

INSULIN HYPOGLYCAEMIA

IN THE

TREATMENT OF SCHIZOPHRENIA

by

W. Malcolm Millar, M.B., Ch.B. (Edin.),

Assistant Physician, Royal Edinburgh Hospital
for Nervous and Mental Disorders.



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Since its introduction to general medicine in 1922 insulin has been used as a therapeutic agent in an increasing number of diseases and disorders. In the treatment of the psychoses it has played its part mainly in an attempt to promote appetite and nutrition generally in cases of malnourishment. Only rarely was insulin reported as having any beneficial action on the psychosis itself. Since it was regarded as essentially a physical adjuvant, any mental improvement noted with its use was considered to be incidental.

In 1928 Manfred Sakel began treatment of certain mental states with special interest in drug addiction. With this beginning he developed a completely new form of treatment in which insulin was administered in high doses and in the absence of carbohydrates. Since 1930 the technique has been evolved with the object of deliberately producing a state of hypoglycaemia which was allowed to deepen to the point of coma. Hitherto this state had always been regarded as a dangerous and undesirable complication, which should be prevented by the administration of adequate carbohydrate. Sakel found, however, that, if proper precautions were taken, these dangers had been magnified, and discovered that a protracted state of coma had a therapeutic value in combating mental diseases.

The observations which Sakel made on a few cases of accidental deep hypoglycaemia in the treatment of drug addiction/

addiction encouraged him to extend the method to the psychoses. In 1933 he published a report in which he pointed out the beneficial effects of deep hypoglycaemia, particularly in the treatment of Schizophrenia. Since 1933 he has worked out a method which, he claims, is both effective and safe, and which has stood the test of several years trial.

In Vienna, at the Pötzl Klinik, 46 cases had been treated at that time and it was claimed that 70.7% had responded with a full remission, and a further 17.3% with a good social remission. In November 1936 Max Müller of Munsingen reported on a series of 136 cases treated with the Sakel method, and confirmed the good results, especially in cases of less than six months duration.

Since then the so-called hypoglycaemic shock treatment of schizophrenia has been used extensively in all parts of the world. It was introduced into America by Glueck and has since been reported upon by Wortis, Moersch, Ross, Katzenelbogen and others. Several hundreds of cases have undergone treatment and opinions have been very conflicting, both with regard to results obtained and to the method employed. Though there are at present many reputable advocates of the method, at the same time many authorities have opposed it on practical as well as on theoretical grounds.

In order to clarify the situation to some extent, at least in this country, Dr. Isabel Wilson was asked to make an investigation of the matter and to deliver a report to the Board of Control of England and Wales. This was in February 1936. In a careful and unbiassed account Dr. Wilson gave a description of her impressions of the treatment as/

it was actually carried out in Vienna under Dr. Sakel, together with a detailed account of the technique, its dangers and theoretical considerations. Certain recommendations were added, including one that the treatment should be started in a public Mental Hospital in this country. Previously, and independent of the above report, Dr. Pullar Strecker, who had studied the Sakel method in Vienna, was invited to carry out the treatment in a number of cases in the Royal Edinburgh Hospital.

During 1937 a number of reports have been published in this country dealing with the results of treatment. On the whole favourable reports were given by James, Larkin, Hamilton and others. Whereas the British Medical Journal, in a leading article, hailed the new form of treatment as an advance, the Lancet opposed it on various grounds.

After a period of twelve months, in which eleven cases were treated, it was decided to continue the method in this hospital as the results were promising. The writer was privileged to study the technique under the guidance of Dr. Strecker, and since July 1937 has carried out the treatment personally in a series of 25 cases.

The purpose of this essay is to outline the technique and clinical observations of the treatment, and to deal with the difficulties and dangers, theories of cure, and the interpretation of results. A table is given indicating the results, and six illustrative cases are added which are considered to be representative.

are the symptoms, and as far as possible are the effects in some cases, that the method has been designated "Insulin Shock Therapy". It is therefore sharply distinguished from any other form of insulin therapy.

Case Material

For the most part the treatment has been confined to those cases which have been diagnosed as Schizophrenic reaction types. Certain cases, however, are not of this group, but it was considered advisable to include other types for experimental purposes. Glueck, Bychowski and others consider that depressions are sometimes successfully treated, and other types which have been tried are acute manias, compulsion and anxiety neuroses, and toxic and exhaustive states.

Of the 25 cases treated in the present series all were males. Of these there were 7 simplex, 6 paranioid, 5 catatonic stupors, 3 hebephrenic, one catatonic excitement and one paraphrenic belonging to the Schizophrenic group. One case of simple depression and one long standing anxiety neurosis were also included in the series.

General Survey of Treatment

The treatment consists of subjecting the patient to gradually increasing doses of insulin, administered daily for six days, by intramuscular injection with the object of producing deeper and deeper hypoglycaemia. The effective part of the treatment is considered to begin when coma appears, and for a period of one or two months thereafter coma is produced daily. So severe and at times alarming are the symptoms, and so dramatic are the effects in some cases, that the method has been designated "Insulin Shock Therapy". It is therefore sharply distinguished from any other form of insulin therapy.

Four phases of treatment are recognised.

I. Introductory Phase.

An initial dose of 10-20 units of insulin is given and this is increased daily until a dose is reached to which the patient reacts with a "Shock". This dose varies between 15 and 400 units. The shock may be either a coma or an epileptiform seizure, the former being by far the more common. The injections are given early in the morning, the patients having fasted for 12-14 hours before. This phase usually lasts about a week to 10 days, but may be more prolonged.

II. Shock Phase.

This is the effective period of treatment and consists of a daily repetition of the "coma dose" of insulin until improvement has been established, or alternatively after 50 such shocks have been given. Müller insists upon 60 days as a minimum but we find that the number of shocks - usually 20-30- is a better criterion.

III. Resting Phase

Originally the treatment was carried out intermittently with several days of rest at a time. This resting phase is now represented by one day in seven (usually Sunday). It has been found that such a day of rest is valuable both as a holiday for the patient, and to act as a day of observation to judge improvement. After a severe reaction, such as an epileptiform seizure, a day of rest is also given.

IV. Stabilisation Phase

In certain cases the shock dose is gradually reduced over a period of a week or two until the patient leaves hospital.

Treatment in Detail

As there are great variations in the details of treatment the methods adopted in this hospital will be described here, with occasional reference to alternative methods in certain instances.

A special ward has been secured for the purpose. It is a large airy room, and accomodates six beds comfortably, besides tables, chairs and other articles of furniture. The room is used not only for treatment, but also as a dormitory. All meals are taken in this room as well. Müller recommends a separate room for sleeping as the treatment room is usually associated with unhappy experiences of the hypoglycaemia period. This has not been found to be the case. The advantages of this system are that the same staff can attend to the feeding and sleeping arrangements as are present during the actual treatment. The patients live as a small family, and under constant observation, and are thereby given every encouragement from day to day by the members of the staff whose duty it is to act as companions and advisers, and to create an atmosphere of normality around them.

The beds are of the ordinary hospital type and have padding at the heads. The walls of the room are also padded and the beds are so arranged that, with the use of two screens, each patient is shut off from the others, and cannot see what is going on about him. It is worth the trouble of arranging and rearranging the beds until this effect is obtained with a minimum of screens, which have the disadvantage that they interfere with proper observation of the patient and interfere with/

with quick and easy access to the patient if required.

With six patients undergoing treatment two or three male nurses are required, and one doctor must be in attendance throughout the morning. A second doctor is always within reach if sudden emergencies arise, which is very seldom. This staff must, however be considered as a minimum, and is only possible where a single large room is used. Many writers insist on a larger staff and this is particularly necessary for the control of psycho-motor restlessness. Certain methods have been adopted, which will be mentioned later, which make it possible for two nurses to control the most violent case, and it is believed that these methods account for the small staff required. A further advantage of the small staff is that it can be given tuition more readily, and this is important, as all members of the staff who come in contact with the patient should be made thoroughly familiar with the signs and symptoms of hypoglycaemia and with the various methods of interruption. Notes should be made by the nurses as to the physical and mental progress of the patient from day to day. It is advisable to furnish each member of the staff with some literature on the subject (such as James' article or Wilson's report) so as to promote an intelligent interest in their work. Before treatment is started certain preliminaries are necessary.

A physical examination should be carried out to eliminate the possibility of organic disease. Certain conditions are considered to be contra-indications to treatment. These include valvular disease of the heart, coronary artery disease, nephritis, either acute or chronic, and respiratory diseases. Electrocardiograms/

Electrocardiograms are an asset in this matter although perhaps not a necessity (Feldhofen). The examination of the patient should also include a blood-sugar curve as this affords a clue as to the initial dose of insulin, and acts as a control for any blood-sugar tests carried out during treatment. It is rare to find evidence of physical disease sufficient to prevent treatment being carried out as the patients are usually young, and comparatively healthy physically. Wasting from malnourishment is never an indication against treatment and it is a uniform finding for the patient to gain weight and strength during the course.

The injections are given at 7.30 a.m., the patient having fasted since the evening meal at 5.30 the day before. The period of hypoglycaemia lasts for about five hours and the work of the day is thus finished by about one o'clock. The Danish brand of insulin -"Leo"- has been used exclusively. For several months the strength used was 20 units per cc. but when a patient required over 200 units the large quantity (10ccs) was uncomfortable. Latterly the strength used has been 40 units per cc. and no appreciable variation has been observed. The injections are made deep into the gluteal region, the upper and outer quadrant of the buttock being selected, as being most free from nerves and vessels. Ordinary record syringes are used - 1, 2, 5, and 10 cc. sizes -. The dose can be regulated to the nearest 2 units.

Great care must be observed with certain patients, who realise that food will antagonise the effects of insulin and will hide sweets and such like under their pillows or in their clothing, with a view to eating them surreptitiously during the hypoglycaemic period.

I. Introductory Phase/

I. Introductory Phase.

The dose of insulin is increased daily by 5-15 units, and during this phase it is common for the patient to overcome the hypoglycaemia spontaneously. This is one of the many indications of the very efficient "buffering" system of the body which tend to antagonise the action of insulin.

During hypoglycaemia in this stage the following symptoms may be observed:- Stickiness of the forehead with later sweating; drowsiness; lethargy; exhaustion; apathy; euphoria; talkativeness; whistling and singing; repeated requests for glucose. Apprehension and fear are uncommon symptoms and should they be present they are more an indication of the illness than the hypoglycaemia. Often psycho-motor restlessness is seen, and this may be very severe. At the end of four to five hours the patients either recovers spontaneously or requires glucose, which he is able to drink himself. 200 gms Dextrose B.P. are given dissolved in water with lemon or orange to flavour it, and made up to one pint. After a rest for half an hour or so the patient is allowed to get up and dress for lunch. At the end of this phase little effect is noticed in the majority of patients except that there is more cooperation and quietness. Noisy, excited, apprehensive or sleepless patients show some improvement and all but a few subject themselves to the morning injections with no evidence of discomfort or disapproval. In catatonic stupors light hypoglycaemia, as seen in phase I, tends to cause an "awakening", bringing to light a loose system of paranoid ideas. This it is, as it were, brought into line with the other types, and phase II is thereafter proceeded with.

II. Shock Phase

This is the vital period of treatment, and it is during this/

this period that signs of improvement are noted from day to day. Whereas in Phase I the patients require very little observation, and are able to come out of hypoglycaemia by themselves, in Phase II constant attention is required and interruption has to be carried out by the doctor or staff.

Throughout the period an ever changing series of clinical pictures are seen and, in order to understand their precise significance, it is desirable to study each separate manifestation as closely as possible.

In the first place it must be remembered that there are two separate processes at work and running, as it were, parallel courses. There is a symptomatology of hypoglycaemia and there is a symptomatology of the altering psychosis. One must be careful to differentiate between these so that symptoms referable to the psychosis are not attributed to the hypoglycaemia, and vice versa. For instance, when the patient is restless, this may be due either to the hypoglycaemia or to the psychosis. While undergoing treatment the mental picture of the patient may show a cycle of changes during the course of 24 hours. In the early morning he shows his usual psychotic state; in early hypoglycaemia he is euphoric and talkative; later he is comatose; after interruption he may be excited for a few minutes to a few hours; finally, when he has recovered completely from the hypoglycaemia he returns to his original state or shows some improvement, either temporary or permanent.

Symptomatology

Frostig has classified the symptoms of shock under four headings/

1. Vegetative vaso-motor Syndrome in Wet Shock.
2. Motor Syndrome.
3. Disturbances of Consciousness.
4. Mental Syndrome.

At this point it may be necessary to define the terms "Wet Shock" and "Dry Shock". In the majority of instances a shock is characterised by coma, with loss of conjunctival, blink and even corneal reflexes, and the presence of pathological reflexes such as Babinski. There is invariably associated with this state a profuse sweat, salivation, and falling temperature. Hence it is known as "Wet Shock". In "Dry Shock" there is little or no sweating, and little or no fall in temperature, and it is characterised by epileptiform convulsions.

1. Vegetative vaso-motor syndrome in Wet Shock.

- (a) Changes in pulse rate. Usually there is an acceleration in the presence of restlessness. A marked bradycardia, as low as 30/min. is not uncommon.
- (b) Progressive drop in temperature. In one of our cases the lowest reading was 94° F.
- (c) Perspiration and salivation. This is one of the most common features and occurs in about 90% of cases. The sweat stands out as large beads on the forehead, and may be so profuse over the whole body that the bedclothes and nightclothes are soaked. Salivation may cause choking, spluttering and even aspiration with consequent pneumonia. A constant stream of saliva flowing from the mouth is common.
- (d) Pallor and flushing. Flushing is the more sign in the early stages; pallor is usually the sign of a very deep coma and often a danger signal before collapse.
- (e) Fluctuations of blood pressure. Most commonly there is an initial rise, but this is by no means constant and is of no value as to the progress of coma, and have lately been discarded.

2. Motor Syndrome

A. Convulsion Syndrome in Dry Shock.

- I. Early Epileptic Seizure before the end of the third hour. This is characterised by dry skin and absence generally of the symptoms noted in (1) above. There is a warning cry, accompanied by pallor and rapid pulse. There is conjugate deviation of the eyes usually to the right; tonic spasms starting in the face and extending over the whole body; then tonic-clonic spasms of true epilepsy; cyanosis; spontaneous Babinski sign. The pupils show no characteristic reaction, but are usually dilated. The corneal reflex may be absent for a few seconds.
- II. Late Epileptic Seizure. This comes on after coma has appeared. The seizures are more tonic, and may be accompanied by pronation of the arms. These seizures tend to repeat themselves unless interruption is carried out.

B. Motor Syndrome in Wet Shock

Motor restlessness and tremors are frequent. These precede and may even continue during coma. The patient may be very violent and noisy, throwing himself about the bed, kick, turn, shriek, squeal, shout, snort and pant, and contort himself into alarming positions. He may beat himself severely on the chest and face or bite and scratch himself. One patient had to be prevented on several occasions from trying to put his finger in his eye. As the coma deepens the motor symptoms become more and more primitive, and less coordinated and purposeful. Sakel draws attention to the phenomenon and considers that there is a loss of inhibition of the higher centres "layer by layer". At the same time it would almost seem that the noises emitted regressed in a similarly striking fashion. At first one would hear moans and cries, with pleadings/

pleadings for help. The voice would then become more inarticulate, slurred and thick. Finally the noises heard can scarcely be recognised as human at all. Other motor symptoms noted are as follows:- Clonic twitchings, either local or general.- these may be very severe and frightening, but are always transient and never dangerous.-; generalised torsion cramps; tetanic cramps; spasms of tremor; athetotic movements usually accompanied by abnormal reflexes such as Babinski. Generalised hypotonus may be seen with loss of all reflexes - both tendon and pathological. All the above are the usual accompaniments of a shock and are not to be looked upon as dangerous symptoms requiring immediate interference.

"Emotional Spasms" are described by Feldhofen and constitute an entity in themselves. They precede deep coma. Cramp-like movements are seen and resemble a baby mimicking emotional gestures of different sorts. In rapid succession are seen such changes as:- the face distorted tearfully; a sudden outburst of laughter; an angry expression; muttering; perseveration of words like "Aye, aye"; a brief period of quiescence and then a repetition of the symptoms. Throughout the episode consciousness is restricted.

In the later stages spasm of adduction or pronation of the extremities are to be seen and these usually accompany a gross variation of the pulse rate. During the spasm the pulse rate is about 140/ minute, and in the interval between spasms it drops suddenly to 70/ minute or less. If the pulse is counted every five seconds over a period of a minute the readings would be as follows:- 5,6,6,6,7,11,12,12,12,12,6. Breathing may also be accelerated with the pulse rate. Inspiration may be very laboured, as the chest remains in a position of deep inspiration, and the accessory muscles of respiration/

and alae nasi are brought into play. So powerful may be this inspiration that a stridor is often heard and the alae nasi vibrate and are indrawn. The lower lip may also be sucked into the mouth, and the tongue incarcerated in the throat. As this state is an indication of a very deep coma it should be regarded as a complication rather than as a sign of hypoglycaemia.

3. Disturbances of Consciousness

A. Syndrome of disturbances of consciousness in Dry Shock.

I. There is unconsciousness during and immediately after a seizure.

II. There is a clouding of consciousness for some time (about 5-30 minutes) after a seizure and before full consciousness is recovered.

B. Syndrome of disturbances of consciousness in Wet Shock.

The order of change of consciousness is as follows:-

(a) Somnolence.

(b) Sleep.

(c) Incipient coma, in which the patient cannot be roused when called; that is to say, is not responsive but just rousable.

(d) Sopor, or deep sleep, from which the patient can be roused by certain strong stimuli such as passing the nasal tube forcibly, pricking with a needle or testing for the Babinski sign with great force. We prefer to give this stage the name of light coma as the reaction to these strong stimuli is reflex in nature, consciousness having entirely disappeared.

(e) Coma, or deep coma. The patient cannot be roused even with the strongest stimuli. The first sign of this state is

a/

a Babinski sign. Then follow:- Loss of blink and conjunctival reflexes; loss of corneal reflex; Loss of swallowing and coughing reflexes and sometimes of the organic reflexes. In the deepest coma of all the light reflex may be absent, and there may be complete hypotonus with disappearance of Babinski sign. Except in extreme cases the pupil, at this stage, is constricted and not, as one might expect, dilated.

Many different definitions of the word "Coma" have been used, and it is necessary to have an accurate definition. No single criterion must be used. The whole picture presented must be taken into account. Sakel's definition of a coma as appearing with loss of corneal reflex must not be the only guide, as many deep comas are present - with loss of conjunctival and blink reflexes and even disappearance of a Babinski previously noted - while it is still possible to obtain a true corneal reflex by brushing cotton wool over the centre of the cornea. Sometimes placing the finger in the eye will give no response when cotton wool will.

Light coma is not considered to have any therapeutic value, and should not be reckoned in the duration of coma proper. Deep coma alone is of significance and the duration of this should be at least half-an-hour, but never more than one-and-a-half- hours. It is exceedingly rare for a deep coma to remain uncomplicated for longer than this time.

4. Mental Syndrome.

As was mentioned earlier, all the symptoms seen in hypoglycaemia must not be taken as due to hypoglycaemia. The converse also holds good. Some mental symptoms are directly due/

due to the hypoglycaemic state itself. For instance, when the patient awakens he is more accessible, talkative, cheerful, amenable. This state only lasts for a few minutes and is soon lost when full consciousness is restored. The fact that these symptoms are of such short duration would suggest this. A comparison has been drawn between this state and any other intoxication. Patients describe their symptoms as very akin to drunkenness, and this may be very nearly the case. In some cases a phenomenon known as "reactivation" of the psychosis is seen, and is believed to be due directly to the hypoglycaemia, independent of the disease process itself.

These mental symptoms of hypoglycaemia are described by Moersch, Fraser and other writers, in their observations of hypoglycaemia in mentally normal patients. Fugue states have even been described. The so-called "Insulin Psychosis" of diabetics is also allied to this state.

Sensitivity and Adaptation

Two phenomena are observed in relation to the dosage of insulin from day to day. It is a common occurrence to require to reduce the dose of insulin injected as the treatment progresses, in order to obtain the same depth and duration of coma. In one patient, for instance, 110 units were required to produce coma on the 19th day of treatment, whereas on the 53rd day 20 units gave the same effect. This has been termed "sensitization" and it is important to keep it in mind when regulating the dose each day. A reduction of as much as 8-10 units daily is sometimes necessary in order to prevent dangerous symptoms arising.

In the early stages of the treatment physical reactions such/

as violent psycho-motor restlessness, intermittent pulse and respiration are more common than in the later weeks. Although the mechanism is obscure it is evident that there is a gradual "adaptation" on the part of the body generally to the daily insulin hypoglycaemia. This occurrence should also be borne in mind when a "rest phase" is given lasting longer than 24 hours, as the power of adaptation is soon lost. Thus, if no treatment is given for 2 days or more, the patient having been previously subjected to deep coma daily- a repetition of the coma dose will call forth a strong physical reaction which may be dangerous. At the same time most of the sensitization has been lost, and the misleading picture of light hypoglycaemia with severe physical symptoms is seen. It is advisable therefore to avoid long breaks in treatment, and to make the Monday dose the same as the Saturday dose in the ordinary course of events - as recommended by Parfitt.

So far as individual doses is concerned we have found 260 units as the maximum and 25 units the minimum. Langfeldt reports a case of coma produced with 7.2 units injected intravenously. At the other extreme 400-500 units are sometimes necessary to produce the same effect.

Blood Sugar

A series of blood-sugar curves, carried out during hypoglycaemia and for some hours after, revealed in the majority of cases, that the maximum lowering of the blood-sugar occurred between the second and the third hour and did not, as one might expect, run parallel with the depth of coma. Very low readings have been obtained, and on one occasion (using the Hagedorn and Jensen method) the level had descended to 17mgm%,
After/

After interruption with glucose by intranasal catheter the blood sugar showed a second fall and in one case (Case IV) this was a constant finding, and was associated with a deepening of coma. No correlation with the blood sugar could be found in the blood pressure, pulse rate, temperature or the depth of coma, and it is therefore of little value in this direction. Cameron, working on the electroencephalogram, attempts to draw some parallel between depth of coma and blood-sugar levels and brain-waves. With readings as low as 40 mgms% no symptoms were apparent in some cases, and recently, in one case of deep coma with positive Babinski sign and loss of conjunctival reflex there was a reading of 120 mgms%. John reports a case in which signs of hypoglycaemia were seen with a blood sugar reading of 360 mgms%. In the case of "protracted hypoglycaemia" reported in this series (Case II) it is of interest that there was throughout a hyperglycaemia. This serves to demonstrate the uselessness of injection of glucose in these conditions, and the advisability of central stimulants such as caffeine.

Management of Hypoglycaemia

Before injection each morning a note should be taken of the pulse, respiration rate, temperature and blood pressure. The urine should be tested for sugar and albumin. A rise of temperature is a contra-indication to the treatment for as long as it is maintained.

During the first hour or two no signs are apparent, and only routine pulse readings are taken . The patient, during this/

this period is usually quiet, and attempts to go off to sleep. To avoid over-production of adrenaline he should be kept as quiet as possible, but should he wish to read, play patience, chess and such games, every encouragement should be given him. He may be allowed to smoke, and may have drinks of water if required.

At the end of two hours there is usually some restlessness and care should be taken that the patient does himself no harm. The management of this period is important, as prolongation will result in an over-production of adrenaline sufficient to neutralise the effect of insulin. The pads at the end of the bed, and on the walls are provided to prevent the patient from harming himself. It must be impressed upon the staff that any attempt to "hold down" the patient only results in redoubling his efforts. All that is necessary is to control the movements so that the patient does not hurt himself, particularly by falling out of bed. Two nurses are sufficient to sit, with their backs to the patient, to act as further pads. A patient who required at least three, if not four, persons to hold him down, when he was released and allowed to kick unrestrictedly, soon quietened down altogether.

When the patient becomes comatose he should be propped up if hypotonic and quiet, or allowed to lie over on his side with a supporting pillow at his back if hypertonic. This avoids the danger of aspiration of saliva, which is often excessive and frequently causes spluttering. When this is done the nasal tube should be passed as a precaution. Great care must be observed in this manoeuvre, and the following method has been adopted as both safe and sure. A No 12 (red rubber) catheter is used. This fits closely in the nostril/

nostril and will not slip out. After lubricating with glycerine the end is inserted into the nostril, care being taken to keep it close to the septum in the middle meatus, otherwise bleeding might take place and obstruction might be encountered. When the point of the tube reaches the epiglottis it should be gently oscillated up and down until the patient swallows. A tap on the larynx may aid this. Swallowing invariably takes place at the end of expiration. The tube is then firmly slipped into the oesophagus, and one immediately knows that all is well if there is no coughing, and if gas or gastric contents are forced up the tube. This noise of gas escaping may be misleading, and taken for air coming from the trachea, but it has a different character, so different as to be diagnostic in itself. To make certain, the contents of the stomach should be drawn off with a syringe and tested with litmus. To prevent leaking of gastric contents up the tube a small piece of wood is used as a plug. At the appropriate time glucose solution is introduced down the tube, which is connected to a large glass funnel. To enable only one person to carry out interruption when indicated the funnel is fixed to a trolley at about two feet higher than the level of the patient. The funnel is filled up, connected to the tube, and glucose is allowed to run in to the stomach. If the patient is reasonably still he can be left, while another patient is being attended to,

In the great majority of cases this method of interruption is used. While the patient is comatose he should be under close supervision and the pulse, colour, and character of pulse and respiration should be noted every quarter of an hour. A behaviour chart has recently been used for this purpose and has been found to be effective. Symptoms and signs are arranged in groups, with the more severe symptoms towards the foot/

foot of each group. One is enabled, by this method, to tell at a glance how the hypoglycaemia is progressing. A specimen is included later. Times of onset and interruption can be seen clearly, and make for safety, the exact duration of coma being estimated in a moment.

Hitherto 200 gms glucose have been given as a standard amount regardless of the dose of insulin given. Any quantity less than this is likely to produce "after shock", particularly where the patient has been given more than 200 units insulin. Petrie suggests that the patient should be given 10 gms, glucose more than the number on units of insulin injected. This method of interruption should be used as the standard method.

After a few minutes, during which the coma may appear to deepen, and such alarming symptoms as choking, cyanosis, apnoea with pallor and violent psycho-motor excitement may occur, consciousness returns and responsiveness is obtained. 10-15 minutes is the average time taken for the patient to recover after interruption. During this period care must be observed that the glucose solution is not vomited up and subsequently aspirated. To avoid vomiting in those cases where it occurs frequently, it is necessary to run a few drops of atropine sulphate solution, with a little water, into the stomach about 15 minutes before interruption. Danger also arises if the tube is withdrawn too slowly after interruption has been carried out. The tube must be nipped firmly between the fingers and withdrawn sharply. There is always a certain quantity of glucose solution in the tube when this is withdrawn, and it is apt to be dropped in the region of the larynx causing choking. Should the patient choke he must be turned over on his side without delay, and if necessary artificial respiration should be performed. This latter is not actually necessary but cuts short/

short the attack. In all but certain selected cases, therefore, the intranasal method of interruption should be employed. It is regarded as "therapeutic interruption".

When the patient awakens he is usually found to be very wet, having been sweating and with a low temperature. The nightclothes should be changed after a rub down before the fire, and the wet sheets removed. For the next half hour the patient should rest. Biscuits and tea, or more glucose solution, should be given. We find that most of the patients help themselves to glucose, especially when it is made up with lemons and oranges, which make it quite a pleasant drink. We have, for some time, kept a small "library" of books and magazines in the insulin room. Magazines, particularly picture magazines, are very popular, and help to while away the time until lunch. Often a patient will return to a book he has been reading just before going into hypoglycaemia. It is not advisable to smoke as nicotine intensifies the action of insulin (Langfeldt, Strecker)

It has been emphasised by Larkin that the time immediately after awakening is a particularly impressionable one, and that every endeavour should be made to create an atmosphere of normality. Conversation should be carried out with the patient, newspapers are given round, and the work of the day discussed. In every way the patient should be encouraged and "mothered".

General Indications for Interruption

1. After the 5th hour.
2. With gross irregularities of the pulse - under 40 and over 140 per minute continuously. Slight irregularities are common in the stage preceding coma and should be disregarded. It has been/

been noticed that the pulse, given to irregularity on the first phase of treatment, settles down later.

3. Hypertonus in extension and pronation. These spasms are not infrequent in light coma, and should be disregarded, but in the presence of deep coma, they are a sign of bulbar involvement, and hypoglycaemia should be terminated. They are easily recognised and easily differentiated from the other type by the pulse irregularity mentioned earlier.

4. Stridor, cyanosis and the use of accessory muscles of respiration. Alae nasi are usually vibrating.

5. In "hunger uproar". This is to be differentiated from ordinary psycho-motor restlessness, during which the patient may call for glucose. This state is very uncommon and we have, as yet, had no need to interrupt for this reason.

In all the above intranasal glucose is sufficient to bring the patient to consciousness. After the first few minutes all will be well.

Indications for Intravenous Interruption.

According to Frostig about 7% of all hypoglycaemias require intravenous or other emergency interruption. It has been the practice in this series to use the intravenous method rather more often than this. Some patients, particularly those who are apprehensive and depressed, find that the return to consciousness is a long and terrifying experience. It has been described by one of them as "an indescribable nightmare". This patient felt that he had returned to the dark ages, perhaps the Stone Age, and was struggling to learn some ritual dance to enable him to wend his way through a dreadful maze. This nightmare/

nightmare recurred each day after interruption with intranasal glucose. Others have attempted to describe their symptoms in a rather different way. In these cases interruption was carried out by the intravenous route and they had no more complaints. As this experience has been quite common the use of the intravenous method has become more frequent.

The indications for intravenous interruption are these:-

1. Cessation of respiration and laryngeal spasm. This occurs in about 5% of hypoglycaemias.
2. Premature incidence of coma. If deep coma occurs before the third hour interruption should be carried out almost immediately. In some instances coma has been allowed to continue for as long as 15-30 minutes, but the patients have to be treated on their individual merits. There is a great danger that a premature coma may deepen and become irreversible. (James)
3. Epileptiform Convulsions. In the early seizures intranasal glucose is recommended by Feldhofen, and it is certainly the easier method where there is myoclonus.
4. Cardio-vascular Collapse. During this emergency there is an almost complete cessation of circulation. The pulse is impalpable and the veins cannot be distended, making it impossible to give an intravenous injection at times. 1 cc. of a 1:1000 solution of Adrenaline is therefore injected subcutaneously. In extremity, intracardiac injection of 2-4 ccs of 33% glucose is recommended.
5. Vomiting. It may be impossible for glucose to be retained in the stomach because of this. Atropine sulphate may be injected as an adjuvant.
6. In all cases where the intranasal method has proved to be dangerous, difficult, or uncomfortable. This includes:-
 - (a) Repeated laryngeal spasm every time the tube is passed.
 - (b) In patients with abnormally narrow nostrils.
 - (c) Where /is

- (c) Where it has been found that coma deepens after intranasal glucose. (See Case IV)
- (d) Where return to consciousness is a terrifying experience.

Technique and Apparatus for Intravenous Injection

As it was found that there were considerable demands made upon the intravenous method of interruption the use of 20 cc syringes, requiring recharging several times in the course of one interruption, was clumsily and slow. There was also the objection that, with a restless patient, it was almost impossible to avoid damaging the vein or inject some glucose into the tissues. To overcome these difficulties an apparatus was devised (described more fully later) which consisted of a 200 cc. graduated glass cylinder, containing 33% glucose, which acted as a reservoir. Glucose is pumped under pressure from this reservoir, through a length of rubber tubing, to the needle. This apparatus has been in use for several months and has proved to be efficient. It is possible by this means to inject, at one time, as much as 200 ccs. and no changing of syringes is required. It has the further advantage of being very simple to work, and is light and easily handled. This enables one to deal with emergencies promptly, even in the presence of convulsions and restlessness. The apparatus is mounted on a trolley, and this can remain in the insulin room throughout the day and night, prepared for any emergencies such as after-shock.

When an intravenous injection is to be carried out the trolley, with needle, forceps, cotton wool and spirit are taken to the bedside. A pneumatic band is applied to the upper arm of the patient, care being taken to inflate to the proper pressure (about 60 mm.) In the case of a dangerous emergency/a large bore needle in

emergency a large bore needle is required (No.2 intravenous) and one of the larger veins of the cubital fossa is selected. When routine interruption is indicated a small, almost hypodermic needle is used (No. 16) and a small vein in the forearm is selected. We have not, as yet, had any difficulty with this method, and there is almost no possibility of "using up" the veins, even by a daily injection over a period of weeks. Sclerosis of veins is comparatively rare.

The awakening after intravenous interruption is most dramatic. Within 2-5 minutes the patient is fully conscious and recovers with none of the excitement seen with intranasal interruption.

Other methods of interruption include Adrenaline 1:1000 solution. This is not used except after a seizure. In order to combat the deepening of coma following intranasal interruption 'Pituitrin' was tried. The hope was that it would inhibit the reaction on the part of the pancreas to secrete insulin when glucose was administered. No change was noticed and the method abandoned. The work of Cohen and Libman is of value in this connection.

Time of Interruption

Sakel lays great stress on interruption, its time and method. Thus, catatonic types are interrupted early, when they are talkative and approachable long before coma supervenes.

Excited patients should be interrupted when they are quiet, euphoric and dreamy.

Paranoid and hebephrenic types should be given deep coma and this coma should last for $1\frac{1}{2}$ -2 hours. So far as possible this rule has been observed though 2 hours was never achieved by any patient in deep coma as defined earlier.

Too/

Too early interruption leads to persistence of the psychosis, whereas too late may end fatally. Bychowski, Porch'er and others claim that the period of deep coma is not necessary, but this view is not common. Most agree that the effective part of the treatment lies in the production of shocks.

Difficulties, Dangers and Complications

Dussik describes three groups of complications:-

1. Those connected with other organs.
2. The result of excessive absorption of glucose.
3. Central Nervous conditions.

1. Complications connected with other organs.

These arise in the heart and the respiratory apparatus, and may occur either during or soon after hypoglycaemia. It is rather difficult to understand their mechanism, as the heart, for instance, can exist normally when the central nervous system shows alarming symptoms from sugar deprivation. Weak and irregular pulse with actual cardi-vascular collapse, cyanosis or Adams-Stokes syndrome are described. Digitalis is of little use in a weak circulation. Coramine 1 cc. by mouth has been found to be effective to combat these dangers. It should be given three times a day. In the more acute phase Coramine and caffeine injections are advocated, together with a very slow injection of 20 ccs. 33% glucose and $\frac{1}{4}$ mgm. Strophanthin. Adrenaline is dangerous in these states.

Pulmonary oedema is a severe complication but fortunately rare. This usually follows interruption of a prolonged shock with intranasal glucose.

Complications the result of excessive absorption of glucose.

In some cases interruption is followed by deepening of coma/

coma. This is explained by the fact that the greatly depleted liver makes up its deficiency with the entire feed, causing no change in the blood sugar level. In most cases this deepening is transient, and within half an hour awakening should take place. In some it is necessary to inject 60-100 ccs. 53% glucose intravenously before consciousness is restored.

Too rapid absorption of glucose can also cause diarrhoea and vomiting, with rise of temperature. This may continue for several days and may even prove fatal, but usually lasts for 12-24 hours. Large amounts of very dilute glucose solution is recommended. Vomiting can be treated with Atropine.

3. Central Nervous Complications.

I. Persistent Stupefaction. In spite of interruption the patient remains in a condition resembling deep sleep. Pyramidal signs are present, and despite all efforts to awaken him he remains in this state, perhaps for several days. (See Case II). A hyperglycaemia is usually present. Other symptoms are rise of temperature, rigors, hot dry skin and headache when awakening. Easton describes a case which lasted for several days.

2. Return of Epileptic Seizures.

After interruption cramps may continue, there is great psycho-motor restlessness of the contortionist type, tachycardia and dyspnoea, flexibilitas cerea, all developing into an epileptic seizure.

The treatment for both conditions is the same. Several measures can be tried in succession if one proves to be ineffectual. As there is already a hyperglycaemia further injection of glucose is unnecessary. Absorption should be improved/

improved by an injection of an ampoule of Vitamin B₁ preparation (Benerva), by improving oxygenation with inhalation of 5% CO₂ and O₂ , and by stimulants such as caffeine and strophanthin. If these fail then lumbar puncture might be carried out. Injections of sodium luminal may be necessary in status epilepticus.

"After Shock"

This is probably the commonest complication, and the most avoidable. It is due to rapid utilisation of glucose, with recurrence of hypoglycaemic symptoms later in the day - usually 3-4 hours after interruption. Those who have been given large doses of insulin are most prone. It is often found that patients who refuse food during the day are also subject to the attacks.

Feldhofen has found that 150 gms. of glucose is not sufficient for interruption, and recommends 200 gms. in every case. Parfill insists that all who have had more than 200 units should have a further 100 gms of glucose when they awake, and every patient should have his meals supervised. In this series only three patients showed this form of reaction and on each occasion it was found to be due to insufficient glucose. The above recommendations are now carried out and no patient is allowed any exertion until after a good lunch - which is supervised.

Although there are many varieties of alarming symptoms very few are immediately dangerous. It must be emphasised that it is essential to know which conditions to allow to continue and which to interrupt. In this way the treatment can be made safe/

safe, and at the same time effective shocks can be obtained. Only 7% of all shocks require immediate interruption.

After Care

After the patient has fully recovered consciousness he is allowed to be up and dressed. Throughout the rest of the day he should be employed in some manner. Garden work, occupational therapy, ward work, recreations such as billiards, chess, bowls, and cards. In the summer months the patient should be outside during the afternoons for walks, picnics and the like. It is of great value if the patients can be under the benevolent supervision of intelligent nurses. To avoid after-shock and to combat drowsiness in the afternoons it is advisable for the patient to carry a stick of barley sugar in his pocket to eat if he feels in any way unwell.

No attempt is made to probe too deeply into the patient's symptoms during treatment, as this seems to stir up the psychosis.

In most cases where there has been a complete or incomplete remission the patients are discharged as soon as possible after the cessation of treatment. All patients are asked to report at regular intervals after discharge.

Mechanism of Cure

As schizophrenia itself is not wholly understood it is difficult to arrive at a satisfactory explanation of the mechanism of cure by insulin shock treatment - if, indeed, it is admitted in the first place that this can be reckoned as a cure at all. A few of the theories are here reviewed. It is/

It is, of course, assumed for the purpose of discussion that hypoglycaemic shock does actually have a curative effect on schizophrenia.

Sakel put forward the suggestion, when the method was in its early stages of development, that coma produced a blocking of nerve pathways which he called pathological. The disease process of schizophrenia had previously opened up abnormal association pathways so that stimuli were transmitted along these, giving rise to abnormal reactions. Normal pathways were closed. The production of coma temporarily arrested the pathological transmission and encouraged the use of the neglected normal. This theory suffers from being too simple and having no true pathological or physiological substantiation.

Freudenberg reviews the current opinions on the subject. Quoting Kronfeld and Sternberg he indicates that hypoglycaemia brings about a beneficial effect in three ways.

- (a) Its quietening effect on instinctive activities.
- (b) The induction of euphoria, with change in the habitual mood and decrease of psychotic trends.
- (c) A reappearance of normal somatic sensation. The contents of the individual somatic experiences lose their psychotic significance. From these internal changes a longing for contact with reality results, and is available to break through autistic behaviour.

Approaching the problem from the patho-physiological standpoint certain opinions are held. It is assumed in the first place that schizophrenia is basically a metabolic disturbance, and that the function of insulin is to bring about a physiological equilibrium once more. Acute schizophrenics are held to have laevulose tolerance curves in/

in which there is a rapid rise and a retarded fall. Chronic cases show a slow rise and an even more retarded fall. The explanation of this is that the ergotropically over-stimulated organism of the acute schizophrenic attempts to retain large quantities of sugar in the blood stream ready for use. Thus there is present a "metabolic apathy" associated with deficient absorption of glucose from the intestine and a disturbed regulation of the vegetative nervous system, including the cerebral cortex. In the acute cases there is an increased stimulation of the apparatus, and in the chronic cases there is a diminution and finally complete failure on the part of the autonomic nervous system to respond. Together with these reactions there is found an increased resistance, as measured by the response to injection of 1/15th of a unit of insulin per kilo of body weight. In normal subjects there should be a lowering of 20-30% of the blood sugar in 30 minutes. After a further 30 minutes normality should again be reached. A delayed return to the normal level indicated that the antagonistic action of adrenaline has been disturbed, and this is taken to mean a diminished preparedness for reaction on the part of the autonomic nervous system generally. Other indications that this disturbance is present in schizophrenia are that, whereas normally there is a rise in blood pressure when posture is changed from sitting to standing, in schizophrenia the blood pressure is said to fall. The temperature does not fall to the same extent when a schizophrenic is in a cold bath as it does normally. It is postulated that this damping down of the activities of the vegetative nervous system inhibits the oxidation of the toxic products of metabolism. These products are believed to be responsible for the production/

Production of the schizophrenic reaction. Thus the action of insulin is to induce the oxybiotic process necessary for detoxication.

Rudolph suggests that the improvement following insulin hypoglycaemia is due to an increase in the alkali reserve of the acid-base ratio. Normal subjects can adjust the acid-base ratio in two ways - through the kidneys and through the lungs. In schizophrenics there is diminished excitability on the part of the respiratory centre to change the acid-base equilibrium. The normal acidity that occurs during sleep is also found in the waking hours. Golla pointed out in 1929 that an attack on this depression of the respiratory centre would perhaps be successful in combating the psychotic process. Thus, any means which would bring about an alteration in the acid-base ratio in the direction of alkalinity would have this effect. Ultra-violet light are said to have similar, though less intensive an influence in this direction. By this means the respiratory centre once more returns to its normal functioning, and cerebral respiration is enabled to remove the toxins accumulated in the brain cells. Insulin is believed to have, in addition to this action, a directly irritative action on the cell membrane itself, rendering it more permeable, and facilitating the exchange between the cell and its surroundings. Thus, according to this hypothesis, improved brain oxidation and the alkalosis occurring during hypoglycaemia may be two factors in the recoveries seen in this method of treatment.

Pickworth, reviewing the work of Himwich, pointed out that, in hypoglycaemia in dogs, the blood returning from the brain became progressively more arterial as the blood sugar lowered/

lowered, while that from muscle continued venous. He explained this observation by suggesting that insulin caused a dilatation of cerebral capillaries. The local pathological spasm which is presumed to be present in schizophrenia was thus removed, and the normal capillary patterns were restored, along with the normal sequence of the mental and emotional states. In strychnine poisoning there has been demonstrated a disorganisation of the cerebral capillary patterns, with consequent convulsions. A similar disorganisation is postulated as taking place in the convulsions of hypoglycaemia. Insulin should have a more selective action on the capillaries of those areas of the mid-brain which are concerned with sugar metabolism, and the functional inhibitions of schizophrenia might be supposed to be related to those areas - at least anatomically.

It is an interesting observation that the intra-ventricular injection of acetyl choline and eserine in man produces very similar reactions as are produced in hypoglycaemia. Henderson and Wilson found such symptoms as sweating, salivation, cramps and coma common features of these states.

Mental Effects

At present it is impossible to estimate the permanent value of the mental effects observed in this treatment. Many beneficial results which are seen are transient, and often present themselves only during hypoglycaemia itself, or immediately after interruption for a short time. The most striking change seen occurs during early hypoglycaemias, and is characterised by a period of lucidity. A hebephrenic patient/

patient, for instance, of some years duration seemed suddenly to "wake up", look around him, ask where he was and how he came to be in hospital, and would even carry on a seemingly rational conversation for some time. Very frequently, however, this state does not last any length of time - about half an hour or so - and often does not recur. In those patients who ultimately show a complete remission this period of lucidity is daily prolonged during hypoglycaemia and later "overflows" into the rest of the day. There is therefore an ever-widening circle of normality as the treatment progresses. It is this daily improvement which, when observed in several patients, is apt to make one think that it is the treatment, and that alone, which is coming to grips, as it were, with the psychotic process. It is admittedly a remarkable experience to see an apprehensive, hallucinated, deluded patient daily improving and casting off his symptoms one by one.

At this point it may be advisable to mention that few patients object to the treatment being carried out once it has been started. Many writers have objected to this method as being terrifying to the patient. This is not the case. In most cases there is soon experienced a feeling of well-being, amounting to euphoria, and it is a much more common experience to find the patient objecting before, than after, treatment. In the series of 25 cases treated, involving some 900 hypoglycaemias, sedatives were required, in all, about 20 times. The most consistent mental effect of insulin hypoglycaemia is sedation.

Symbols:

Complete remission	+++
Incomplete remission	++
Partial Remission	+
Unimproved	-

Consideration of Results

In a recent review of 2000 cases by Müller a very high percentage of complete and partial remissions was claimed following treatment. Three groups of cases were taken: those under 6 months duration, those under two years and those over two years. In the first group (under 6 months) there were 57.2% complete and incomplete remissions. In the second group (under two years) there were 27.3% complete or incomplete remissions, while in those over two years duration only 11.3% showed such remissions. The average for all three groups is 40.4%.

Originally Sakel claimed much higher remission rates for these groups.

The case material in this series includes 18 cases treated and 7 unfinished. Of these, three were acute cases (that is, under 6 months duration), 7 were of two years duration or less, and the remaining eight were of longer duration than two years. The results will be seen on the table.

Table of Results:

Certain points require explanation with regard to the tabulation/of results.

Results

Deussen, Strecker, Frostig and others have laid emphasis on the uniformity of the results which should be published. The following criteria are observed:-

Complete Remission:

- (a) Fit for work, of a responsible nature.
- (b) Without subjective or objective recognisable symptoms of a psychotic nature.
- (c) No defects in the intelligence. The emotional and volitional sphere of the total personality normal.
- (d) Insight into the illness.

Incomplete Remission:

- (a) Fit for work of a responsible nature.
- (b) Schizophrenic symptoms not objectively recognisable.
- (c) Slight defects in the intelligence, emotional and volitional sphere recognisable when subjected to a psychiatric examination.
- (d) Insight into illness not complete.

Partial Remission:

- (a) No longer fit for a more responsible or independent occupation.
- (b) Schizophrenic symptoms of a psychotic nature still proved objectively and subjectively admitted to.
- (c) Defects in the intelligence, or volitional sphere still recognisable (even by a layman)
- (d) Suspicion of dissimulation as regards insight into illness.

Unimproved:

No change observed except during the hypoglycaemic period.
Symbols/

tabulation of results.

Duration of illness is taken to include that period from the onset of the first schizophrenic symptom until the date of starting of treatment. Recurrent cases (R) are also dated from the onset of their first symptoms.

The column marked "Doses" indicates the amounts required to produce coma. Where two figures are marked the first represents the initial coma dose, and the second the final dose required.

The results are assessed, as far as possible, according to the standards mentioned above. No attempt was made to take into consideration the possibility of a relapse, and the cases were judged on their merits at the time.

As all cases have been treated within the past 10 months no indication is here given of the duration of remissions.

Conclusions:

At the end of 10 months it is very difficult to estimate the value of this treatment, but certain conclusions have been made, which may be of interest.

Although the results here mentioned may be inconclusive, and the case material small, there can be little doubt that insulin hypoglycaemia produces profound changes of a beneficial nature. Most of these changes are of a transitory order, and their nature difficult to estimate. The periods of lucidity seen so often in hypoglycaemia; the euphoria and increased approachability; the marked gain in weight and the undoubted sedative/

sedative effect of the treatment must actually be seen to be appreciated. There can be no question that the treatment itself produces these effects, as most of them disappear when it is discontinued.

It is unlikely that insulin, as some would hold, has a specific effect upon schizophrenia. It must be regarded as a symptomatic cure for a symptomatic illness.

Occasionally one does encounter complete remissions which, it seems, would never have recovered otherwise. One has the impression, however, that it is only in the essentially recoverable cases that insulin has a beneficial effect, and it may be that, in some way, it accelerates this process of recovery. In other words, recoverable cases are given the best chance to recover. One must take into consideration, in this connection, that a patient undergoing treatment has more supervision and encouragement during the weeks of treatment than at any other time.

As conclusive evidence has not, as yet, been obtained it may be advisable that this method should be carried on. In future, if one was to make a selection of the material, only recent cases would be taken. Paranoid cases should be given preference. Recurrent cases and those in which there is a physical factor present should also be taken.

Before an accurate estimate of the results can be made it would be necessary - as was done by Moersch - to take a similar number of controls.

Opinions generally are still inconclusive, but it is certain that the first wave of enthusiasm, which comes with all new forms of treatment, has died down, and at present scepticism is more in evidence. Nevertheless, further research into this mystifying disease has been stimulated, and this in itself is of undoubted value.

TABLE OF RESULTS

Type	Age	Duration of Illness	Days of Treatment	Comas	Fits	Doses	Results
Catatonic	19	1 yr.	31	4	0	100-85	++
Paranoid	27	5 yrs.	42	18	0	250-90	++
Stupor	35	2 mths.	42	17	0	200-85	+
Depression	40	7 yrs.	35	5	0	150-100	-+
Hebephrenia	24	5½ yrs.	46	20	0	60-50	-
Stupor	28	2 yrs.	44	15	0	100-50	-
Hebephrenia	28	9 yrs.	41	12	1	170	-
Hebephrenia	38	3 yrs.	41	23	1	50-55	-
Stupor	17	6 mths.	62	22	0	100-45	+++
Excitement	19	3 wks.	93	20	6	250	++
Paranoid	24	2 yrs.	64	14	1	215	++
Simplex	40	9 yrs	64	14	0	100-25	+
Stupor	20	2½ yrs.	35	7	1	150	+++
Simplex	25	1½ yrs.	34	16	2	110-62	++
Paraphrenia	35	9 yrs.	61	23	2	Unfinished	
Paranoid	24	2 yrs.	47	30	0	55-36	+
Paranoid	18	1½ yrs.	36	29	0	72-48	++
Simplex	24	2 yrs.	35	18	2	165	+++
Simplex	31	5 yrs. (R)	27	19	0	185	+++
Simplex	24	1 yr.	33	20	0	110-48	Unfinished
Simplex	20	2½ yrs.	17	6	3	Unfinished	
Anxiety	31	15 yrs.	17	5	0	Unfinished	
Paranoid	30	10 yrs. (R)	12	0	1	Unfinished	
Hebephrenia.	23	3 yrs.	11	0	1	Unfinished	

Cases completed	18		
Complete remissions	4	22%	} 55%
Incomplete remissions	6	33%	
Partial remissions	4	22%	
Unimproved	4	22%	

C A S E I.

Male aged 20; occupation - law student; admitted on 22nd
January 1938; case of paranoid schizophrenia.

Family History - cousin of the mother is known to be insane.

Personality - typical leptosome body build with a schizoid personality - shy, sensitive, dependent, over-conscientious, timid, studious.

Present Illness - Fifteen months' duration - gradual development of paranoid delusions directed particularly against his mother, with impulsive outbursts of violence for no adequate reason. Believed his food was poisoned and for weeks refused all food. His employers complained that his work was unsatisfactory, that he would not apply himself and that he was always coming in late in the mornings. He became unmanageable at home; refused to obey his parents; was more and more "distant" to his family, cold, callous and unfeeling; accused his mother of immorality. Has feelings of influence and says his thoughts are being stolen from him, that they are loud and others can hear them. Thinks there is a strange and hidden meaning in all he sees and hears. Occasional hallucinations of hearing, which he tries to conceal.

With a constitutional predisposition and a very insidious onset of the present illness, the ultimate prognosis is considered unfavourable.

Treatment - Treatment was started on 1st March 1938 with 20 units insulin. On the 8th day he had his first coma with 80 units, and on the 11th day admitted to being very much better; he was less worried, on the whole much more cheerful and feeling physically fitter than he had ever been. No sign of abnormality was noticed in behaviour and he no longer expressed his paranoid ideas, had no feelings of influence or ideas of reference. He was able to work in the Occupational Class in the /

in the afternoons and showed a considerable amount of skill there.

By the 36th day he had received 29 shocks and, as his behaviour was normal in every way and as he was otherwise symptom free, treatment was discontinued. On the first day of coma he required 80 units and on the last 48.

For the first fortnight he was very excited and had "emotional spasms" frequently before going into coma. After this there was no sign of psychomotor excitement and coma supervened quietly and was accompanied by profuse sweating, salivation, generalised hypotonus, positive Babinski and loss of blink, conjunctival and corneal reflexes. Interruption was by intranasal glucose and return to consciousness took place in 10 - 15 minutes without any difficulty.

Result - Complete remission.

Notes - This case demonstrates:-

- (1) The best type of coma with little or no excitement and complete hypotonus.
- (2) That leptosomic types require very little insulin.
- (3) Sensitization.
- (4) That the paranoid type seems to be amenable to treatment as well as, if not better than, other types.

Treatment - Treatment was started on 1st November 1937 with 40 units. On the 10th day he was receiving 15 units and 15 minutes he was in a light coma. Detail seen only a very profuse sweating had been noticed during the hypotonus. No improvement in his mental condition. On the 15th day (1st day of treatment) he was receiving 20 units and was only with a very light and short coma, sweating being still the most /

C A S E II.

Male aged 24; student; case of paranoid schizophrenia.

Family History - negative.

Personality - Previously a very conscientious, shy, good-natured and helpful boy. At the age of 14 contracted poliomyelitis and has now a disfiguring scoliosis with torticollis. His physical appearance is almost repellent.

Present Illness - Dates back two years and was precipitated by a sequence of failures at the university where he had intended studying for the Ministry. Was in a mental hospital from 9th February until 31st August 1937, and the diagnosis then was paranoid schizophrenia.

The main symptoms then, and also at the present admission, were peculiarities of behaviour with occasional impulsive outbursts, delusions that "there was an organised system of 'band-strumming' irritating him". Hallucinations of hearing and ideas of influence were also present and he began during the last few months to develop rather exalted ideas about himself, thinking he was cut out to be prime minister or the leader of a new political organisation. As no improvement was shown and he had frequent impulsive outbursts, breaking windows, smashing things, it was decided to start a course of insulin treatment.

Treatment - Treatment was started on 1st November 1937 with 10 units. On the 19th day he was receiving 160 units and for 15 minutes he was in a light coma. Until then only a very profuse sweating had been noticed during the hypoglycaemia, and no improvement in his mental condition. On the 18th December (31st day of treatment) he was receiving 200 units but reacting only with a very light and short coma, sweating being still the most /

most prominent feature. By now he was working in the gardens and seemed more contented.

Treatment was resumed on 4th January with 40 units. The dose was gradually increased until by the 59th day he reacted with a deep coma to 210 units. By this time he was no longer troubled with the idea that people were speaking about him and was given full parole and was working all afternoon in the gardens. Since the start of the insulin treatment he has had no impulsive outbursts.

On the 64th day of treatment he was given 215 units at 8 a.m. At 10.30 myoclonic twitchings starting in the face and becoming generalised were seen. Eyes were staring and he was sweating profusely. At 10.45 he gave a cry and went into an epileptic seizure; breathing became more and more difficult; face became cyanosed; pupils were large and irregular and reacted very sluggishly to light. Tonic spasms were followed by clonic, with spontaneous Babinski. Pulse became thready and rapid (120 - 130 p.min.). 60 ccs. of 20% glucose were injected intravenously. At 11.0 200 gms glucose were given intranasally. At 11.15 his colour was returning and he was rousable but not responsive. He had a disgruntled expression and seemed to resent interference. At 12 noon he relapsed into a deep coma, sweating, salivating, and twitching, respirations shallow and irregular, and there was pallor of the face. Pulse 110 and a little stronger. A further 100 ccs. glucose were given with .5 cc. adrenalin. At 12.35 his colour was returning but he was still not responsive or rousable. He was starting to shiver. At 2.40, despite a further 200 ccs. glucose intravenously and 200 gms. intranasally he was still in coma. Lumbar puncture was performed and about 15 ccs. taken off. B.P. was 116/70, pulse 120. At 4.0 p.m. he was still in light coma, though a further 160 ccs. of glucose had been given. He had been shivering and his temp. was now 100.6, pulse /

pulse 118, and B.P. 130/68. skin very hot, dry and flushed. At 5.0 there was no change and his temp. was 103. At 7.0 he was just rousable, temp. still 103. At 9.30 temp. was 101.6 and he was roused sufficiently to answer questions. He had a peaceful night but in the morning complained of severe headache, worse when he got up (? lumbar puncture). He remained in bed for the next two days and was still complaining of slight headache at times but of nothing else. Treatment was discontinued as he had had by now 64 days of treatment although only 6 days of shock.

Progress - On the 6th March, about a month after treatment, he was still occasionally complaining of people speaking behind his back and was rather depressed about this. Since then he has been free from symptoms and has shown some insight into his condition. At his own request he was discharged on 30th April.

Result - Incomplete remission.

Notes - This case demonstrates:-

- (1) Protracted hypoglycaemia, its signs, symptoms and treatment.

C A S E III.

Male aged 31; occupation - mixer in biscuit factory; case of schizophrenia simplex.

Family History - negative.

Personality - a schizoid personality of high intellectual ability for his class. For a working man has an excellent knowledge of literature, philosophy, psychology and the sciences. A rather ambitious, keen individual with many interests. Had a schizophrenic breakdown lasting $2\frac{1}{2}$ months, five years ago, precipitated by working conditions. From this he made a good recovery.

Present Illness - Of a fortnight's duration on admission (on 13th March 1938). Had again been over-worked in the biscuit factory (14 - 16 hours a day); weighed just nine stones (normal 11 stones) and was just recovering from bronchitis.

Illness characterised by vague paranoid delusions, believing that he was the victim of an unknown and mysterious system; constantly puzzling out the mystery and never finding a solution. Believed he was being accused of homosexuality; wrote to the king to ask his pardon for this son; thought his wife was his half-sister and his child was an adopted daughter; complained of intense pain between his eyes. Was so preoccupied with this puzzling mystery that he could concentrate on nothing else. Took very little food and did not sleep at all for several nights before admission. All attempts to work were given up after a few minutes' trial. He would try to read but could only turn the pages over listlessly. He would start to smoke but soon would lay down his pipe and try to interest himself in something else. Very soon this, too, would be given up. He did not seem to be able to escape /

escape from his perplexity.

Treatment - Treatment was begun on 2nd April 1938 with 20 units insulin. For the first few days he was very miserable and apprehensive about the treatment. On the fifth day, two hours after an injection of 60 units insulin, he became very talkative and euphoric. He said that his wife had already noticed a change in him (he had gained 6 lbs. in weight). He took up a magazine and stated cheerfully: "I can read like billy-o"; still, however, lacking in power to concentrate and actually only idly turning over the pages of the magazine. This was the first sign of a change in his mood from depression to elation. During the hypoglycaemia and for $\frac{1}{2}$ hour after interruption his predominant mood was one of elation henceforth.

The shock dose (80 units) was reached on the 7th day. By the 12th day he had gained 1 stone in weight altogether and, to all appearances, had returned to his normal cheerful self. He displayed keen insight into his illness and adopted a rather detached outlook on his trouble. He admitted that he had had some funny ideas about his wife, believed she was his half-sister and that his child was not his own. On the 25th day of treatment, after having received 18 shocks, the treatment was tailed off and stopped on the 4th May 1938, the 27th day of treatment.

Progress - Patient is eager to return to work and has shown in the ward that he is perfectly able to concentrate for any length of time. His mood remains cheerful, his outlook on his illness is admirable and he has full insight. He is eager even to go into explanations of his various delusions.

Result - Full remission.

Notes - This case demonstrates:-

(1) /

- (1) The physical benefit derived from insulin treatment.
- (2) The change from apprehension to euphoria during hypoglycaemia.
- (3) That an otherwise recoverable case has a shorter stay in hospital with insulin treatment.

Family history - Father was three times in a mental hospital with attacks of melancholia. The paternal uncle suffered from some form of mental illness.

Personality - Self-assertive, headstrong and quick-tempered.

Previous illness - Was in hospital during War following scalp wound. Diagnosis - dementia praecox.

Present illness - Dated from his mother's death in 1949. Became morose, sleepless and complaining of heaviness in the head. A year later, there being no improvement, he was admitted to hospital. Since admission the illness has been variable with no improvement. At times he is quiet, surly, preoccupied and apparently miserable, believing that he is going to die. At other times he is wildly excited, violent and impulsive, throwing articles at staff and patients. Precipitated himself at the window and believed he was about to die. Dramatized his fear of death by making himself rigid, throwing his head back and declaring that he was dead. Occasionally he is docile and amiable. Usually he is unapproachable and non-operative, resentful of any interference. His stream of thought is disconnected and irrelevant. He is often talkative, usually incomprehensible and occasionally perseverating. There is no apparent association between phrases. His mood is incongruous with his thinking and he will suddenly laugh for no obvious cause. There is a total lack of spontaneity of thought or action, and he has no power of sustained interest. No hallucinations are present, although he admits to hearing unreal "voices" before admission. There is no intellectual depression.

C A S E IV.

Male aged 40; occupation - ironmonger; admitted on 9th October 1937; case of ? schizophrenia simplex.

Family History - Father was three times in a mental hospital with attacks of melancholia. Two paternal uncles suffered from some form of mental illness.

Personality - Self-assertive, headstrong and quick-tempered.

Previous Illness - Was in hospital during War following scalp wound. Diagnosis - dementia praecox.

Present Illness - Dated from his mother's death in 1929. Became morose, sleepless and complaining of heaviness in the head. A year later, there being no improvement, he was admitted to hospital. Since admission the illness has been variable with no improvement. At times he is quiet, surly, preoccupied and apparently miserable, believing that he is going to die. At other times he is wildly excited, violent and impulsive, throwing articles at staff and patients. Precipitated himself at the window and believed he was about to die. Dramatised his fear of death by making himself rigid, throwing his head back and declaring that he was dead. Occasionally he is docile and amiable. Usually he is unapproachable and unco-operative, resentful of any interference. His stream of thought is disconnected and irrelevant. He is often talkative, usually incomprehensible and occasionally perseverating. There is no apparent association between phrases. His mood is incongruous with his thinking and he will suddenly laugh for no obvious cause. There is a total lack of spontaneity of thought or action, and he has no power of sustained interest. No hallucinations are present, although he admits to hearing unreal "voices" before admission. There is no intellectual impairment /

impairment, and some insight. He knows that he is a patient in a mental hospital and his whole attitude is one of despair and misery towards it. He is well orientated.

Though there are some manic-depressive features in this case, there seems little doubt that the reaction is preponderantly schizophrenic. His attitude to everything is distorted and unpredictable. There is present an intra-psyche ataxia.

Treatment - Treatment was begun on 5th November 1937. For the first two days he could scarcely be persuaded to remain in bed, was obscene and very noisy. On the 7th day, with 90 units, he was more amenable and euphoric during treatment. Interruption with glucose drink at 1 p.m. but it was not till 6 p.m. that he fully awoke. Until then he spoke with a slurred, thick voice, but did not know where he was and had a vacant expression. On the 9th day he had his first light coma with 80 units. On the 22nd day he was responding to 100 units with a light coma coming on $2\frac{1}{2}$ hours after an injection. The dose was, therefore, reduced until by the 46th day 40 units produced a deep coma. After interruption with 200 gms. glucose by intranasal tube the coma deepened with loss of corneal reflex, profuse sweat and salivation and hypertonic spasms with flexion and extension. This coma continued until interrupted by 60 ccs. glucose intravenously. This deepening of coma after interruption by nasal feed had occurred several times before. It was, therefore, thought advisable to interrupt by intravenous route each day and this overcame the difficulty.

Treatment was continued on the 6th day, when the coma dose was only 30 units.

Hypoglycaemia in this case was characterised usually by profuse sweating, great excitement, whistling, screeching, roaring /

roaring, contorting and grimacing. The coma even with such a small dose invariably supervened before 3 hours and scarcely ever deepened until after interruption with intranasal glucose. Return to consciousness was always slow and showed the same symptoms as in hypoglycaemia only more pronounced; he was extremely talkative, cheerful and amiable for some hours after-wards. No improvement in his mental condition was noted. He gained a few pounds in weight.

Present illness - Of a year's duration on admission, at first acute, quiet and unapproachable.

Result - Unimproved.

Notes - This case demonstrates:-

- (1) That chronic cases do not always require large coma doses.
- (2) The danger of deepening coma after interruption by intranasal glucose and the advantage of it in these cases.
- (3) The phenomenon of sensitization.

On admission was in a state of great excitement, was hearing unreal voices which told him that he was the Christ, Robert Burns, and other great personages. He refused food, declaring that it was poisoned. Soon after he relapsed into a state of stupor with negativism, mutism and cataplexy, refused food and lost weight. Occasionally he would mutter to himself, grince and turn his eyes upwards as though he were conversing with unreal persons.

This patient showed some features of a manic-depressive reaction and is, at the same time, of the pyknic body build. The insidious onset, the bizarre nature of his delusions, the presence of hallucinations and his manneristic behaviour are sufficient to justify a diagnosis of a schizophrenic reaction.

Treatment - Insulin was started on 10th July 1947 with 15 units. On the 15th of treatment three days after an injection of 15 units he began to improve. This was the /



C A S E V.

Male aged 19; occupation - carpenter; admitted 3rd
February 1937; case of katatonic stupor.

Family History - negative.

Personality - shy, timid, but intellectually well endowed;
brought up by his grandmother who dotes on him .

Present Illness - Of a year's duration on admission.

Gradual onset - was at first morose, quiet and unapproachable,
began to brood over his sins and thought that he was in danger
of hell fire and that he had V.D. He thought he heard the
voice of God telling him that he was about to die. About a
month before admission he had several periods of great
excitement in which he became impulsively violent, throwing
furniture about the room and striking his grandfather.

On admission was in a state of great excitement, was
hearing unreal voices which told him that he was the Christ,
Robert Burns, and other great personages. He refused food,
declaring that it was poisoned. Soon after he relapsed
into a state of stupor with negativism, mutism and akinesia,
refused food and lost weight. Occasionally he would mutter
to himself, grimace and turn his eyes upwards as though he
were conversing with unreal persons.

This patient showed some features of a manic-depressive
reaction and is, at the same time, of the pyknic body build.
The insidious onset, the bizarre nature of his delusions, the
presence of hallucinations and his manneristic behaviour are
sufficient to justify a diagnosis of a schizophrenic reaction.

Treatment - Insulin treatment was started on 10th July 1937
with 15 units. On the 3rd day of treatment three hours after
an injection of 45 units he began to whisper. This was
the /

the first time he had spoken for three months. He asked for a cup of tea and some buttered toast which he ate well. He asked for more toast and butter which was given and eaten with some degree of heartiness. On the fourth day of treatment, two hours after an injection of 65 units, he was sitting up and asking in a strong voice for a toasted roll and milk. He was able to keep up a conversation for the next hour and dressed himself very well and expressed a desire to go home. He said he felt perfectly well, but had no idea of the time of day or the date.

On the 6th day of treatment he said he felt very much better and wanted to go down town. That afternoon he was taken into the town and showed considerable interest in all that went on around him. At times his conversation was clear and spontaneous but at others he was apt to become dreamy and slipped back into his stupor again. He would awake from this with a start, smile and apologise for "dreaming". His thinking was more rational and he expressed no delusions or hallucinations, and he co-operated reasonably well.

After this initial clearing up of the katatonic symptoms the dose of insulin was increased daily until a deep coma was produced. He was given 10 deep comas, after which he showed a further improvement and, as he himself was rather unwilling to carry on with the treatment, it was stopped on the 7th August 1937.

Progress - This patient, although considerably improved at the end of treatment, was not discharged as he was lacking in initiative, refused to work and was generally lazy and untidy in his habits. He gained weight, slept very well and showed no delusions or hallucinations of any sort. Since then he has shown further improvement and is likely to be discharged in the next month or two.

Notes -

The treatment in this case was dramatic in its earlier effects in bringing about a re-adaptation to his environment. Further treatment with deep shock, however, did not bring about any further advance. Perhaps this was due to the rather short course.

Result - Partial remission.

Present Illness - 12 - 16 months' duration with a previous attack 7 years ago characterized by a paralytic reaction towards his father and hallucinations of hearing.

Present attack started with depression, hallucinations of hearing, followed by abnormal behaviour - refusal to go out of the house, refusal to speak and finally refusal to take food.

On admission gave the appearance of a benign stupor with perviousness, refusal of food and the use of nocturnal.

Required daily tube feeding until 11th February 1935 when insulin treatment was begun.

Insulin Treatment - On the 10th day he was given 120 units. 45 hours after injection he was persuaded to drink glucose and ten minutes later ate a meal consisting of soup and fish and potatoes - this was the first time he had taken any food since admission. For the next ten days of treatment hypoglycaemia was interrupted by glucose drink when he became euphoric and very irritable. Immediately after he took a meal with no perspiration sometimes he even asked for more. On the 21st day, as no further progress was noted, hypoglycaemia was allowed to continue until a deep coma was produced.

On the 25th day of treatment he had had 24 hours and was able to take at least one good meal a day - this just after interruption. He was now more talkative and socially responsive.

C A S E VI.

Male aged 37; occupation - miner; admitted on 26th October 1937; case of paraphrenia.

Family History - negative.

Personality - Bright and promising boy, clever and industrious; shy and sensitive; has always been quiet and not fond of company.

Present Illness - 12 - 18 months' duration with a previous attack 7 years ago characterised by a paranoid reaction towards his father and hallucinations of hearing.

Present attack started with depression, hallucinations of hearing, followed by abnormal behaviour - refused to go out of the house, refused to speak and finally refused to take food.

On admission gave the appearance of a benign stupor with peevishness, refusal of food and the use of neologisms.

Required daily tube feeding until 11th February 1938 when insulin treatment was begun.

Insulin Treatment - On the 10th day he was given 130 units.

4½ hours after injection he was persuaded to drink glucose and ten minutes later ate a meal consisting of soup and fish and potatoes - this was the first time he had taken any food since admission. For the next ten days of treatment hypoglycaemia was interrupted by glucose drink when he became euphoric and very dreamy. Immediately after he took a meal with no persuasion; sometimes he even asked for more. On the 22nd day, as no further progress was noted, hypoglycaemia was allowed to continue until a deep coma was produced.

On the 55th day of treatment he had had 23 comas and was able to take at least one good meal a day - this just after interruption. He was now more talkative and sociable, occasionally /

occasionally worked in the wards or in the gardens and had lost much of his apathy. He had also gained $\frac{1}{2}$ st. in weight. Treatment was discontinued although he was still quiet, shy, disinclined to associate with the other patients, preferring to sit by himself and occasionally read.

After 10 days, treatment was resumed as he had not taken any food by himself during that period and had relapsed almost into his stuporose state. Treatment was resumed on 5th May and continues.

Notes - This case demonstrates:-

- (1) That light hypoglycaemia is effective for stuporose states.
- (2) That high doses of insulin are effective in the treatment of patients who refuse to eat.

AN APPARATUS FOR INTRAVENOUS INJECTION

The following apparatus has been designed for use in the intravenous injections of glucose required in Sakel's Insulin Shock Treatment of Schizophrenia. It can, of course, be used for any other intravenous injection.

The apparatus consists of a graduated measuring cylinder (250 cc.) A, which contains the glucose solution. This is connected to a pressure bulb B, with a bladder reservoir C through a train of traps, D, E, F, G, D and G being empty tubes and E and F containing concentrated sulphuric acid. The acid bubblers E and F are provided to sterilise the air for producing pressure in A. The bubblers E and F are so arranged that the air must pass through the acid, in whatever direction the air is moving. The tubes D and G are provided as an absolute safeguard against the least possible trace of acid entering the rubber tubing or solution. H and L are two three-way taps, and N is the intravenous needle. M (see fig.2) is a glass 'window' consisting of a male record cone, allowing the blood from the vein to be seen before the tap L is connected to the reservoir.

In use the tap H is turned through from B to the circuit and the bladder C (which has a containing jacket of linen) is inflated hard. This is done gently to obtain the maximum effect of the acid on the air entering A as the pressure is raised. (The tap L is, of course, kept closed.) When the pressure is up, the apparatus is ready for use.

On/

On opening the tap L from A to N, the sterile solution is forced out through the needle at any desired speed according to the opening of the tap.

In use, the tap L and cone M are kept immersed in spirit until required, when the needle is slipped on to M and inserted in the vein, with the tap L open from N to the third leg of the tap, i.e., to the air. As soon as blood appears in M, the tap is turned to connect N to A, and the solution is forced into the vein, the rate being controlled by the opening of the tap L. After the final injection for the day, the pressure is released very gradually by opening the tap H. As the reservoir A can be of any size, a large number of injections of any desired volume can be made in rapid succession, the only change required being a fresh sterile needle.

For filling A, a reservoir of sterile solution is kept with ordinary dust-proof joints which can be flamed before use if desired (see fig.3). This is connected to A through the third leg of the tap L, tap H being open. The clips of the reservoir are opened with the reservoir higher than A and the solution siphons into A.

For convenience, the whole apparatus is mounted on a small trolley (see fig.4) upon which are also provided two clips which hold a large funnel which is used as the reservoir for containing the glucose solution for nasal tube administration. The tube leading from the funnel has a glass junction piece which is inserted into the end of the nasal tube and the required amount of glucose solution is poured into the funnel and allowed to run into the stomach via the nasal tube.

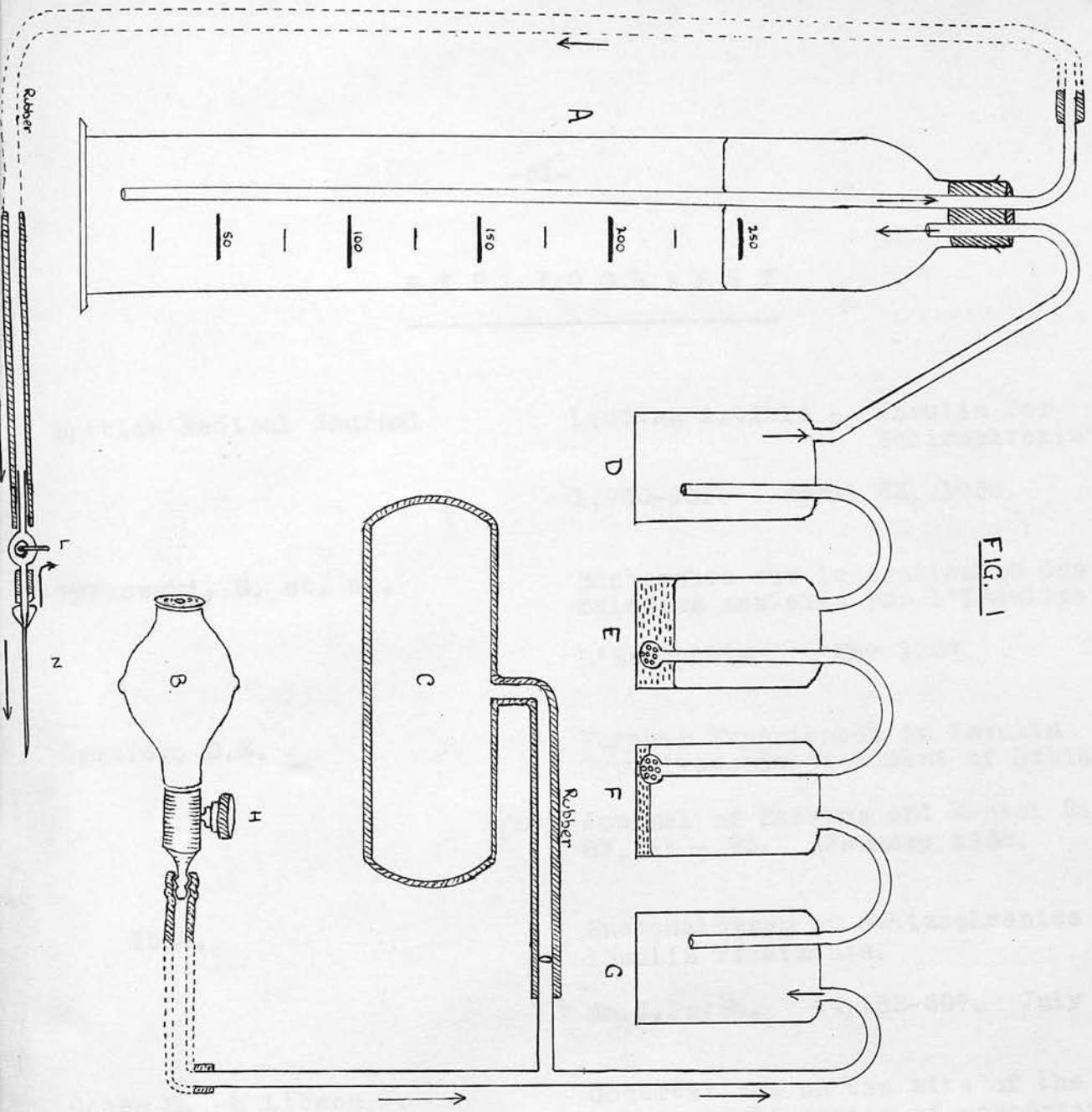


FIG. 1

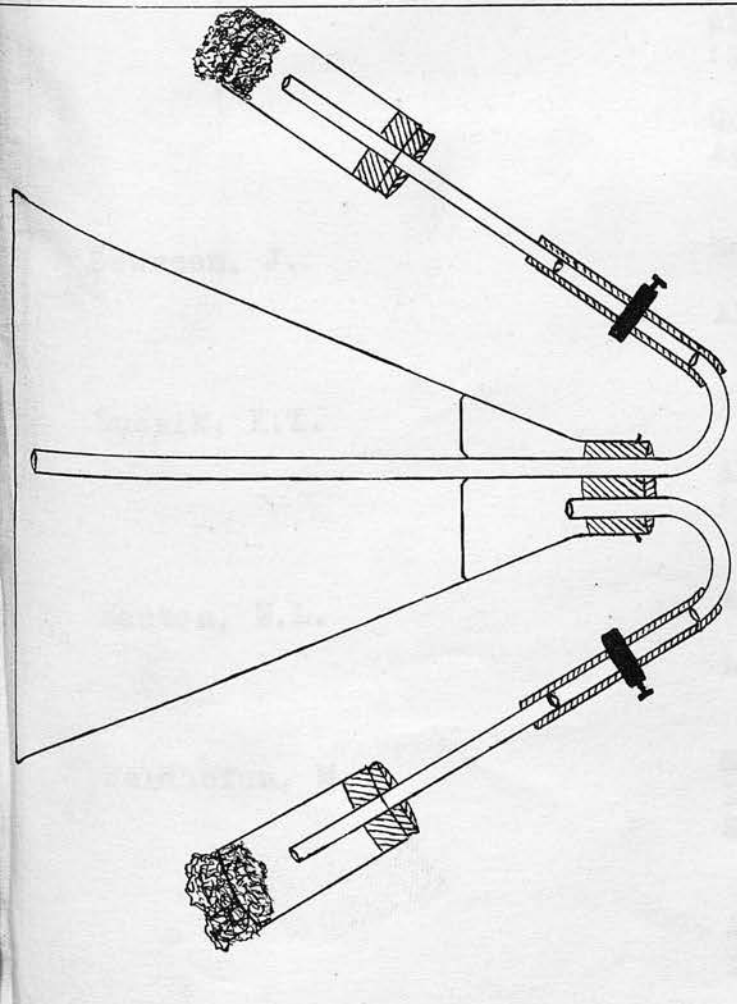
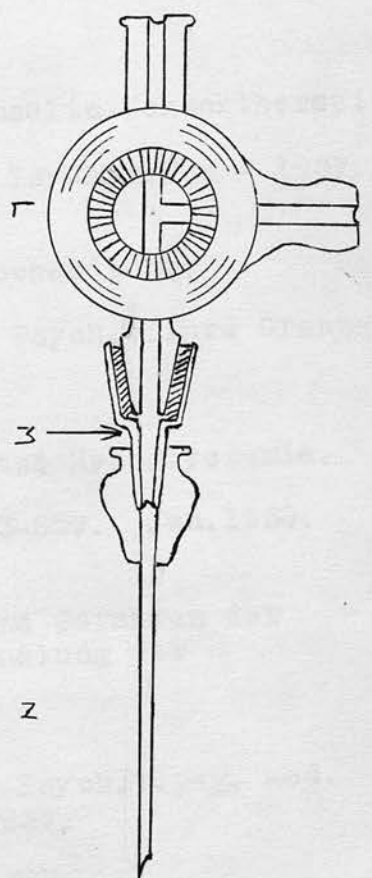


FIG. 3

FIG. 2



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