, and the coma was interrupted. The second, a male, who had been in his seventeenth coma for an hour and a half, developed inspiratory stridor which increased rapidly and he became very cyanosed. 1 c.c. of adrenaline was injected subcutaneously, followed immediately by 6 mgrm. of lobeline and 60 c.c. of glucose solution intravenously. He recovered almost at once. In both cases after a rest of a few days the treatment was resumed with smaller doses. No further respiratory trouble occurred. Gillies (7) reported a case of severe laryngeal spasm with cessation of respiration which took place suddenly in the pre-coma period. Insulin treatment was stopped for 2 days, and then resumed with smaller doses. Again a similar attack of laryngeal spasm occurred, and treatment was permanently discontinued.

This complication is not very common and responds quickly to the appropriate treatment. In addition to the adrenaline, lobeline and glucose injections, oxygen and carbon dioxide mixture should be available, and artificial respiration should be resorted to if necessary.

Acute Œdema of the Lungs.

This is a severe complication, but fortunately very rare. Only very few cases have been reported (8). It may be due to some degree of pre-existing latent myocardial degeneration which manifests itself in insufficient left heart reserve during or following an intense and unduly prolonged coma. A dissociation of the action of the two ventricles takes place, the right contracting forcibly, while the left is in an asystolic condition. Acute œdema of the lungs came on 45 minutes after interruption of the coma in a male patient, a paranoid schizophrenic under my care, and his case was reported at a meeting of the British Psychiatric Insulin Society. His bodily condition prior to treatment was good, although no electrocardiographic investigations were possible. The coma dose of 75 units was reached rather rapidly at the sixth daily injection. The first seven comas were uneventful, and were gradually lengthened. The eighth coma began 2 hours and 40 minutes after the injection of 75 units. He was left in coma for 1 hour and 55 minutes, during which he had two tonic spasms

alternating with hypotonus. He perspired freely, and at no time did his pulse or respiration give rise to any concern. His coma was interrupted nasally while in hypotonus. Twenty minutes later, whilst still unconscious, he had a fairly long and intense hypertonic spasm. He was very rigid and in opisthotonus. He was given 120 c.c. of glucose solution intravenously and the rigidity subsided but he was restless. While I was preparing to do a lumbar puncture, indicated in such a condition, the patient's respirations suddenly became hurried and shallow, and dypsnœa soon became severe. Cyanosis was increasing and he was very restless in his endeavour to breathe. He expectorated a large quantitiy of watery frothy fluid which was also streaming from his nose. His pulse was feeble and intermittent. Morphine gr. $\frac{1}{4}$ and atropine gr. $\frac{1}{100}$ were given subcutaneously, lobeline 9 mgrm. and coramine 5 c.c. intravenously followed by 10 c.c. of euphyllin in 10 c.c. of glucose solution also intravenously, but very slowly. Some amelioration in his breathing and pulse followed shortly after, although there was still a good deal of dypsnœa and cyanosis. Moist sounds were present over his whole thorax. Continuous inhalation of oxygen was given but it was not tolerated at first owing to restlessness. He expectorated more frothy fluid and later vomited in an explosive way most of the glucose solution he had received through the nasal tube, approximately 2 hours previously. A further 10 c.c. of euphyllin with 10 c.c. of glucose solution were injected intravenously. His breathing slowly but gradually improved and expectoration ceased. His temperature then was 102·4° and pulse 120, of poor volume but regular. His respiratory embarrassment lasted 3 hours but he remained in a stuporous condition for 14 hours. After 9 days of pyrexia and bronchitis he recovered. Further insulin therapy was discontinued.

Additional measures for this complication are venesection and very slow intravenous injection of $\frac{1}{25}$ gr. of strophanthin in 20 c.c. of glucose solution.

Convulsions.

Fits are of fairly frequent occurrence in some patients and at times are followed by mental improvement (9). Their ætiology is not yet satisfactorily explained. As I stated previously, 28 patients under my care had 81 fits. Early in the evolution of the technique of this treatment fits were considered to be severe emergencies and hypoglycæmia was interrupted at once intravenously, while now the nasal route is used, and only at the conclusion of the fit (6). Nevertheless there is the possibility of their recurrence and even a *status epilepticus* may set in. Gillies (7) observed 9 fits in a patient over a period of 5 hours after coma, and Parfitt (10) reported a case of 23 fits occurring after termination of the coma over a period extending up to 3 days, at the end of which the patient was in a desperate condition. Both these cases recovered.

The treatment of *status epilepticus* due to hypoglycæmia consists in inhalations of oxygen and carbon dioxide mixture, lumbar puncture (withdraw

20–60 c.c.), lobeline (subcutaneous or intravenous), and if the heart is in a satisfactory condition luminal (1 c.c. of 20% solution subcutaneously). If the blood sugar is found to be high, adrenaline must not be given because according to Strecker (8), it increases the tendency to fits.

Delayed Return to Consciousness.

Usually the patients wake from hypoglycæmic coma within half an hour of the administration of glucose by nasal tube ; if not, an intravenous injection of from 20 to 150 c.c. or more of 33% sterile glucose solution brings them round immediately. In rare instances, however, this does not happen and in difficult cases coma persists in spite of hyperglycæmia.

Delayed return to consciousness occurred in 4 instances in cases under my care and other workers (6 and 11) have reported similar experiences from time to time. This complicaton may be associated with too rapid an increase in the dose of insulin, as it tends to occur early in treatment, but it is more likely to complicate an unduly prolonged and intensely deep coma. Two of our cases, paranoid schizophrenics, were not showing mental improvement after several weeks of treatment and, as is recommended, they were subjected to longer and deeper comas.

Following the failure of the intravenous glucose to rouse them, severe cases develop great restlessness. Successive tonic spasms take place in which there is extensor rigidity of limbs with foot inversion and pronation of arms, opisthotonus, cyanosis and respiratory distress. The temperature rises and the pulse is rapid and often unobtainable. The blood and cerebro-spinal fluid sugar is very high, 300 or more mgrm. per 100 c.c. (it can be estimated at the bedside quickly by the Crecelius and Seifert method). The transition from coma to rousable stupor may take many hours or several days.

The following measures are recommended : Vitamin B_1, 1,000–5,000 units intravenously, with 10 c.c. of calcium chloride 10% solution. The latter is given to counteract the existing alkalosis. I have observed that much larger doses of vitamin B_1, 10,000 units repeated if necessary, produce more rapid effects. Oxygen and carbon dioxide in continuous inhalation. As there is a good deal of dehydration in this condition large quantities of fluids are given, the stomach is washed out with saline and 300–500 c.c. left in situ, also saline is given intravenously or subcutaneously, 1 to 2 litres and repeated. Lumbar puncture relieves restlessness. Blood transfusion is recommended as being of the utmost value (2).

After-Effects.

After-effects, mild, such as somnolence and perspiration, or severe, such as rapid onset of coma and even convulsions, yield to administration of glucose. They are due to insufficient carbohydrate reserve, the patients having vomited their glucose or their food during the day. The danger consists in a patient

becoming rapidly comatose at night, when he may be thought to be sleeping naturally. Dr. Wilson (14), in her report of the study of insulin therapy, mentions that the first fatality recorded in Vienna occurred at night. The patient had a coma unobserved, developed a *status epilepticus* and died. Hamilton (15) observed after-effects in 13 instances. They varied from drowsiness to coma and occurred between 9 p.m. and 3 a.m. He recommends a substantial evening meal supplemented by 3 to 7 oz. of glucose solution at bedtime as preventing after-effects, as well as not interfering with the next hypoglycæmic coma. All patients undergoing insulin treatment should sleep under observation.

Steps to be Taken to Minimize Dangers.

The dangers of insulin therapy have been greatly exaggerated. The mortality reported is less than 1% in thousands of cases treated all over the world. Real danger exists only when applied to patients physically unfit to receive it. Therefore, the previous history of every case should be obtained and a detailed physical examination should be carried out repeatedly, also laboratory examinations of the urine, especially for albumin and casts, and of the blood, for sugar and urea estimations. In order to exclude latent heart disease, electro-cardiograms should be taken. The treatment must be postponed in general debility and all febrile conditions, including even coryza. Absolute contra-indications are the evidence of any cardio-vascular, pulmonary, renal, hepatic and pancreatic disease.

Previous practical experience should be gained so that the treatment can be confidently carried out. The nursing staff should be instructed by lectures and practical demonstrations and supplied with detailed printed instructions. The rules of the technique should be strictly followed. Constant medical attendance during all the phases of the treatment is absolutely necessary, and at no time should the physician be out of reach, because in emergencies very quick action is essential in order to avoid fatalities. All the equipment should be ready at hand and additional medical aid should be obtainable when necessary.

Each case has to be managed individually. On gradually reaching the coma dose bear in mind the undue sensitivity to insulin some patients may develop. Coma, at first of 20 to 30 minutes, can be gradually lengthened to suit each case, but should never be continued beyond a period that allows of an easy return to consciousness. During coma, the pulse should be felt frequently and great variations in rate below or above normal, or irregularities, as well as persistent respiratory embarrassment, should be warnings for interruption.

Conclusion.

The danger during insulin therapy of the psychoses is negligible and the occurrence of serious emergencies very infrequent. In 4,379 patient insulin days, 3,205 comas were induced and only 6 serious emergencies arose. No

fatality occurred. With more careful selection of patients in order to exclude the physically unfit and greater experience in the technique, this low incidence of emergencies could be reduced even more.

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Discussion.

Dr. ISABEL WILSON (Board of Control), in reviewing the papers, said first of all how much she appreciated the honour, as an official, of being asked to take part in the discussion on a clinical problem. She thought they were beginning to know more than had been known in the past about the basis of schizophrenia; on the previous day they had heard Dr. Gjessing, they already knew of the past work of the Maudsley Hospital and of work in other centres, and she felt they were now appreciably nearer than they had been to some definite idea of the problem they had to tackle. Incidentally, she wished to say how glad they all were to see Dr. Sakel amongst them, especially those who had learnt in Dr. Sakel's wards in Vienna. This was a particularly happy occasion on that account.

There were people who were sceptical, and reasonably so, of the results of any new treatment, including this one, and, considering the history of insulin treatment generally, it had been an encouragement to her to find that one or two other people besides Dr. Sakel had been working on this problem from different angles. It was discovered in Oslo by accident that a patient could be cured through the production of hypoglycæmia. Day and Niver, in America, had independently of others worked out the insulin treatment. French workers had investigated the effect of insulin on mental conditions. If one blackbird in the garden was in a state of alarm, that might be hysterical, but when all the birds were shouting one might be sure that there was a cat in the bushes.

One striking description of technique had been given to the meeting in the shape of Dr. James's cinematograph film, and from the discussion in this second session two or three points had emerged. The first of these was the value of standardization of technique. This, as many of them knew, had been put forward particularly by Frostig, whose work was now available in an English translation in the *Archives of Neurology and Psychiatry*, 1938, xxxix, 219. Dr. Sakel had said that in modifying technique too much one ran the risk of getting away from the recognized and known methods, and it was important that those who were going to work with insulin or cardiazol or any of these drugs should know the orthodox standard methods of using each drug before going on to undertake mixed or modified treatments.

Then there had been various modifications of technique mentioned by certain authors. Dr. Russell had mentioned the summation therapy. There were three ways of using cardiazol and insulin together, namely, a crossed method, an alternating method, and this summation method which was now coming so much into use. Dr. Sakel also had alluded to it.

A new modification had been brought forward by Dr. Walk and Dr. Mayer-Gross, namely, triazol treatment, and there were one or two interesting points arising out of that. One was that these authors were using twilight states and believed that possibly these had therapeutic value. This was particularly interesting because these twilight states remaining after treatment had been considered disadvantage by Salm and others. Those familiar with epilepsy knew the distrust they had in *petit mal* as a factor in inducing mental deterioration.

Then there was the psychological side of the treatment, which had been put before them by Dr. Larkin, particularly in relation to the Freudian theories. Those familiar with the literature would know that there was hardly a worker with insulin or cardiazol or anything else who did not rely on psychological methods of some sort. One could not treat patients with chemical substances and expect that to work the whole miracle.

She had been interested in Dr. Larkin's observation of the nurses who, when they were stimulating the lips of the patients, moved their own mouths in sympathy.

That was not a new observation entirely. They all knew the illustration of the football enthusiast who, while watching a match, grew so excited that he kicked the man in front of him. The classic example to her mind was the case of two children one of whom was using the toothbrush while the younger child was looking on with admiration and spitting into the basin at the appropriate moment.

The dangers of the treatment had been put before them systematically by Dr. Finiefs. There were one or two points about the dangers that were of interest. It had been said that too much stress was laid on the dangers of insulin treatment, but any surgeon dealing with a condition in which he got a mortality of 1% or 1·5% was more concerned about the one patient he lost than about all the other patients who recovered, and he rightly devoted his efforts to prevent that happening. It was very clear, as everybody agreed, that the more experienced the worker in this treatment the less was the danger. The fatalities and the serious accidents had occurred almost entirely with people who had not had a long experience of the treatment. That was not absolutely so, but was somewhere near the truth. It was important, therefore, to gain experience before going too far with the treatment.

One other danger referred not only to insulin but to cardiazol, and Dr. Dick and Dr. McAdam had mentioned cardiac complications in cardiazol treatment. Other workers in Budapest and Vienna had stated after electrocardiographic examination following treatment that no damage had been done. But in the light of the paper by Drs. Dick and McAdam it might be necessary to revise that finding, and possibly what was needed was much more electrocardiographic examination than had hitherto been done. That was partly borne out by Dr. Gjessing's finding that minor variations in the electrocardiographic record occurred as a result of variations of nitrogen metabolism. It had been suggested that the results from insulin and cardiazol could not be proved to be better than the results without these treatments. From the statistics of one worker it appeared that there had been 60% of remissions when methods other than treatment by insulin and cardiazol had been employed and 59% of remissions with administration of cardiazol. At the same time this worker stated on clinical grounds that he was entirely convinced of the value of the new methods. Hitherto many of them had based their belief in the value of this treatment upon individual experience, but Dr. Sakel had produced an independent statistical analysis taken over a wide area and worked out by a skilled statistician, one who was not swayed by his own enthusiasm, and the results were altogether beyond anything they had known in their experience. She thought that this was one of the most encouraging things that any of them had had brought to their attention. There was one aspect of theory that did not come forward until Dr. Finiefs' paper, namely, the oxygen theory. The relation of oxygen supply in the blood to the oxygen content of the brain-cells and their functional activities seemed to be a place in which in the future the key to this whole problem might be found. A great deal of work had been done on the physiology of cardiazol and insulin patients by Georgi and Strauss; but the vasomotor side of it went very much further back, to the work done at the Maudsley Hospital in 1928, to the work of Lorenz in 1929, and to other work.

She wished to add one word about what Dr. Russell had said with regard to the turning-point in metabolism during insulin treatment on the ground that the brain glucose varied directly with the blood sugar. Heaven forbid that she should tackle the biochemists on their own ground, but her reading of the work was that the brain glucose depended on the blood sugar until the lowest depths of hypoglycæmia were reached and at those depths there was a sort of lag and the brain got left behind. She put that forward as her amateur interpretation of that work.

She thought they had had one of the most remarkable meetings ever held in the Association, and they looked forward to the future with the greatest interest and hope. It was particularly fortunate that the Association now had a Research Bureau at its disposal. This was more needed now than ever before, and she, personally, looked forward to a great development, not only of the practical work in the hospitals but to a better understanding of that work as it would be furthered by the Research Bureau.

Sir LAURENCE BROCK (Chairman of the Board of Control) said that he had an announcement to make which he thought would be of interest, but before he made it he hoped he might be allowed to say how much he had appreciated the discussion which had taken place at that meeting. He congratulated the Association on what he believed was one of the most memorable meetings in their annals, and one which proved beyond doubt the great advantage of taking a single subject and having a unified series of papers upon it, instead of a number of disconnected debates on unrelated subjects.

Two years ago at the meeting at Folkestone he was able to announce that there was in preparation a report by Dr. Wilson on insulin. The Board had now, he was glad to say, in preparation another and he believed an even more important report on cardiazol. The Board was so much impressed by the rapid progress of this treatment in England that it seemed that everything possible ought to be done to place the technique on a proper basis. Accordingly he asked Dr. Rees Thomas and Dr. Wilson to go to Budapest, where they were given every opportunity of seeing the treatment in the hospital in which it had originated. On their way back they took the opportunity of visiting Vienna and Frankfurt, and saw the latest developments in insulin work there. A full report had been prepared, and Dr. Thomas, while he was in entire agreement with it, would endorse him in saying that the work was very largely that of Dr. Wilson. The report included not only an account of what they saw in Budapest and Vienna, but also an examination of the various theories which had been advanced to account for the success of this treatment, and an attempt to collate the exceedingly baffling statistics. This work had necessarily occupied a considerable time in preparation. He could not say exactly when it would be ready. It was very difficult to persuade printers that anything medical was ever urgent, but he hoped that it would be produced quite early in the autumn. The insulin report was a " best seller " ; he believed this new report on cardiazol and insulin would beat all records.

Dr. H. PULLAR STRECKER (London) said that his remarks were based upon two or three years' experience both of insulin and cardiazol methods. He believed that these new methods had come to stay. There did not seem to be much doubt that the immediate results surpassed those of the treatments hitherto used. Their therapeutic range was not confined to cases of schizophrenia. The difficulty, of course, was not to get the patients to improve, but to prevent them from relapsing. It was here that the skill, patience and perseverance of the physciain would tell. It would be unfortunate if the idea that mental disorder could be cured by a few convulsions or comas became prevalent. This occasionally did occur, but certainly not as a general rule. The full course of treatment should always be given, and all the other adjuvants should be used.

Cardiazol treatment was very simple. It could be carried out by almost anyone with a minimum of preparation and assistance. If in triazol there was offered a means of lessening the few technical difficulties or disadvantages of cardiazol, so much the better. Triazol had been tried at Brooke House, and he could confirm the advantages claimed. In particular the amnesia seemed to be much stronger than with cardiazol. Perhaps a word of warning might not be out of place. The very advantages of cardiazol treatment constituted a danger—the danger, namely, that the public or perhaps even the profession might come to believe that any case, whatever its type or duration, could be cured. Insulin treatment required a maximum of time, preparation and assistance, and could be carried out only in a hospital and not by everyone. It was quite safe, however, in the hands of those who were prepared mentally as well as technically for emergencies and who were content to bide their time and not anxious to obtain their results too quickly. No doubt the dangers of insulin treatment had been as much overrated as the unpleasantness of cardiazol. As regards the unpleasantness, Dr. James, who had shown the excellent film on the previous day, would agree that the treatment was not as drastic as would appear from the film. Those who had seen the actual treatment with insulin and cardiazol would qualify any such impression. The expenditure of time

on this treatment was amply rewarded by the extensive and lasting results of insulin, and while the results of cardiazol sometimes tended to wear off quickly, the most satisfactory results were obtained by combining the two methods.

With regard to the question whether it was justifiable to submit to this treatment recoverable cases—that is to say, cases with a good prospect of spontaneous recovery —this was naturally a matter of opinion and experience. It was obvious that those who were sceptical of the new methods would prefer to await developments, while those who had seen good results with the new methods had attained confidence with regard to safety and would be inclined to use them early, knowing that this gave the patient a better chance of recovery.

Dr. H. GILLIES (West Ham) referred to the contradictory experiences and figures which were forthcoming. He thought it reasonable to regard some of the confusion and discrepancy as really arising from the statistical methods employed. To furnish statistics which had been prepared by a professional statistician, not a medical person, as Dr. Sakel had done, was worse than useless. To take his own series of insulin cases, it would take very little juggling to prove from statistics either (*a*) that insulin was a complete cure for schizophrenia, or (*b*) that it was of no use whatever. The honest impression of a well-trained observer was worth very much more than reams of statistics. It was his own impression that insulin and cardiazol acted to produce remissions, and if the results were better with insulin that could be explained because of the more lengthy course and the more elaborate paraphernalia used in insulin treatment. These paraphernalia incidentally were pregnant with histrionic and even phallic significance. It might be helpful to point out that the academic results of any treatment were of no interest to the patients. If the insulin and cardiazol treatments increased the number of remissions and lessened the stay in hospital, their use should be continued, and should not be ignored because of the absence or otherwise of a psychological rationale.

Dr. R. GJESSING said that there was one point he desired to emphasize about statistics. It was very difficult to keep real statistics until it was known distinctly what a worker meant by " recovered ", " much improved ", and " improved ". It should be possible to have international standards for this. Their aim was to get information about the underlying disorder, so that every patient could be put in his proper category before and after treatment. Until then they were in darkness.

In his hospital about 200 patients had now been treated with insulin, some with insulin and cardiazol. In some of the patients the duration of disease had been as long as six years. It was impossible to get good figures with these long-standing cases, but nevertheless, very surprising results had been forthcoming with these patients also, and he wished to emphasize the duty of helping these old patients even if not many of them could be expected to recover. Patients classed as incurable did sometimes recover to a quite surprising extent, to the extent at least of appearing quite normal to anyone who was not a psychiatrist.

Dr. SAKEL agreed with Dr. Gjessing that they should never rely overmuch on statistics because they did not know the nature of the disease. In his opinion they were dealing with symptoms, not with a disease. They had no test to define the nature of schizophrenia and they could not set up a test of cured or not cured. They were dependent on psychological examination and investigation of the patient, and could only say whether he acted in a manner which they called normal or abnormal. He did not believe in a mental disorder, because it was not yet known what the mind was. He had made a definition of recovery. A recovered patient might be said to be one who apparently showed no signs of abnormal behaviour, no hallucination, had complete adjustment, and complete insight into his previous psychotic symptoms, one who was able freely and completely to talk about his psychoses in the same way as people spoke of a dream, and, furthermore, one who

had no subjective barrier between himself and other persons. He would describe such a person, with some hesitation, as recovered, or if some feeling of barrier remained, as a good remission.

A patient might be described as "improved" if he could be returned to the ordinary social environment and was not psychotic in a general way; at the same time he might have no insight, and he might say with regard to his previous illness, "I did hear voices, but now I do not. It was true that they persecuted me, but that has ceased." Such cases he did not call more than improved.

Then there were other cases in hospital which, though they could not be discharged, registered some improvement and were able, for example, to take their meals at table in the ordinary way.

Dr. J. H. PAMEIJER related a few experiences from Holland. He had not himself applied these treatments, but as Inspector of Mental Hospitals in Holland, the results of both forms of treatment had been communicated to him. In the mental clinics attached to the four Dutch Universities about 700 patients had been treated with insulin since 1936 and 1,200 with cardiazol. The results did not differ much from those published elsewhere. His general impression was that individual cases did more or less completely recover. He had witnessed surprising mental changes and the passing of abnormal states to an unexpected extent. Their opinion as to the value of these active agents was far from being settled, and he wanted to utter a word of warning by giving a short account of some of the serious complications which had been recorded.

Among the 700 patients treated with insulin he had collected six cases in which death had occurred, either from prolonged coma, cardiac trouble, acute pulmonary œdema, or the activation of tuberculosis. Other complications, without fatal results, included high blood-pressure. As to the cardiazol treatment, out of the 1,200 patients treated, seven cases of pulmonary abscess occurred, with no deaths, and there had been many cases of cardiac trouble, with two deaths; seven cases of activation of pulmonary tuberculosis not noticed before, with one death; and also cases of interlobar empyema. Altogether in these 1,200 cases four had died. There had also been 15 cases of fracture amongst the patients subjected to cardiazol treatment, including three fractures of the shoulder-blade, three of the humerus, three of both femurs, two of one femur, and one of the lower jaw. Some other complications of a surgical kind included rupture of ligament, several dislocations of the humerus, including one double dislocation, and many dislocations of the jaw. These were not indications to abstain from treatment, but only a warning. Apparently some of the complications were due to lack of experience of those using the treatment. The treatment should be preceded by exact observation, both as to the mental and the somatic state. Doubtful cases of psychosis should be eliminated. The examination should not be limited to the usual clinical observations, and special tests should be applied. If needed, an X-ray examination of the chest should be made, all with a view to eliminating those patients for whom the treatment would be too dangerous. All needed examinations should be made to establish the correct dosage and the proper type of shock. After-care observations were of importance. Lastly, in fatal cases, it was important to carry out post-mortem examinations with a view to ascertaining the macroscopic or microscopic changes.

Dr. E. LARKIN said that he himself had a strong tendency towards insulin, but he had worked with cardiazol a great deal. He knew that there was a certain amount of prejudice against cardiazol in the minds of many people. A point always worth investigating in any case of fracture, such as those to which Dr. Pameijer had just referred, was the number of years that the patient had been in the mental hospital. Patients who had cardiazol soon after admission did not get any trouble at all, but patients who had been in for a number of years were apt to have their bones in a bad state, due to lack of vitamin D in their diet, and fracture occurred almost spontaneously. In the cases treated with insulin there was a tendency to

bleed very easily, no doubt due to the lack of vitamin C. This was a point one must always think of in criticizing the treatment, because these casualties might be avoided by proper vitamin and other diet.

Dr. E. J. FITZGERALD (Witham) said that statistics at any time were extremely confusing and misleading, but in the hands of professional statisticians they were apt to be more puzzling than ever. The papers by Dr. Cook and Dr. Larkin had raised several problems. There were two types of patient in the average mental deficiency colony, in the first place the large body of neurotic persons, of slightly below normal mentality, and also a considerable number of schizophrenics and schizoids, who descended lower and lower in the scale and constituted a serious problem. In view of the facts put forward by Dr. Cook and Dr. Larkin, it seemed to him that those in mental deficiency institutions who wished to do the best for their patients should make some attempt to treat the heterogeneous collection labelled as mentally defective.

Dr. A. A. W. PETRIE said that at Banstead, of 115 patients treated with cardiazol 40 had either been discharged or were much improved, having virtually reached the level of going out; 13 others had improved, 29 slightly improved, 10 physically improved without mental improvement, and 23 remained unimproved. The figures also showed that the greatest number of successes were among patients who had not been more than two years in the hospital.

There were two points about the psychology which he thought were perhaps worth referring to in the case of cardiazol treatment. One of these was the apprehension of the patients. He had taken the trouble to question a number of people who were getting better and he found this apprehension to be a very real point against cardiazol. Some of the patients asked, said that the experience was worse than death, and they emphasized it, and sometimes by their conduct during treatment they proved it, even doing dramatic things on the morning of the injection in order to evade it. They seemed to feel it as a sort of irritation which spread through their body. He was not referring to those who were left in a pent-up state by not having had a fit. A number of the patients described it as like an anæsthetic; some who had had anæsthetics compared it exactly with that experience, and others said it was even worse, but a smaller number did not trouble much about the experience. He had also listened to patients who had been treated with insulin. These also compared the experience to that of undergoing an anæsthetic, some said it was worse than an anæsthetic. Therefore the sense of apprehension was not absolutely confined to the cardiazol-treated patient. One learned a great deal from the patient who was recovering and from the patient who was in the incipient stage. He had questioned a number of people as to how they felt before they recovered. One girl described it by saying: "I knew what I wanted to do, but my body would not act. My mind would not control my body, and I was simply unable to do anything." That was very much the state of a dream.

Dr. M. A. COLLINS recalled a remark by Sir George Savage, "There is no such thing as insanity." Most people claimed that they were treating schizophrenia, but when asked what that was, they could not say. If they understood that this treatment was used for that aspect of ourselves which was called the mind it would help to overcome a great deal of resistance to it. There was no doubt that it was the physical side which was the important one. The mind was only one aspect of the personality, just like the face, which made a man pleasant or unpleasant to his fellows. He wanted to congratulate the Research and Clinical Committee on organizing the present discussion, but he hoped that the discussion would lead to the throwing over of the classification of insanity upon which that Committee had also spent a great deal of time. He could not see the slightest use in classifying something before they knew what it was. Much had been said about the dangers of insulin and cardiazol. There was one other danger that ought to be mentioned, namely, that none of them knew what the after-results of this drastic treatment might be in a few years' time. Was there any danger of producing a community of epileptics?

Dr. ISABEL WILSON said that she was sorry to have omitted inadvertently any reference to the paper by Dr. Cook from her previous remarks. What she felt about it had been expressed by Dr. Collins and Dr. Fitzgerald.

Dr. T. RUSSELL FRASER (Maudsley Hospital) said that one of the dangers of insulin treatment was the irreversible coma. He and his colleagues had had some little experience of this and had been concerning themselves with some methods other than the conventional ones of avoiding it. It was highly probable that this might be one of the complications of the treatment which would ultimately produce damage in the patient's brain. Such damage was more likely to occur after one of these long comas than after a normal and desirable coma. A point not sufficiently stressed was that when a patient did not recover after being given glucose the apparent state of coma was different from insulin coma, there was much more restlessness and movement. It seemed to him important to have some more accurate method of assessing dosage and treatment. The insulin dose itself was, of course, exact, but the treatment the patient had was really the depth of his hypoglycæmia and its duration, and one had the feeling that the coma reported by one person was quite a different matter from the coma reported by another. He had felt that some such term as pre-coma might be useful to describe the onset of any neurological phenomenon. One could then at the end of treatment say that there had been so many hours of coma and so many hours of pre-coma. It had been found of value to note fairly accurately the time the patient took to waken from the beginning of the insulin-feed until he could talk reasonably well. If that interval was prolonged it was always a danger sign. If there were a standard dosage for the patient each day and it was found out originally what he could bear each day in the matter of length, and noted whether he walked properly each day, it seemed highly probable that the danger could be miminized.

Another point was the treatment of the condition when danger arose. The obvious treatment was intravenous glucose, but one point that might be stressed was that a great deal of intravenous glucose should be given. In his hospital they were accustomed to give 200 or 300 c.c. of 30% glucose immediately they thought there was danger. They also felt it important to give plenty of fluid. These patients showed as a rule some indication that their circulation was not at its best, and that might have very much to do with the circulation of glucose through the brain. Secondly, if the glucose alone did not immediately produce wakening, they put in a large volume of saline, 1,000 to 2,000 c.c. If the pulse-rate was not high, they gave adrenalin regularly, whether glucose was given or not. Of course, the usual stimulants were used.

Dr. DONALD BLAIR (Cane Hill) said that Dr. Russell had pointed out the advantage of summation, and in doing so had mentioned that many fits were a great advanage. The question, however, was exactly how many. Triazol had the additional advantage that it could produce with one injection a number of fits, say four, at reasonably-spaced intervals; it could be controlled by giving luminal if necessary. That was another means of summation which might in future be of some value.

Dr. T. A. MUNRO (Colchester) said that Dr. Sakel had given his figures to a lay statistician to analyse. That seemed to him a most extraordinary thing to have done. Who of them writing a paper would give their facts to a lay person to set in order? How could the non-medical statistician be aware of the incalculable amount of clinical detail which made all the difference in judging the figures? He also felt that Dr. Sakel's control group represented a most remarkable collection of queer patients.

Dr. SAKEL replied that a questionnaire was sent to each medical superintendent in the New York State Hospital Service, and it was the superintendent who submitted his own statistics. The statistics then went to the Statistical Bureau for collation.

The value of the treatment was appreciated by each superintendent, and it was only the end-results which came into the hands of the professional statistician. As to the controls, here again the results were from 25 State hospitals, but the valuation of each patient and the rate of recovery, both in the control group and the treated group, was done by the superintendent and the staff meeting together.

Dr. W. M. FORD ROBERTSON (Glasgow) drew attention to a rather interesting piece of work by Kerr and Ganthus. These workers had injected rabbits with basal doses of insulin, and they had found that the time of onset of the convulsions had no relationship to the initial true sugar level. What they did notice with the insulin they were using was that a large number of rabbits subjected to the insulin showed an immediate initial mild hyperglycæmia with a subsequent fall. They divided the rabbits according to the initial rise or absence of rise or immediate depression, and their conclusions were that the initial rise that occurred in some of their animals was related to the glycogen reserve in the animal and not to the initial blood-sugar level. Their work did suggest that biochemists might quite profitably undertake investigations into the significance and the chemical nature of glycogen reserves in their patients with a view perhaps to getting some criteria which would enable them to evaluate the insulin sensitivity of the cases.

Dr. SAKEL referred to the influence of atmospheric pressure in determining such results. Other experiments with rabbits had shown that they entirely depended upon the atmospheric pressure which determined whether the convulsions appeared earlier or later.

Dr. ROUGHTON mentioned that some work was now being done in the Biological Laboratory at Cambridge on the breakdown of glycogen in muscles.