

Report on cardiazol treatment and on the present application of hypoglycaemic shock treatment in schizophrenia / by W. Rees Thomas (medical senior commissioner of the Board of Control) and Isabel G.H. Wilson (medical commissioner of the Board of Control).

Contributors

Great Britain. Board of Control.
Rees-Thomas, William, 1887-
Wilson, Isabel Grace Hood.

Publication/Creation

London : H.M.S.O. [printed by Eyre and Spottiswoode], 1938.

Persistent URL

<https://wellcomecollection.org/works/tgvb8snn>

License and attribution

This work has been identified as being free of known restrictions under copyright law, including all related and neighbouring rights and is being made available under the Creative Commons, Public Domain Mark.

You can copy, modify, distribute and perform the work, even for commercial purposes, without asking permission.



Wellcome Collection
183 Euston Road
London NW1 2BE UK
T +44 (0)20 7611 8722
E library@wellcomecollection.org
<https://wellcomecollection.org>

BOARD OF CONTROL
(ENGLAND AND WALES)

REPORT ON CARDIAZOL
TREATMENT
AND ON
THE PRESENT APPLICATION
OF HYPOGLYCÆMIC SHOCK
TREATMENT IN SCHIZOPHRENIA

BY

W. REES THOMAS, M.D., F.R.C.P., D.P.M.
(Medical Senior Commissioner of the Board of Control)

AND

ISABEL G. H. WILSON, M.D., M.R.C.P., D.P.M.
(Medical Commissioner of the Board of Control)



LONDON
HIS MAJESTY'S STATIONERY OFFICE
Price 1s. 0d. net

General Paralysis and its Treatment by Induced Malaria

Report by
Surgeon Rear-Admiral E. T. Meagher, R.N. (Retired).

Preface by
Sir Hubert Bond, K.B.E., F.R.C.P.

2s. net, post free 2s. 2d.

Hypoglycæmic Shock Treatment in Schizophrenia

A Study by
Isabel G. H. Wilson, M.D., D.P.M.

1s. 3d. net, post free 1s. 5d.

Memorandum on Occupation Therapy for Mental Patients

6d. net, post free 7d.

Departmental Committee on the Cost of Hospitals and other Public Buildings

Final Report

2s. net, post free 2s. 2d.

All prices are net

HIS MAJESTY'S STATIONERY OFFICE,

LONDON, W.C.2: York House, Kingsway;
EDINBURGH 2: 120 George Street; MANCHESTER 1: 26 York Street;
CARDIFF: 1 St. Andrew's Crescent; BELFAST: 80 Chichester Street;
or through any bookseller



22501382152

BOARD OF CONTROL

(ENGLAND AND WALES)

REPORT ON CARDIAZOL
TREATMENT
AND ON
THE PRESENT APPLICATION
OF HYPOGLYCAEMIC SHOCK
TREATMENT IN SCHIZOPHRENIA

BY

W. REES THOMAS, M.D., F.R.C.P., D.P.M.

(Medical Senior Commissioner of the Board of Control)

AND

ISABEL G. H. WILSON, M.D., M.R.C.P., D.P.M.

(Medical Commissioner of the Board of Control)

Crown Copyright Reserved



LONDON

PUBLISHED BY HIS MAJESTY'S STATIONERY OFFICE

To be purchased directly from H.M. STATIONERY OFFICE at the following addresses:

York House, Kingsway, London, W.C.2; 120 George Street, Edinburgh 2;

26 York Street, Manchester 1; 1 St. Andrew's Crescent, Cardiff;

80 Chichester Street, Belfast;

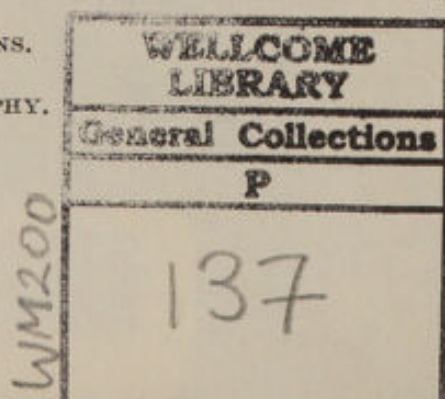
or through any bookseller

1938

Price 1s. 0d. net

TABLE OF CONTENTS.

	PAGE
I. INTRODUCTION	3
The scope of the report. Places visited and thanks to those who gave assistance.	
II. CARDIAZOL TREATMENT	5
Definition of the treatment. History. The drug. Dosage. "Speed shock." The solution and the injection. The fit. Preparation of the patient and care after the fit. Staffing and general arrangements. Difficulties and possible dangers. The safety of the method. Contra-indications (Cardiovascular disease, Renal disease, Respiratory disease, General physical disease, Menstruation, Trauma with unconsciousness).	
III. PRESENT APPLICATION OF INSULIN (HYPOGLYCAEMIC SHOCK) TREATMENT	14
The therapeutic use of insulin in mental disorder, in small, moderate and large doses. Hypoglycaemic shock treatment, certain methods, (i) Standardisation, (ii) Combination or alternation of insulin with cardiazol, (iii) Protracted shock. Present technique of hypoglycaemic shock treatment as generally understood. Duration of treatment, dosage, sensitisation, diet and resistance. Medicaments used in treatment. (Insulin. Adrenalin. Vitamin B. Oxygen and CO ₂ . Alkali. Calcium. Transfusion. Quinine.) Other points in technique. (Estimation of the depth of coma. Smoking. Suction. Precaution against after-shock.) Interruption by plan, on somatic grounds, by various methods. Mortality. Difficulties and dangers in the light of experience hitherto. (Nervous, Respiratory, Cardiovascular, Metabolic).	
IV. INSULIN AND CARDIAZOL TREATMENTS COMBINED AND CONTRASTED	24
Practice; Alternating treatment, summation treatment, crossed treatment. Theory: The difficulties: The physiological changes during treatment, by insulin, by cardiazol, by prolonged narcosis. Theories as to the mechanism of improvement, (the elimination of diseased cells, changes in the vegetative system, hypoglycaemia <i>per se</i> , some unknown effect of a convulsion, avitaminosis produced by high carbohydrate intake, the production of alkalosis in patient usually too "acid," increase in cell-membrane permeability, alteration in water-salt regulation, anoxia with consequent re-distribution of cerebral blood, alteration of tissue respiration, psychological stimulus or help.) Tentative views resulting from a consideration of theories.	
V. RESULTS	43
Diagnosis and selection of cases. Remissions apart from the use of insulin and cardiazol. Results and their classification. Outline of results from some series of published cases. Outline of results from England. Relapses. Results of treatment by cardiazol or insulin in various clinical types of cases.	
VI. CONCLUSIONS.	
BIBLIOGRAPHY.	



PART I

INTRODUCTION

To the Chairman of the Board :—

In the autumn of 1937 we were instructed to visit Vienna, Budapest and Frankfurt to study the Cardiazol treatment of schizophrenia and the present application of Hypoglycæmic Shock treatment, and to visit some English hospitals to observe the conditions in which these treatments were carried out there, as well as the demands made by them upon the accommodation and the staff. The following report embodies the main points which were brought to our notice at these visits and by a study of some of the recent literature.

Our very grateful thanks are due to those who generously gave their time and attention to helping us, to Professor Dr. Pözl, Dr. Dussik, and Dr. Palisa at the University Psychiatric Klinik in Vienna, to Professor Benedek and his staff including Dr. Angyal and Dr. Gyárfas at the University Psychiatric Klinik at Budapest, and to the Directors and members of the staff at the Budapest Mental Hospitals at Lipotmezo and Angyalföld and at the hospital of Szent Janos.

We are particularly indebted to Dr. von Meduna, the originator of the Cardiazol treatment, for the trouble he took on many occasions during two weeks to demonstrate the treatment at Angyalföld hospital, to describe both his experiences with it and his views on the theoretical basis of the work, and to show us some of the experimental investigations which are being carried out with Dr. Franz Reitmann on the effect of various drugs upon induced convulsions.

We take, too, this opportunity of thanking Professor Kleist and his staff at Frankfurt for the consideration with which they received us and the care they took to show us not only Cardiazol treatment as practised at the University Psychiatric Klinik but many points of great psychiatric interest in other directions.

We were also helped with information and advice by the staff of the British Legation in Budapest and by their physician, Dr. Fiala, as well as by Mr. Dowden of the British Consulate in Frankfurt, for which we are grateful.

In England one of us visited the mental hospitals at Bexley, West Park, Goodmayes and Arlesey and was there given opportunities to see Cardiazol treatment, and to profit by the experience of those carrying it out. We much appreciate the arrangements made by the Medical Superintendents and the time given to us by members of the medical staffs concerned. If little direct reference is made

to the observations at these English visits it is mainly because the results achieved, which were as yet tentative, will probably be recorded by those actually at work in the hospitals.

The Nederlandsche Vereeniging voor Psychiatrie en Neurologie was responsible for a meeting in Amsterdam, addressed by Dr. von Meduna on Cardiazol treatment and by Dozent Dr. Müller on Insulin treatment. For the kind invitation to attend the meeting and for the cordial hospitality there we are very grateful.

As regards the literature of the subject, the number of papers is so large and is increasing so rapidly that nothing approaching a complete bibliography has been attempted. Two sources of information to which we have turned may, however, be mentioned particularly.

The first has been the special volume of the Schweizer Archiv für Neurologie und Psychiatrie (Ergänzungsheft zum Band XXXIX. Die Therapie der Schizophrenie, Füssli, Zürich, 1937) on the Therapy of Schizophrenia. In May of 1937 a remarkable Congress was held at Münsingen Mental Hospital, near Bern, at which the treatment of schizophrenia by cardiazol, insulin, continuous narcosis, and by some other methods, was discussed by workers from many countries. The report, in the number of the Schweizer Archiv mentioned above, contains over 60 papers and communications, many of them of the greatest interest, and it is an invaluable accumulation of practical and theoretical knowledge and of stimulating speculation.

The second source has been advance copies of papers by a number of writers both in this country and abroad, which were unpublished at the time at which they were lent to us, the authors having generously placed the results of their experience at our disposal. To these papers, now published, the usual reference is made in the text of the report and in the bibliography. We offer here our thanks to the writers.

Finally we must add one personal point:—while we are both agreed as to the general findings of the report, one of us (I. G. H. W.) was mainly responsible for the actual text of it.

W. REES THOMAS.

ISABEL G. H. WILSON.

BOARD OF CONTROL.

June, 1938.

PART II.

CARDIAZOL TREATMENT.

DEFINITION.—The cardiazol treatment of schizophrenia consists in the production of epileptiform fits by the intravenous administration of cardiazol. It was thought out and developed by Dr. Ladislaus von Meduna of Budapest.

HISTORY.—Following reports by Nyirö and Jablonsky, Glaus, and Steiner and Straus on epilepsy and schizophrenia in the years 1929 to 1932, Dr. von Meduna reached a conclusion which he expressed as follows⁹²:—

“There is a biological antagonism between Epilepsy and Schizophrenia. If we succeeded in producing epileptic attacks in schizophrenic patients, these attacks would alter the chemical, humoral and hæmatological milieu of the organism in such a way that a possibility of overcoming the illness might be created, because the milieu altered in this way would be unfavourable soil for schizophrenia.”

The next step was to select a safe convulsant drug. Camphor was chosen for the purpose and the effects of injection were studied in animals⁸⁸, after which the treatment of patients was begun and the first results reported in 1935⁸⁹. Cardiazol was then, for practical reasons, adopted instead of camphor. Dr. von Meduna has since published further details of his work in book form⁹² and in a number of papers. Reports from Europe, Australia and America are also to be found in the literature.

THE DRUG.—Pentamethylenetetrazol⁶⁶, under the German trade name of Cardiazol (Knoll) or its American synonym, Metrazol, is used in English-speaking countries; most of Dr. von Meduna's work has been done with this. Other preparations with which good results have been obtained are Corvis (Lewenstein) used in Holland, Pentazol (Hommel) used in Switzerland, and a Hungarian product, Tetracor.†

Susceptibility to convulsion from cardiazol at the lower ranges of the usual convulsant dosage has been tested as a diagnostic procedure in suspected epilepsy^{18, 70, 76, 127}, a positive result being regarded as corroborative of clinical evidence of an epileptic tendency, but not, if taken by itself, conclusive. In other words it is sometimes, but not always, the case that a patient who has a convulsion after a small dose, is epileptic.

DOSAGE.—The initial dose recommended by Dr. von Meduna is 5 c.c. of a 10 per cent. solution. As will be seen, if a patient proves to be resistive to the convulsant action of the drug, he recommended

† Mayer-Gross and Walk have recently reported on “Cyclohexyl-ethyl-triazol in the convulsion treatment of Schizophrenia.” *Lancet*, June 11, 1938, p. 1324.

if necessary a gradual and careful increase of dose up to but not exceeding two successive injections of 1.6 g., i.e., a total of 3.2 g. in one day.

Quite recently, the maximum total dose allowed by Dr. von Meduna has been considerably increased, however. In a paper on "The most frequent mistakes in convulsion therapy" he writes⁹⁶ of a patient who had three doses, i.e. 1.60 g. plus 1.60 g. plus 1.40 g., a total of 4.60 g.—an extreme case who developed neither cardiac nor respiratory symptoms of any serious significance, nor abnormality in a subsequent electrocardiogram.

Dr. von Meduna talks of the "therapeutic" dose when he means the comparatively small, non-convulsant dose which is used when cardiazol is given as a cardiac or respiratory stimulant, and of the "supertherapeutic" dose when he means the large, convulsant dose used for the treatment of schizophrenia. The "therapeutic" or ordinary stimulant dose is about one-fifth of the "supertherapeutic" or convulsant dose, so that in practice there is no likelihood of confusion between the two effects. It is of interest to enquire what relationship the maximal "supertherapeutic" high or convulsant dose has to any known or estimated lethal dose.

On the basis of animal experiments a fatal dose for man has been calculated to be about 3 g.⁸³. There is only one recorded fatality from uncomplicated cardiazol poisoning, that of a laboratory assistant who, with suicidal intent, drank 100 c.c. of a 10 per cent. solution, and died in about an hour. Analysis of the body fluids and tissues in this case revealed an amount of cardiazol reckoned to be the equivalent of a dose of 3.2 g. subcutaneously, in a man weighing 65 kilograms (Esser and Kühn)^{26*}. The recognised harmlessness of cardiazol as a convulsant when properly used must be considered in relation to this danger when it is improperly used. From Dr. von Meduna's experience it appears obviously safe to push convulsion-resistant patients gradually up to a dose of 3.2 g. and occasionally above that; it would appear to be unsafe to give such high dosage inconsiderately or too early in treatment. In this connection it must be remembered that late fits, say four minutes or more after the injection, are probably due to the fact that all or some of the drug has missed the vein and has been absorbed from the subcutaneous tissues. It is important, before pushing the dose up to high levels, to be sure that failure or delay of a fit is in fact due to low susceptibility and not to technical error.

The clinical dosage may be further considered. The initial dose is 5 c.c. of the 10 per cent. solution, i.e. 0.5 g. of cardiazol, given intravenously. Some workers use a smaller dose¹³⁸, but Meduna uses that quoted because it is less uncertain in effect than a smaller dose and because, if no fit occurs, the patient suffers such unpleasant symptoms.

* We are indebted to Dr. Nicolay of Messrs. Knoll, Limited, for procuring for us this and some other literature on cardiazol.

If the fit does not come within one minute after the first dose, a second greater than the first by 0.1 g. is given (so that in this instance a dose of 0.5 g. would be followed by one of 0.6 g.). The interval of one minute is long enough for Dr. von Meduna and for his experienced nurses to make up their minds that a fit is not going to occur. For beginners, after discussing the natural question as to how long should elapse before one can be persuaded of the ineffectiveness of the first injection, he goes on to say⁹⁶: "In such cases I advise waiting for two minutes, and if then the confused state which has doubtless arisen after the injection has diminished, the excitement has disappeared and the fine tremor of the eyelids or twitches in the region of the eyes have stopped, without a fit having followed, then assuredly the second dose (i.e. one raised by 0.1 g.) can be given. I myself do not need to measure the time exactly after the first injection but can see after 30 to 40 seconds whether an attack is to be expected or not." This rapidity of procedure appears to be necessary because of the quick elimination of the drug, calculated by Hildebrandt and Mugge⁶⁶ at 0.85 m.g./k.g. per minute.

The following table gives a dosage scheme⁹⁷; it will be noted that so long as a given dose is effective in producing a fit, there is no increase of dose on that or on subsequent days.

Graduation of Intravenous Dosage of Cardiazol.

Day.	1st Dose.	2nd Dose—To be given in one minute if the first fails to excite a fit.	Note.
First	0.5	0.6	If a fit follows any 1st or 2nd dose, use that amount as the 1st dose of the next treatment day. So long as fits occur, the dose is not increased. If no fit follows the 2nd dose (for example on the second day) stop for that day and begin next day with the dose shown for that following (in this case the third) day. Continue at the same rate of increase if necessary, until both doses have been given at 1.6—i.e. 3.2 in all. If this is not effective, give up treatment.
Second	0.7	0.8	
Third	0.9	1.0	
Fourth	1.1	1.2	

So long as fits do not occur, injections may be given daily. When they do occur, treatment is given every alternate day, omitting Sundays. Try 20 to 25 fits before giving up a case as hopeless. While fits do good, go on up to 30 or 35 fits. Three fits

should be given after apparent recovery.⁹⁶ Treatment is given by some workers twice and by others thrice weekly.

Sensitisation may arise; severe fits from a dose equal to that ascertained to be convulsant for the given patient suggest that a lowering of dose is desirable to discover the smallest effective amount for the now sensitized patient.

Tolerance, on the other hand, sometimes occurs, so that after a number of effective injections the patients may cease to have fits until there is a slight increase of dose.

SPEED SHOCK.—The occurrence of the fit depends to some extent on the speed of injection, which should not be less than 1 c.c. per second (von Meduna⁹²) and may well be more, up to 3 c.c. per second (Georgi and Strauss)⁴³.

The possibility that "speed shock" may be a contributory factor to the production of cardiazol fits appears to us to be worth considering; by that we mean that the effect produced by the rapid intravenous introduction of fluid may per se predispose to the fit. "Speed Shock" is a condition which is not very well known. The name was given in 1931 by Hirschfield⁵⁶ and his colleagues to certain phenomena produced by the rapid intravenous injection of almost any substance, whether pharmacologically active or inert; the primary disturbance, in their view, occurred in the liver cell and the reaction might end fatally.

Such reactions to intravenous injections have been described by Sollmann¹²⁹ as having "the common characteristics of the histamine phenomena. They occur without incubation and are not transferable." Reactions of a mild type "have been called 'nitritoid crises' . . . and consist in excitement and anxiety, flushing of the skin, sweating, precordial distress, tremors, cough and dyspnoea; vertigo, headache and vomiting; chill and fever; joint pains. The serious cases rapidly develop intense asthma, cyanosis, fall of blood pressure, and asphyxial death." Muscular spasms have occurred in animals. Writing of the substances which may produce such a condition Sollmann says: "Indeed, it would be difficult to devise a solution which would be absolutely devoid of such (anaphylactoid) effects. Even normal saline solution and transfused blood may produce some 'reaction.' The degree of disturbance and the violence of the symptoms vary greatly according to the nature of the substance, the speed of the injection, and the susceptibility of the individual."

If the view which we have suggested be correct, the rapidity of injection of the cardiazol in the recognised technique of Dr. von Meduna is necessary to the effectiveness of the process because it produces speed shock which renders the patient liable to convulsion.

We suggest that "speed shock" is responsible for the bright flushing of the skin which follows injection in some patients more than in others and in some clinics more than in others, for some of the post-injection subjective symptoms, and probably for putting

the patient into a spasmophilic condition (a condition of "Krampf-bereitschaft") analagous to that into which he is put by hypoglycæmia and in which he is ready to respond to the convulsant action of cardiazol.

In view of the findings in a patient who died (p. 13), it is of interest that pulmonary thrombosis has been found in animals which succumbed to "speed shock."⁵⁶

THE SOLUTION AND THE INJECTION.

Ampoules with contents ready for injection are supplied by Messrs. Knoll, but the variability of dosage in different patients and considerations of economy make it more practical to make up a fresh solution from which the required quantity can be taken.

Gillies⁴⁶ recommends the use of the following formula: cardiazol powder 1.0, di-sodium phosphate 0.01, distilled water ad 10.0. The solution may be sterilized by heating for thirty minutes in a water bath at 100° C. It is best prepared daily.

Cook¹³ writes that after extensive trial of a buffered solution, as above, he now uses a simple aqueous solution (pH 7.7). It is a 10 per cent. solution made up freshly every two or three days, "sterilized by auto-claving at 110° C. for 20 minutes and kept in air-tight rubber capped bottles."

The technique recommended by most workers is to use a wide bore needle (Kennedy⁶² 8/10, Hunter Gillies 9/10 m.m.⁴⁶), to hold the arm only when the injection is just about to begin, and to use to distend the veins a piece of rubber tubing, to be loosened only when most of the injection has gone in. Care must be taken to avoid injecting the solution outside the vein, and, as far as possible, to avoid damage to the venous wall.

THE FIT.—In a few seconds the patient may cough, blink or cry out, and then the attack suddenly sets in with tonic spasm. The mouth opens widely for 8 or 10 seconds; to prevent tongue-biting a tampon is carefully set between the teeth and held there till the mouth closes. The tampon should be horse-shoe shaped and may be made of rubber, of three sizes of rubber tubing fitted one within the other, or of wadding tightly wound with gauze (the last two methods are used in English hospitals where we have seen the treatment), and it should be inserted in such a way that the tongue is pushed back and the cheeks are not left in the way of the closing teeth; this needs a little practice.

Clonic twitching follows the tonic phase, and the patient becomes grey and cyanosed. Neurological signs and the general course of the attack correspond to those of the idiopathic fit; the whole fit is over, as a rule, in about 80 seconds from the time of injection; the longest delay quoted to us by Dr. von Meduna was 3½ minutes, but longer delay has been known.

PREPARATION OF PATIENT; CARE AFTER THE FIT.

Contra indications to treatment will be discussed later.

A thorough physical examination must be made before treatment is undertaken at all. Finiefs²⁸ cites von Meduna's view that "it must include complete examination of urine, and estimates of blood-sedimentation rate, blood urea, blood sugar and blood pressure," and he recommends that the patient must have an enema the night before. No morning meal is given. Before the injection the patient should empty the bladder, as incontinence may occur during the fit. Dentures should be removed and night garments loosened at neck and waist. After the fit the patient will probably be confused and may roll or fling himself about in a dazed way for a little; usually he sleeps. Von Meduna restrains the restlessness with folded sheets; Van der Meulen and Rombouts⁶⁸, wrote of this practice that in their opinion it was "neither necessary nor desirable"; in Frankfurt the restlessness appeared to be simply controlled by the nursing staff and in England, so far as our observations go, the same applies.

Euphoria and eroticism are not infrequent. Vomiting sometimes occurs after the attack but is seldom troublesome. The patient remains in bed for his mid-day meal and until the late afternoon; improvement in appetite and eating are usual and may have to be met by the provision of extra food. There may be a complaint of backache as the result of the violent muscular movements.

STAFFING AND GENERAL ARRANGEMENTS.

Patients may be treated each in his own single room, or one at a time in a clinical room, going to bed in an adjoining dormitory as soon as the distressing features of the attack are over, or they may be treated in a dormitory where the patient immediately under treatment is screened off from the others for a time, or in a dormitory without such precautions. There is certainly alarm and distress raised in patients who either see or hear others during treatment, and one of the first two methods is much to be preferred.

Dr. von Meduna in speech (in Amsterdam) and print⁹⁶ has said that he considers treatment in a single room to be harmful, and calculated to alarm and distress the patient. He advises treatment of ten or fifteen patients together in one dormitory, screening each patient actually under treatment by portable cloth screens on iron uprights which fit into tin brackets on the legs of the bed. These screens, which run the length of the bed, can be transferred in a few seconds to the brackets of the next bed. Small portable screens of wood and cloth are used to hide the view of the convulsed patient (as seen from the ends of the bed) from the others. The screen method is quick and satisfactory, in von Meduna's opinion, for all but one or two very nervous or restless patients, who must be treated separately.

Quiet and skilled nursing, an orderly method in injecting, the absence of "too many interested spectators and white coats" (Rombouts, in discussion)⁸³, all conduce to ease and calm in treatment. Von Meduna remarks that one doctor and two or three nurses could treat 60 to 80 cases in one morning, or, more practically, 20 in one hour. It will be found convenient to have two nurses, or even three, for the actual injection. Of these, one is at each side of the patient, the nurse on the side chosen for injection holding the rubber band which is used as a tourniquet until almost all the injection is in the vein, and both are prepared to control restlessness and to prevent the patient from falling off the couch after the injection. The third nurse watches the jaw, holding it pressed upwards in patients subject to dislocation, and putting the tampon between the teeth. Patients must be watched after treatment until they have fully recovered consciousness and have ceased to be very restless.

DIFFICULTIES AND POSSIBLE DANGERS.

1. The treatment is very unpleasant unless, as sometimes happens, the patient has an adequate amnesia after it. His anxiety and reluctance are almost always observable as soon as he improves enough to express himself^{62, 124}.

2. Symptoms are particularly distressing if no fit follows the injection. Patients complain that they are freezing, or dying, or that lightning is running through them. They may have visual hallucinations. It is desirable to begin with a dose which may be expected to produce a fit; to stop the injection at once if the fluid is missing the vein, so that the syringe may be removed and filled with an adequate dose which will produce a fit when injected, this time into the vein; to give the injection fast, as described, and to give the second injection, if one is necessary, one to two minutes after the first. To allay the patient's anxiety, Humbert and Friedmann⁵⁷ on the Continent and Cook¹³ in England give scopolamine and morphine before the injection, but this is only necessary with the most apprehensive patients. Barbiturates and luminal lessen the efficacy of cardiazol and may interfere with treatment; paraldehyde¹³ also has proved to be unsatisfactory for this purpose. The "summation treatment" of Georgi is described in a later section; it consists in allowing the patient to become comatose and in a condition in which a fit will readily occur, by giving him an appropriate dose of insulin about 1½ hours before the cardiazol is given. This of course avoids the unpleasantness of treatment by cardiazol alone.

3. The veins may be difficult to find, or they may become obliterated; this happened much more frequently with the stronger solution of cardiazol formerly used, but still occurs at times with the present technique. If clotting occurs, the danger of pulmonary embolism must be remembered⁵⁶.

4. Cyanosis often appears alarming and cessation of respiration at the end of the clonic phase may cause anxiety. Almost invariably, however, these manifestations are spontaneously overcome; if not, a few movements of artificial respiration, or pressure on the chest for that purpose, will overcome them. Lobeline has been found to restore normal respiratory rhythm in rabbits under cardiazol¹⁰⁰.

5. Dislocation of the jaw may occur with the wide opening of the mouth at the beginning of the first tonic phase; it can often be prevented by holding the jaw firmly, and when it has occurred is easily reducible before the patient recovers consciousness. Occasionally other dislocations (e.g. of the shoulder) and fractures, have been reported.* The former seem to occur during the stretching movements after the fit; the latter are apparently due to muscular violence. Care should be taken to cover the frame of the bed with bedding where there is a danger that the patient may strike himself against it; if there is a head to the bed the patient should be placed far enough down, or be moved down as soon as consciousness begins to go, so that he does not strike his scalp against the wood or metal during the sudden extensor or head-retraction movements at the onset of the fit.

6. The occurrence of spontaneous epilepsy during or after treatment has been feared by many workers. Until quite recently it would probably have been true to say that in a range of cases estimated at upwards of 1,500 (Cook)¹³, such an event was quite unknown.

In January, 1938, however, Dr. J. A. Hobson of Woodside Hospital, London, described a case at a meeting of the Psychiatric Section of the of the Royal Society of Medicine. The patient was a woman with a 5 years' history of schizophrenia. There was no family history of mental disorder or epilepsy nor any personal history of fits. She was given 27 injections of cardiazol with 20 fits, over a period of about 9 weeks ending on July 9, 1937, the usual dose given being 4.0 c.c. of the 10 per cent. solution. She reacted on one occasion to a dose of 2.5 c.c. She improved very greatly during treatment. On the seventh day after the treatment was discontinued she had an attack which was described as exactly like a cardiazol fit; on the following day she had another, and on three further occasions fits again occurred. The last was at the end of November, 1937. According to the latest report of her in May, 1938, she had had no more fits, but she had relapsed into much the same condition as before treatment. We are grateful to Dr. Hobson for giving us these details, which have not hitherto been published. The case appears to be unique, and although there is no etiological evidence one way or the other, we can only suggest that the most probable explanation of these fits after treatment may be the existence of a latent epileptic tendency in the patient.

7. The attack and its concomitants naturally put some strain on the cardio vascular and respiratory systems.

* A medical superintendent has just written as follows: "One of my cases sustained fracture of the necks of both femora due to muscular contraction following his first injection of cardiazol."

The safety of the method.

In practice the difficulties and dangers are so few that it is fair to say that the treatment is almost universally regarded as easy and safe. Von Meduna, for instance, wrote⁹² that in 2,000 injections with over 1,000 fits, he never saw any sort of serious complication.

CONTRA-INDICATIONS

These are :—

- (a) Cardio-vascular disease.
- (b) Renal disease.
- (c) Respiratory disease.
- (d) General physical disease, pyrexia.
- (e) Menstruation.
- (f) History of trauma with unconsciousness.

(a) *Cardio-vascular disease.*

One of the patients, reported as having died under treatment, had aortic insufficiency and myocardial degeneration; Von Meduna writes: "with such a severely damaged heart a drastic treatment of this kind should not have been undertaken."⁹³ Since this misfortune, electrocardiographic examination has always been done before treatment in the hospital concerned. Observations by Dobozy⁹² and by Lax⁹³ on a series of cases showed no serious or persistent electrocardiographic changes after treatment, nor any unsatisfactory effect of treatment on the healthy patient.* Albuminuria in one case was attributed by them to a pre-existing essential hypertension.

Another fatality occurred in a patient who died of respiratory disease, apparently of vascular origin, for it was associated with thrombophlebitis of the pelvic veins; this was believed, from autopsy findings, to have been of long standing.

(b) *Renal disease.*

The close relationship between renal and vascular disorder explains this contra-indication. In the Frankfurt University Clinic⁶⁵, a woman with slight nephritis and circulatory disturbance developed hemiplegia under treatment, this was the only complication seen in 100 treated cases.

(c) *Respiratory disease.*

There is some evidence that the treatment may activate a latent tuberculosis, possibly by mechanical disturbance.^{141, 95} Von Meduna⁹⁷ is of opinion that in each individual case the advantage of securing good co-operation, appetite, and posture in a patient hitherto resistive and catatonic should be weighed against that

* Auricular fibrillation and heart-block were, however, reported by Dick and McAdam in "Cardiac Complications in Cardiazol Treatment," see JI. M.Sc., September, 1938.

risk. The third patient who died during treatment was found at autopsy to have a respiratory complication in the form of a retro-sternal goitre, as well as bilateral hypernephromata from which death would have not been surprising, even if she had not had cardiazol treatment.

(d) *General physical disease.*

The undesirability of treating patients with active physical illness is obvious. With experience, essentially sound but superficially debilitated patients may be treated, for they often have an increase of appetite and gain weight. Adequate food is required to meet the increased demand. The first fatal case quoted above (a) had had influenza before treatment.

The three patients whose death during treatment is recorded, therefore had each some earlier physical disorder,⁹⁷ i.e., (1) aortic insufficiency with myocardial degeneration, and recent influenza; (2) thrombosis of pelvic veins; (3) retrosternal goitre and bilateral hypernephromata.

Autopsy findings²⁶ in the case of suicide by cardiazol were cardiac dilatation, hyperæmia in heart and brain, myocardial changes including oedema, slight fatty changes in the liver, and cloudy swelling of the kidney epithelium—i.e. nothing beyond the changes which might be expected in death from a convulsant.

(e) *Menstruation*

(f) *History of trauma with unconsciousness*

} are contra-indications
} on which no comment
} is necessary.

The bio-chemical and some further physical changes in cardiazol treatment are more conveniently considered in other parts of this report, where also notes on the selection of cases for treatment, and on the results to be expected will be found.

PART III.

PRESENT APPLICATION OF INSULIN TREATMENT. (HYPOGLYCÆMIC SHOCK TREATMENT).

Before discussing hypoglycæmic shock treatment in detail, an outline of the various uses of insulin in psychosis may be useful.

THE THERAPEUTIC USES OF INSULIN IN MENTAL DISORDER.

Apart from its use in psychotic *diabetics*, insulin is applied in three ways in psychiatry.

1. IN SMALL DOSES, to improve appetite and nutrition. This is a well-known method, which need not be further discussed.

2. IN MODERATE DOSAGE, to calm patients who are restless and excited. This effect was described by Steck¹³⁰ and by Klemperer, who used it for delirium tremens, and it is not unknown elsewhere.¹⁴⁴ In a communication to the Board, Dr. Fox, of Brislington House, has described his use of this treatment, which he developed independently, following up work at Bethlem Royal Hospital. He writes of its admirable effect on the physical and mental health of those patients whom he selects as suitable for treatment.

3. IN LARGE DOSES (hypoglycaemic shock treatment) to produce coma or convulsions, or both. This method, associated all over the world with the name of Sakel,^{119, 120} who originated, developed and taught it, had also other discoverers; it was touched upon by Torp,¹⁴² who, however, did not follow up his clue, while Day and Niver¹⁴ in America, wrote:—"in March, 1936, we discovered, quite by accident and before becoming aware of similar work that was being done in Europe, that dementia præcox patients were usually resistant to very large doses of insulin and to hitherto unknown extremes of hypoglycaemia, that when they were finally given a dose that produced shock, the psychotic condition improved; and that, when such shock was often repeated, complete remission occurred in from six weeks to three months in most cases" . . . "We then undertook a two year research." Here is an illustration of an event so common in the history of science, the independent discovery in several quarters of a fact for which developing knowledge has prepared the way.

Acknowledgment and credit are everywhere rightly given to Dr. Sakel for his untiring clinical investigation of the possibilities of his treatment and for the part he has played in teaching it to other workers.

HYPOGLYCAEMIC SHOCK TREATMENT; CERTAIN METHODS.

1. STANDARDISATION.

Frostig believes that the time has come for simple standardised rules for the application and safeguarding of the treatment; he has set them out in his well-known "Richtlinien,"³⁸ a work which has just appeared in English under the title of "Sakel's Pharmacologic Shock Treatment for Schizophrenia. Tentative Directions and System of Recording"; the translation is by Wortis and the publication is in *Archives of Neurology and Psychiatry*, Volume 39, No. 2. (Feb. 1938) page 219. Knowledge of this clear and simple paper cannot fail to help the worker to "avoid misunderstanding through deviation from the original method and through obscurity in recording results," but rules of any kind can only form a framework on which the most careful individual observation and management must be built; indeed it has been said that "the great difficulty of treatment is that one can't be systematic."⁴⁵

ii. COMBINATION OR ALTERNATION OF INSULIN WITH CARDIAZOL TREATMENT. (See Part IV).

iii. PROTRACTED SHOCK.

This is the extension of hypoglycæmia over 4 or 5 or even up to 12 hours, with the administration of enough sugar to keep the cells alive but not enough to raise the level of the blood sugar or to wake the patient. Developed independently by Sakel¹²¹ and by Kraulis of Riga⁶⁷, it is believed by them to have good results in certain cases. We understand, however, that the mortality rate is high.

PRESENT TECHNIQUE OF HYPOGLYCAEMIC SHOCK TREATMENT, AS GENERALLY UNDERSTOOD.

(I) DURATION OF TREATMENT.

This is regulated partly by the response of the patient; in cases not showing much response treatment for a period up to 50 days is accepted as proper by Frostig³⁸; Müller¹⁰² says that less than 60 days of treatment is insufficient for a decision as to a negative result, and some cases have improved after 90 days. Strecker¹³⁶ says "60 to 90 days before giving up a case."

(II) DOSAGE, SENSITISATION, DIET AND RESISTANCE.

The range of shock dose is enormously wide; it is quoted by Küppers⁷³ at 15 to 300 units. In Vienna in 1937, however, we saw a case who required, as we were informed by Dr. Dussik,²¹ 400 units as a shock dose, and a case has been known to go into coma with as little as 13 units.

Beno⁵ lays great stress on keeping the pre-coma dose steady for several days before going on to the coma dose and he believes that this gives opportunity for valuable observation of the reactions of the patient, and adds safety in cases which tend to have epileptic attacks. Dussik²⁰ says that while the dose may be increased by 10 units between one day and next, it is unwise to increase at this rate for several days successively; that is too rapid a total increase, and trouble may arise. Sudden changes of dosage are recommended by experienced workers, notably by Sakel,¹²¹ and by Braunmühl,⁷ who describes his "zig-zag method" of dosage, but we cannot refrain from suggesting that if the inexperienced attempts anything of the sort, he may find himself in difficulty.

If the dose is correct, coma should begin in the 3rd hour after injection, and tonic contractions in the 3rd or 4th hour. If the dose is too high, these symptoms come in the second hour; if it is too low, they are delayed.^{38, 58}

Sensitisation arises in about two-thirds of the cases, according to Dussik,²⁰ and can go so far that the same clinical reaction may be achieved with about half of the original shock dose. One case

shown to us in Vienna has his first shock at 150 units; the next dose was 100 units but with this he had shock in two hours, which indicated that the dose was too large; on a later day he went into a coma with a dose of 60 units. As was said by one of us in "A study of hypoglycaemic shock treatment,"¹⁴⁸ there is room for observation of the effect of the diet and glucose intake in relation to sensitisation. We may refer to the classical work by Himsworth⁵⁴ on "The dietetic factor in determining the glucose tolerance and sensitivity to insulin of healthy men." The conclusion is reached that "the greater the amount of carbohydrate in the diet, the greater the sensitivity of the organism to insulin," and that the development of sensitivity is independent of the standard test dose of insulin given. James⁵⁸ has a record of the food intake of his insulin patients kept by the nursing staff, but on the whole the diet factor does not seem to have received the attention it deserves, in this country. We feel sure that a precise study of carbohydrate intake, including that swallowed and that given by tube and intravenously, in relation to the depth and the symptoms of hypoglycaemia in a series of patients, would do much to elucidate apparently capricious and often alarming variations in response to successive doses of a given amount in the same patient.

Another line on which investigation might be well repaid is that of fluid intake and fluid loss while under treatment, particularly in patients who tend to myoclonus or fits. Teglbjaerg,¹³⁹ writing on water metabolism and epilepsy, quotes Andrews to the effect that "the blood sugar curve after administration of insulin rises immensely in dehydrated animals and is lowered greatly in animals which are 'flooded with water'."

Resistance may be shown to insulin—"patients may develop resistance during treatment" (Küppers).⁷³ "Increased sensitivity may change to high resistance in the same patient" (James).⁵⁸ Formerly, high resistance was definitely taken to mean a bad prognosis; opinion has altered and Dussik says²⁰ "we now know that some patients with a high resistance have quite a good prognosis."

With all these possibilities, it is evident that dosage cannot be settled by rule of thumb, but needs very careful consideration and watching.

(III) MEDICAMENTS USED IN TREATMENT.

(a) *Insulin.*

Established brands of insulin are recommended,^{58, 102} so that reliability may be expected, and varied strengths may be used so that those may be chosen, which will give each patient his dose in the most convenient way. The use of protamine insulate has been suggested,¹³⁶ to produce a long, mild hypoglycaemia, though recent work suggests that it is unsatisfactory.^{114a} Experiments of

this kind, in the hands of those already familiar with the symptoms and the difficulties of the orthodox method, will doubtless prove to be informative.

(b) *Adrenalin.*

Its general use in interruption has been discarded, it tends to provoke motor activity, particularly fits; it is regarded as potentially dangerous and is reserved for (a) peripheral collapse, (b) impending death, when it can be given intracardially, and (c) to provoke excitement in selected stuporose cases.²¹ Sakel²¹ remarks that a patient who had status for many hours was undoubtedly kept in this condition by the unwise use of adrenalin.

(c) *Vitamin B.*

Recommended by Freudenberg^{29, 33, 34} in cases which show tachycardia, vomiting or other toxic symptoms, and in those who do not readily wake from hypoglycaemia, vitamin B₁ is increasingly used in insulin treatment. Freudenberg also uses vitamin B₂ and adrenal cortex preparations. An interesting recent observation is that of Bückmann,¹¹ who cites two cases who developed beri-beri symptoms which he believed to be due to excessive sugar intake during treatment. He recommends as a prophylactic in those who wake slowly and with difficulty from hypoglycaemia the use of 800 to 1,200 units of vitamin B for every 3 or 4 days, according to diet. Betaxin is a convenient preparation.

(d) *Oxygen and CO₂.*

The provision of an excess of oxygen, with 5 per cent. CO₂, is useful, and, indeed, may be said to be essential in cases in whom waking is delayed. The theoretical basis of this modification is that brain cells in such cases can only metabolise carbohydrate in the presence of oxygen excess.

(e) *Alkali.*

In cases which are not responding to insulin by showing hypoglycaemic symptoms, medication by alkali increases the sensitivity.⁵⁸ At the Three Counties Mental Hospital, Finiefs gives sodium bicarbonate 3i twice daily, afternoon and evening, to patients who appear to be sufficiently resistant to need, if not so treated, very high doses of insulin. Insulin itself shifts the pH. to the alkaline side, and the possibility of alkalosis from the concurrent administration of alkali and insulin must be remembered.

(f) *Calcium.*

Braunmühl⁷ gives intravenous calcium to patients who fail to wake from coma after the usual measures of interruption, and he believes this to be useful.

(g) *Transfusion.*

Kubo,⁷¹ in writing briefly of the dangers of treatment, says "Blood transfusion twice proved to be life-saving."

(h) *Quinine.*

Sakel reported in 1937¹²¹ that, in the hope of improving the response to treatment, he was trying the effect of quinine (0.5g. daily for 14 days), to turn "dry shock" into "wet shock" in suitable cases; his cases were too few for any clear result to have emerged.

IV. OTHER MODIFICATIONS IN TECHNIQUE.

(a) *Estimation of the depth of coma.*

The present method of estimating the depth of coma, as used in Vienna,²¹ is to blow air sharply from a large syringe on to the face. If there is no movement of the eyelids or face in response, the patient is said to be in deep coma.

(b) *Smoking.*

It is said that smoking increases the action of insulin and that it should not be allowed within 1 hour of interruption.¹³⁶ Before coma, "a cigarette tides a difficult patient over his hungry period."⁷⁹

(c) *Suction.*

In America, the use of suction has been advocated¹²⁸ for the removal of excess saliva, as has the use of the bronchoscope in cases which aspirate saliva.

(d) *Precaution against after-shock.*

If a patient has been sent to sleep in a non-observation dormitory, the administration of 375cc. of 40 per cent. glucose solution before he goes to bed as well as the instruction in hypoglycaemic symptoms of nurses who will visit the ward in the night is recommended by Gies.⁴⁵

V. INTERRUPTION.

The following on interruption, is taken from a recent work by Dr. Dussik.²⁰

According to plan :—

(a) *By Time*—not more than 5–6 hours in all. Deep coma (i.e. the patient not objecting to the tube), not more than 1½ hours.

(b) *By Psychosis.*—Paranoid cases should be waked from deep coma, Inhibited cases should be waked in excitement. Excited cases should be waked from a quiet coma.

On somatic grounds.

<i>Neurological</i>	Extensor spasm. Epileptiform attack. Myocloniform attack.
<i>Circulatory</i>	Pulse over 140 or under 40; small, quick pulse. Definite arrhythmia. Other sign of heart disturbance.
<i>Respiratory</i>	Kussmaul breathing (i.e. very deep slow breathing). Cheyne Stokes breathing. Cyanotic laryngospasm.
<i>Other signs</i>	of a clinical kind, e.g. severe tongue-bite.

By various methods.

- (1) By tube, normally.
- (2) Intravenous. (a) Somatic indications—if not waking from tube feed.
(b) Mental indications—cases of old catatonic stupor should be put in deep coma, and wakened suddenly.
- (3) Adrenalin should be reserved for (a) Peripheral vascular collapse.
(b) In impending death, to be given intraventricularly.
(c) To provoke excitement in the stuporose.

MORTALITY.

Küppers⁷³ in 1937 put this at 1·5 per cent. and noted that the period during which this figure was reached included the time of working out precautionary rules and discovering the scope of the method. Müller¹⁰² quotes 495 cases with two deaths (0·4 per cent. mortality), and Marzynsky⁸⁷ 164 cases with no deaths. James says⁵⁸ "We believe that the death rate will always prove to be in inverse ratio to the care with which a proved method of technique is adopted and applied." We have as yet no full record of the number of cases treated in England. Two deaths have been reported, one being due to irreversible coma and the other to pulmonary oedema in a patient found at autopsy to have had unsuspected chronic nephritis.

DIFFICULTIES AND DANGERS IN THE LIGHT OF EXPERIENCE HITHERTO.

These may conveniently be studied systematically.

I. NERVOUS SYSTEM.*(a) Failure to wake.*

This may be diagnosed if the patient shows no real, definite signs of waking half an hour after the ordinary "interruption" glucose has been given.²¹

Occasionally, the glucose solution appears to remain in the stomach, and may later be vomited or discovered by tube; this retention may be favoured by giving too large amounts of glucose into the stomach. In this case intravenous glucose is indicated.

Not infrequently, however, there is a high blood sugar, yet the patient remains in coma. Georgi⁴⁴ says "We think that the failure of patients to wake depends on the inability of the cells to take up the sugar given to them . . . We completely agree with Müller that the giving of more sugar in such circumstances is, to say the least, useless, and that other ways must be sought to give back to the cells their capacity to take in sugar." The treatment is to give 500 to 1,000 units of Vitamin B intramuscularly, to perform lumbar puncture, to use oxygen and carbon dioxide mixture, and if necessary, to give intravenous calcium chloride. Venesection to 300 c.c. is also recommended, and the administration of a few cc. of water into the stomach by tube.²¹

(b) *Exhaustion.*

Salm¹²³ describes a peculiar state of indifferent drowsiness and exhaustion in some cases, lasting for a considerable time, which he attributes, partly on clinical findings and partly on autopsy findings in one case, to mid-brain damage. Gies⁴⁵ says that one of his patients after treatment was for a time restless and confused, in "a state like a hysterical twilight state."

(c) *After shock.*

This may be unpredictable, and may occur in spite of apparently ample glucose intake⁵². The possibility must be clearly kept in mind, and sugar given by mouth or otherwise at the onset.

(d) *Muscular spasms.*

Epileptiform attacks.

Their significance will be discussed later. Early attacks may be a sign of overdose. With late epileptiform attacks the patient may be tired after treatment.¹⁰⁶ Treatment of the epileptiform attack is by interruption.

Status epilepticus.

Note Sakel's¹²¹ remark on the relation of adrenalin to status (p. 18), Tube feed with glucose. Give Betaxin 4 ampoules (i.e. 4 cc.), and oxygen. If the heart is unsatisfactory, give caffeine and strophanthus.²¹ Gillies⁴⁷ recommends glucose intravenously and by tube, repeated lumbar puncture, soap and water enema, and morphine gr. $\frac{1}{4}$, and he lays stress on the value of oxygen. Gies⁴⁵ gives luminal. Pullar Strecker¹³⁶ recommends lobeline.

"Myocloniform collapse."

Under this heading "Frostig³⁸ and others have described a spasmophilic condition in which there are generalised twitchings of a myocloniform character, and at the same time, or shortly before, severe collapse symptoms arise." This association is well-recognised; Steinfeld¹³¹, for instance, describes a patient who

"went either into severe epileptiform convulsions or circulatory collapse so profound that immediate intervention was necessary." "The occurrence of even quite severe myoclonic twitching is not by itself an indication for termination when it occurs at the end of the first hour . . . it should be aborted by sugar."¹² Prompt interruption is indicated in myocloniform collapse. Veins may be extremely hard to find, in this condition. Cases have been saved by intracardial injection of adrenalin⁵⁸ or glucose²⁰—possibly the drug, in the extreme emergency, was chosen rather because it was at hand than upon any specific therapeutic value; the stimulant effect of the needle apart from its contents, is worth remembering. Oxygen and carbondioxide are valuable.

Laryngospasm.

If the patient looks well, laryngospasm is not now regarded with such seriousness as formerly, and may be allowed to go on for a little in the expectation that it will come to an end spontaneously. If there are signs of deficient oxygen intake, however, the condition is obviously threatening, and interruption should be carried out. Gillies⁴⁷ describes a case whose treatment had to be abandoned after she had become blue and pulseless with laryngospasm on three occasions.

II. RESPIRATORY SYSTEM.

(a) *Oedema of the lungs.*

Beiglböck,⁴ reviewing a series of cases, says "The complication hitherto most frequently seen and most dangerous is oedema of the lungs, which up till now I have seen 4 times. Its occurrence is not surprising, for in insulin shock there is an increased circulatory rate; if to that an acute insufficiency of the left heart is added, which from our knowledge of the changes in the heart muscle is not unexpected, conditions are favourable for its occurrence. Strophanthin has proved to be a sovereign remedy, together with ample blood-letting and plenty of oxygen." Pulmonary oedema has also been reported by Kronfeld and Sternberg,⁶⁹ and by Beno,⁵ who speaks of the death of a case "dans des conditions dramatiques, en pleine cure insulinique, par oedème pulmonaire suraigu . . . les circonstances de cette mort sont demeurées obscures. Nous ne sommes pas loin de penser que l'état du cœur y a été pour quelque chose. . . ." It was responsible for a death in England, and has occurred here in cases who have recovered. Treatment is by venesection, and by inhalation of oxygen. Pullar Strecker¹³⁶ recommends very slow intravenous administration of $\frac{1}{4}$ mg. strophanthin in 20 cc. glucose. Dr. Finiefs told one of us of a case in which pulmonary oedema occurred and was overcome in about half an hour by lumbar puncture and by the administration of Euphyllin.

REPORT ON CARDIAZOL TREATMENT.

Erratum.

P. 23, seventh line:—For "a rate of over or under 40 " read
"a rate of over 140 or under 40."

x (382)19213 Wt 3000—896 1500 11/38 E & S

(b) *Bronchopneumonia.*

This complication is not unexpected; Berglas and Susic⁶ give it as the case of death in 2 of their cases. It has been reported by others.

III. CARDIOVASCULAR SYSTEM.

(a) *The heart clinically.*

Irregular pulse, poor pulse, a rate of over or under 40 are indications for interruption.²⁰

Digitalis should not be given to a patient who is being treated by insulin; the two work in the same direction upon the cardiac vessels. It is to be noted, too, that if digitalis is given, the use of strophanthin in emergency is barred, because of the dangerous effect of strophanthin on the digitalized heart.

(b) *The heart electrocardiographically.*

In many cases the T. wave is flattened or inverted during treatment; therefore contra indications to treatment are, clinically, angina; coronary sclerosis or inefficiency, pronounced hypertonia, chronic nephritis and severe valvular disease, particularly if tending to produce myocardial damage or fibrillation.⁴ Cases with positive electrocardiographic findings but no clinical disturbance must be considered on their own merits when treatment is contemplated.

(c) *Peripheral vessels.*

The "myocloniform" type of collapse has been described. The treatment for vascular collapse without myoclonus is the same, except that 1 cc. of 1/1000 adrenalin may be given.

(d) *Pulmonary vessels.*

See "Oedema of lungs."

(e) *Cerebral vessels and cells.*

Apoplexy and retinal bleeding⁵¹ and hemiplegia¹⁰² have been described. Cerebral perivascular necrosis has also been described¹⁰¹ in the well-known case of a medical man entrusted with insulin and glucose, who died of an overdose of insulin. Similar findings have been mentioned by Stief.¹³² Acute and probably reversible oedema and some necrobiosis in the central nervous system, probably circulatory (dogs) and xanthochromia of the cerebro-spinal fluid (man) have been seen (Beiglböck)⁴. Transitory dementia of Korsakov type, possibly dependent on such cortical effects, has been noted by Müller¹⁰²; symptoms of this kind are often feared by those who have not used the treatment; and it seems rather surprising that they seem to occur so seldom. As to these cerebral changes various authors say that they do no real harm; "there

is little danger in the treatment in experienced hands¹²⁵” and “permanent damage is the very great exception.”¹⁰² Stief indeed regards the changes as beneficial.¹³²

For cerebral oedema, do lumbar puncture, give hypertonic sugar (such as Osmon, which is 33 per cent. glucose) intravenously, with salyrgan or an equivalent, hypertonic saline intravenously (small amount) and 10 to 15 cc. water in the stomach (Dussik).²⁰

IV. METABOLIC AND OTHER CHANGES.

Day and Niver¹⁴ write of *alkalosis*, which was nearly fatal in one of their cases but which was promptly relieved by treatment when the condition was diagnosed.

Beiglböck⁴, in his survey of Vienna cases, records also temporary (lasting less than 1 year) *disturbance of sugar metabolism* (3 cases), *disturbance of renal permeability* (2 cases), and *oliguria of cerebral origin* (1 case). Another occasional disturbance is *diarrhœa*, to be treated by the substitution of glucose for cane sugar in the feeds (Dussik).

An increased *susceptibility to skin infections and boils* has been noted; on the other hand Wortis¹⁵¹ has cited several cases where severe acne improved remarkably during treatment. Presumably the susceptibility to boils, etc. is related to a high, and the cure of acne to a low, sugar level, the skin condition of any particular patient depending upon the sugar intake in relation to the insulin dose.

PART IV.

INSULIN AND CARDIAZOL TREATMENTS COMBINED AND CONTRASTED: Practice and Theory.

PRACTICE.

Many physicians are now using both drugs, in an effort to reach a maximum therapeutic effect.

Küppers⁷⁵ has described three ways of doing this, as follows:—

(a) *Alternating treatment.*

Insulin is given for five days, and cardiazol on the sixth; then the process is repeated. This method is specially indicated for severe stupor.

(b) *Summation treatment.*

A cardiazol convulsion is induced one and a half hours after the administration of a coma dose of insulin.

(c) *Crossed treatment.*

First a period of insulin treatment is given; then a longer period of cardiazol treatment, and finally another period of insulin treatment.

He added that for recent cases of stupor the pure cardiazol treatment was specially indicated. He obtained his best results by beginning with insulin, and going on to cardiazol if there was stupor. If this method failed he used the Crossed method, and if that also was unsuccessful, he undertook Summation treatment. "In any case the treatment must be energetically carried out."

In a 1937 publication Erb²⁵ writes on the possibility of combined treatment. His method is to vary treatment according to the clinical type of each case. He treats excited or stuporose cases at first with cardiazol; when improvement begins he seeks to consolidate the gain by treatment with insulin. Hebephrenic cases he treats from the first with insulin. When the response to this ceases, he interpolates some cardiazol treatments, returning later to insulin treatment. In all cases which fail to have fits with given doses of cardiazol, i.e. 0.7 g. for men and 0.6 g. for women, he gives up cardiazol and treats with insulin, returning to cardiazol only if the patient shows signs of increased susceptibility to fits as the result of the insulin treatment. In common with many other workers, for paranoid cases he uses insulin alone.

The most interesting of these various methods is perhaps the "Summation" treatment. Introduced by Georgi⁴² at the Münsingen Conference in 1937, it is used in many Continental countries and in a number of hospitals in England. In bringing it forward Georgi wrote of his impression that patients who had epileptic fits during insulin treatment had a better prognosis than those who had no fits, and of his readiness to see in convulsion treatment a "welcome completion" of insulin treatment. He noted that whereas cardiazol produced fits in 65.6 per cent. of his patients not in hypoglycæmia, it produced fits in 72 per cent. if given during the course of hypoglycæmia. He believed that the tendency to fits in hypoglycæmia is greatest during the second hour after insulin injection; that less cardiazol was needed to have a convulsant effect then than at other times, and that his method of combining the drugs was valuable, because it prevented the dread and anxiety which arose when cardiazol was given alone.

He outlines his treatment as follows:—

"Begin insulin treatment according to Sakel, and as soon as the coma dose has been found, proceed to the use of both drugs. Either give insulin six days weekly as usual, giving cardiazol intravenously two or three times a week, one or two hours after the insulin injection or, once the coma dose has been found, give the insulin two or three times weekly only, giving the cardiazol an hour or two later, as in the first method." The second way is to be preferred, as being less tiring to the patient. It will be found that a beginning may be made with a smaller dose of cardiazol than usual, namely "3 c.c. of the 10 per cent. solution." If the coma comes earlier or later the time of giving cardiazol should be altered accordingly, so as to coincide more or less with the "turning

point" in hypoglycæmia which he describes; reference is made to this below. As in simple cardiazol treatments, so in Summation treatment, it is important that the fit should not be missed. Georgi stated that an electrocardiograph should be taken before treatment is begun.

THEORY.

THE DIFFICULTIES.

The field of theory behind the use in schizophrenia of the drugs with which we are concerned is obscure and difficult. We cannot attempt to deal with it adequately from the point of view of the expert biologist or biochemist and only venture on it at all out of consideration for the practical worker, whose opportunity to study theoretical writings may be limited, and for whom even a cursory and partial account may be of some value in directing his attention to fuller and more detailed sources of information.

THE PHYSIOLOGICAL CHANGES DURING TREATMENT.

The following summary from various writings is for reference, as has already been said, we make no attempt at criticism or evaluation of the statements made.

(a) *Changes during insulin treatment.*

The account given below is quoted mainly from Beiglböck and Dussik⁴ :—

An hour or more after insulin injection there appear restlessness, nervousness, weakness, uncertainty, feeling of hunger and sometimes nausea, apathy, then copious sweating, tremor, increasing unrest and change in the colour of the skin, which may be reddened "so that one has the impression that the capillaries are widely open." Tachycardia may occur but bradycardia is more frequent; the pulse is tense, the carotids throbbing, the blood-pressure raised and the pulse-pressure almost invariably increased. In prolonged shock the blood-pressure may fall and cyanosis appear; danger is then threatening.²⁰ Various investigations indicate that capillary functions rather tend to be dissociated than altered in a given direction.¹⁴⁵

Gross⁵⁰ has investigated the biochemical changes which occur in whole blood, in serum and in the cells during hypoglycæmia and describes the dissociation of these changes.

The blood-sugar falls, sugar is given up from the liver and taken up by the cells. The heart muscle is affected, as is shown by a flattening of the T-wave in the electrocardiogram, there is lessening of blood-volume which is probably due to fluid loss, while an increase of circulation rate can be demonstrated by the Congo-red method. Blood-oxygen is on this account increased, though there is

also an increased oxygen consumption; there is a slight rise in the red-cell count and in the hæmoglobin content, and a lymphocytosis.

Salivation is usual: Wespi¹⁴⁵ distinguishes between fine sweat and thin saliva as parasympathetic products, and coarse sweat and viscid saliva as sympathetic products. Instead of sweating there may be "dry shock."

The value of gastric analyses during treatment is not easy to assess in any given case unless the acidity has been tested before treatment also. Dussik¹⁹ remarks that the acid values in the stomach are very high. A brief statement by Freudenberg³⁵ of various acidity levels in different types of hypoglycæmia is to be found in the special number of the Schweizer Archiv. It is worth noting that if large quantities of glucose are given into the stomach, the reaction thereafter may remain alkaline.

According to Beiglböck and Dussik⁴, the serum calcium changes little but the potassium falls, giving a change in the calcium-potassium ratio. Wespi¹⁴⁵ states that the changes of this kind are irregular, while Accornero and Bini² describe inter alia a considerable rise in potassium.

Alkalosis, a shift of *pH* to the alkaline side, is one of the best known changes in hypoglycæmia. Beiglböck and Dussik⁴ speak of a change in the distribution of sodium and potassium which is the opposite to that found in anaphylaxis and say "We believe that we have found the point at which insulin shock is to be understood. We can compare it with anaphylactic shock. It is its opposite in almost everything."

Special attention may well be paid to one of the most striking analyses of the changes during hypoglycæmia which was put forward by Georgi.⁴² He describes the fall of the blood-sugar during the first hour after injection, and its rise during the second or third hour. He believes that once a certain level has been reached the appearance of symptoms depends on *the lapse of time after the injection*, and believes this to be most definite during the second hour, at which time there are all sorts of bio-chemical changes, usually in the sense of a reversal of tendencies noted up to that point. Thus a fall of blood-pressure replaces the original rise, a leucocytosis replaces the leucopenia, etc. He believes that the second hour is decisive and that in it there is a "turning point" physiologically. Hitherto the blood-sugar has sunk, while that of the cells has remained high; the high "sugar potential" of the cell in relation to that of the blood predisposes, Georgi believes, to epileptiform attacks. When sugar is given in interruption of hypoglycæmia, it quickly disappears from the blood, being taken up by the cells so that again conditions favour convulsion. Thus he explains the occurrence of "early" and of "late" fits in treatment. But however conditions may be altered by the administration of sugar, at the "turning point" the blood-sugar rises and cell-sugar

falls, normal levels and relationships as between blood-sugar and cell-sugar only gradually being re-gained.

A digression from the direct effect of insulin to a subsidiary effect of treatment is worth while here to consider the possible fate of glucose after it reaches the stomach. The sugar may be passed on and absorbed, or it may be retained in the stomach, the event being partly determined by the amount given. Thus, Samson Wright,¹⁵² in his well-known text-book of physiology says, "when 300 to 400 grms. are ingested, a proportion of subjects develop very slight glycosuria . . . when large quantities of sugar are taken the stomach empties itself very slowly. Water is attracted into the stomach and the glucose is held up there for some hours. It then passes into the small intestine and is absorbed so gradually that the threshold level is not exceeded." This mechanism may help to explain some cases (where the glucose which had been given was not absorbed) of which we have heard in the course of visits to hospitals, and possibly (though without details of sugar dosage this cannot be positively put forward) incidents such as the following in the case described by Molony and Honan⁹⁸ . . . "3.30 p.m. Nasal tube was passed and it was noticed that the glucose given at 1.30 p.m. returned almost in full quantity." Thus in cases which fail to wake after measures of interruption, the administration of large amounts of sugar into the stomach may defeat its own object. As will be seen later, it does not follow that intravenous administration would effectively wake the patient. Samson Wright¹⁵², further describing the effect of giving sugar says "With amounts over 500 grms. the limits of ingestion are reached and nausea and sickness develop."

Freudenberg³³ points out that in patients who fail to wake the blood sugar level may either be low or high. When it is low there are two possibilities, either (a) that there has been a failure to pass on sugar from the stomach and to absorb it from the intestine, or else (b) that it has been absorbed but there has been such a degree of reflex production of insulin by the patient's own pancreas as to lower the blood sugar level again. When the blood sugar is high, as it was in Molony and Honan's case, there are two other possibilities, i.e. either (c) that the cells, though provided with sufficient sugar have failed to take it up, or (d) that the adrenalin secreted as a counter-measure to the injection of insulin has been excessive. The antagonistic action of insulin and adrenalin and the secretion of either or both by the patient have always to be taken into account in considering symptoms.

Day and Niver¹⁴ lay stress on the sugar values in the cerebro-spinal fluid, and say that patients go into shock as soon as the sugar content of the C.S.F falls to a point between 30 and 15 mg.

Another figure which they give is one of proportion, it expresses the ratio between the sugar level in the blood and that in the cerebro-spinal fluid. They give the ratio of blood-sugar to cerebro-spinal

sugar as normally 10 : 6 or 10 : 8, but find that it is completely reversed in the first hour after the injection of insulin in hypoglycæmic shock treatment, remaining so until after interruption.

A different aspect of the matter is discussed by Kerr and Ghantus^{63, 64}, who studied the amounts of glycogen in the brain in various conditions. They found it decreased by experimental insulin overdosage in various animals; and in considering the relationship of brain-sugar to blood sugar they say "the free sugar of brain was constantly *lower* than that of blood, except in extreme insulin hypoglycæmia."

Reference has already been made to the "arterialisation" of venous blood from the brain during hypoglycæmia, i.e. to the finding, by Himmwich⁵³, that blood normally dark, partly de-oxygenated and "venous," not only in source but in appearance, is in hypoglycæmia bright, fully oxygenated or "arterial." Since the oxygen loss from the cerebral blood is dependent on the metabolism of sugar, the failure of this oxygen exchange might indicate a failure by the brain to utilize such sugar as is supplied to it.

Another and very important point is that of cerebro-spinal fluid pressure. Drabkin and Radvin¹⁷ in an interesting paper on the mechanism of convulsion in insulin hypoglycæmia, speak of anhydræmia associated with a rise in C.S.F. pressure. They say that the production of a sudden profound hypoglycæmia is essential for the development of anhydræmia after insulin. Day and Niver¹⁴ give the rise in C.S.F. pressure as anything up to 400 mm. With this aspect of hypoglycæmia is bound up the question of cerebral oedema as well as of "Hirnschwellung"* and the possibility that water and salt exchange is a factor in the effects noted.

Some of the grosser cortical changes noted in certain cases have been mentioned; they are described by Stief¹³² and Tokay, Accornero,¹ Morsier and Bersot,¹⁰¹ and Salm,¹²³ while Nicolaev¹⁰⁴ describes a regression and change in glia which he attributes to a hypoglycæmic change of liver function.

The permeability of the cell-membrane is a matter of obvious importance in relation to cerebral metabolism. Förstmeier,³⁰ working with patients under treatment, was of the opinion that the permeability of the blood C.S.F. barrier at least was not increased by hypoglycæmia. On the other hand Wechsler,¹⁴³ on the basis of animal experiments, finds that the permeability is increased. Nicolaev (with Werner)¹⁰⁵ remarks on the lessened permeability in schizophrenia, and refers to his own work to show that in cases which respond favourably to insulin treatment the permeability is increased, while Georgi,⁴² speaking of the cell-membrane, mentions

* "Hirnschwellung," swelling of the brain due to increase of fluid in the ventricles and in the peri-neural and peri-vesicular channels and in combination with the parenchymal protoplasm, without oedema.

an increase so great "that one may almost speak of an opening of sluices" with much freer interchange between the cell and its surroundings.

The obvious changes in the neurological findings in coma and thereafter, the motor phenomena and the loss and change of reflexes, are known to every insulin worker, and we can only indicate here some recent work of a more detailed kind on this topic. Küppers⁷⁴ has described subjective findings in a doctor and two students who submitted themselves to insulin shock experimentally. Pupil changes have been particularly studied by Wespi.¹⁴⁵ The work of Angyal³ on the cortical areas, which he believes to be successively affected by hypoglycæmia, is of great interest, particularly as he applies it to treatment, for he believes that symptoms which suggest involvement of deeper areas indicate danger. Morsier¹⁰¹ has set out an illuminating parallel between the attitudes and movements of hypoglycæmia and those seen in certain organic disorders as well as in "la grande hystérie" of Charcot, while Palisa¹⁰⁶ has reported in detail on the phenomena of waking.

Schmid¹²⁵ in Switzerland carried out a study of hypoglycæmia in various organs, and found signs of hypophyseal and adrenal activity, and in particular an increase in the amount and size of cells in the pancreatic islets. Incidentally he is to be thanked for two useful terms in "insulin-rabbits" ("Insulinkaninchen") for animals to which toxic doses of insulin had been given, and "Sakel-rabbits" ("Sakelkaninchen") for those treated by doses proportionate to the amounts given to man in treatment.

Rubenovitch¹¹⁶ claimed that the term "shock" should be reserved for a state in which there is "a modification of arterial tension, of temperature, and of nervous tone" in a given direction. It appears, however, that convenience has outstripped logic and that the word is firmly established among insulin workers, however inaccurate its use may be.

(b) *Changes during cardiazol treatment.*

The obvious clinical changes which follow the administration of cardiazol have been described in Part II.

Georgi and Straus⁴³ have investigated the physiological changes in considerable detail; their findings may be summarised as follows:—There is a rise in blood-sugar after the injection but before the fit, followed by a compensatory regularising in the other direction; Occasionally, however, the order of these changes is reversed. After the fit there is always a considerable rise of blood sugar. In animal experiments the administration of glucose prevents the occurrence of convulsions from ordinary doses of cardiazol and renders milder the convulsions which follow if larger doses are given.

If there is a fit, there is a shift to the left in the blood-picture. The potassium and calcium ratio varies irregularly; the pulse-pressure is increased; there may be hippus. The investigators were

struck by the parallelism which they found between the physiological events slowly occurring in the first two hours of insulin therapy and those which ran their gamut in a few seconds after cardiazol was given.

Many of the changes mentioned were also described by von Meduna.⁹² He stated that the leucocyte shift to the left was about twice as great in patients who remitted as in those who did not. The urinary findings he cites as much the same, after a convulsion, as in idiopathic epilepsy, i.e. increased acidity, increase of ammonia and phosphates and decrease of chlorides.

Kennedy⁶² draws attention to the curious fact that the well known wide gaping of the jaws which occurs with the fit appears to be peculiar to the cardiazol convulsion. Stief,¹³² in a detailed paper, refers to the cerebral findings in epilepsy as well as in treatment by insulin and cardiazol and gives his view that cardiazol treatment leads to cerebral effects which are predominantly vascular and probably depend on vaso-constriction. Morsier and his co-workers¹⁰⁰ in a study of animals subjected to high doses of cardiazol were unable to find any cerebral changes except hyperæmia. Von Meduna⁹⁷ himself said that he regarded cardiazol as a vasodilator. The absence of serious electrocardiographic change has been noted earlier,⁹² as has the cyanosis which is so obvious during treatment.

(c) *Changes during prolonged narcosis.*

These are outside the scope of this paper; but it may be said that they were described at the Münsingen Congress in an article by Kulkow, Weiland and Kakusina,⁷² and that treatment by prolonged narcosis was one of the basic subjects of that congress.

THEORIES AS TO THE MECHANISM OF IMPROVEMENT.

Most of the theories which have been put forward are closely related to each other, so much so that some of them may be looked on merely as different ways of stating the same fact or belief, but they are artificially separated here for the sake of clearness in discussion.

We give first a list of theories, then a note upon each, and finally (and with diffidence) a few words as to the most promising views which seem to us to emerge from the available information.

The list of theories.

Improvement has been thought on various occasions to be due to one or more of the following :—

1. The elimination of diseased cells.
2. Changes in the vegetative system.
3. Hypoglycæmia *per se*.
4. Some unknown effect of a convulsion.
5. Avitaminosis produced by high carbohydrate intake.

6. The production of "alkalosis" in patients usually too "acid."
7. Increase in cell-membrane permeability.
8. Alteration in water-salt regulation.
9. Anoxia with consequent redistribution of cerebral blood.
10. Alteration of tissue respiration.
11. Psychological stimuli or help.

The theories annotated.

1. *The elimination of diseased cells.*

It is suggested that diseased cells, being more vulnerable by the drugs under consideration, are eliminated and that cortical activities are restored to normal because they now function by means of normal cells.

This theory, which is not unlike the earlier theory of Sakel on the specific action of insulin in eliminating abnormal cells or paths, is put forward by Stief¹³² when he says, after describing some of the cortical cell destruction, "One may speak of an interesting, subtle, surgical but bloodless, elimination of nerve-cells."

2. *Changes in the vegetative system.*

It is suggested that abnormal activity or sluggishness of the vegetative system in schizophrenia is counteracted by insulin or cardiazol. Pfister¹¹¹ has written at some length on this theme; his conclusions may be summarised by saying that he believes that dementia præcox patients show a failure of regulation of pulse-rate, blood pressure, temperature, skin response to irritants, water-balance and blood-sugar. He describes schizophrenia as a "system disease of the vegetative control mechanism," that mechanism being at first over-excited and then becoming less and less responsive till it is useless. In his view cardiazol enlivens the vegetative system, while insulin acts as a brake on the sympathetic system and should counteract its excitement in acute cases and prevent its ultimate deterioration.

Our knowledge does not yet seem full enough to enable us to say how far the mechanisms suggested in theories 1 and 2 are responsible for the effects of treatment.

3. *Hypoglycæmia per se.*

It was formerly thought by some that the lowering of the blood-sugar level was responsible for the symptoms observed and for the therapeutic effects; it is now known that symptoms may occur when the blood-sugar curve is rising, or even normal, and that what is important is not the blood-sugar but the cell-sugar level.

4. *Some unknown effect of a convulsion.*

It is suggested that the actual convulsion is the therapeutic agent, the mechanism by which it exerts its effects being unknown. Much discussion has centred round the place of the convulsion in

insulin treatment^{31, 40, 94, 108, 122}; convulsion is of course the crux of cardiazol treatment, according to von Meduna⁹², who writes of the antagonism between epilepsy and schizophrenia, while the development and adoption of "summation" treatment shows how favourably the association of hypoglycæmia and convulsions is regarded by many. It appears to be a fair statement of the position, so far as insulin treatment is concerned, to say that the occurrence of generalised convulsions is always serious, demanding careful management and indicating the need for interruption of hypoglycæmia, and that from the time of the publication of Sakel's first papers onwards it has been recognised that cases occurred in whom a failure to respond to treatment without convulsions was followed by rapid and sometimes dramatic improvement after a fit or series of fits. It is difficult to state the value of insulin convulsions at all precisely; there are many cases which do not improve in the least in spite of a long insulin treatment and a large number of fits, but the impression of the therapeutic effect of a convulsion in an obstinate case is striking when it occurs. On this topic Plattner and Frölicher write that in their series of cases the incidence of fits is higher in unresponsive patients than in those who remit as the result of treatment, i.e. fits occurred in 7.7 per cent. of comas of unresponsive cases, but only in 3.2 per cent. of comas of remitting cases. This experience is in some ways contrary to that just cited, but the whole paper should be studied by those who are interested. Finieffs²⁹ in 1938 reached the conclusion that "The occurrence of convulsions during the actual coma period of insulin therapy is likely to enhance the value of the treatment, whether these fits occur spontaneously in coma or are induced by injections of cardiazol."

It is worth while to consider some of the many factors which may cause or predispose to fits, partly because one or other of them may in time prove to be of real importance, and partly because such a consideration shows how close is the link between one therapeutic theory and almost every other. These factors then are:—a latent epileptic tendency in the patient, high C.S.F. pressure, the administration or secretion of adrenalin, a water-logged as opposed to a dehydrated state of the tissues, the high "cell-sugar potential" of Georgi, vaso-constriction, alkalosis, and avitaminosis. As to this last factor, Demole^{15, 16}, quotes Silberschmidt to the effect that "Hypoglycæmic convulsions may perhaps be attributed to the formation of pyruvic acid of methylglyoxal or other intermediary product of sugar metabolism"; he adds that the formation of these products may be prevented by giving Vitamin B.

The theory of the therapeutic efficiency of convulsion has then considerable clinical support. For pathophysiological basis it has the fact that it is closely linked to other phenomena of hypoglycæmia. Beyond that knowledge does not go, and the real mode of action of convulsion is quite unknown.

5. *Avitaminosis produced by high carbohydrate intake.*

It is suggested that avitaminosis (particularly of vitamin B) whether occurring spontaneously or produced by an abnormally high carbohydrate intake, is part of the therapeutic mechanism. The theory is entirely speculative, particularly in view of the fact that cases may do well with Vitamin B administration throughout their treatment. It is quoted here mainly for the sake of completeness. Demole,^{15,16} who has already been mentioned, proceeds from the problem of avitaminosis to touch on several factors which are mentioned below. He says "Too much alimentary carbohydrate accentuates the appearance of B avitaminosis. Tissues from animals with avitaminosis consume less oxygen and less carbohydrate than the normal, while vitamin B₁ causes the disappearance of the products of the imperfect breakdown of carbohydrates."

Vitamin B₂ may have a relationship to the tissue changes during hypoglycæmia because of its own possible kinship to the respiratory enzyme which will be mentioned later, but that question is too obscure for discussion here.

The theoretical interest of the "avitaminosis" explanation of the action of hypoglycæmic shock therapy is the reason for discussing it; there is little scientific evidence to support it as yet.

6. *The production of relative alkalosis in patients usually too "acid."*

It is suggested that the change in pH induced by insulin may be of value directly by altering the biochemical reactions in the direction of normality, or indirectly by making possible the occurrence of cellular phenomena, as yet undefined, which cannot take place in the abnormal metabolic conditions which exist in the schizophrenic. Day and Niver¹⁴ say that insulin is "the best alkalinizing agent available."

Beiglböck and Dussik⁴ remark that in hypoglycæmia there is such an alkalosis as one has hitherto been unable to produce, and call it "a considerable attack on the otherwise so stubbornly maintained balance of H-ion concentration." With this consideration we are back to the clue put into our hands by the well-known work at the Maudsley Hospital in 1928⁴⁹ when the failure of the schizophrenic to return to normally alkaline pH, after the administration of bicarbonate and the consequent changes, was demonstrated. Once more, the complex relationships of possible therapeutic factors are evident, for in considering alkalosis we note that it depresses respiration, predisposes to tetany, and is itself caused inter alia by anoxia, to which reference is made below, while the administration of alkali to render the patient sensitive to the action of insulin is a recognised procedure. Alkalosis occurs to some extent in cardiazol treatment.

As regards this theory we may say that while there is no proof of the efficacy of alkalosis, it is probably one important factor of several in the therapeutic process.

7. *Increase in cell-membrane permeability.*

The findings as to permeability have been given on p. 29. It is suggested that the metabolism and consequently the whole function of the brain-cells (not to particularize further) is improved and enlivened by this improved permeability. The beneficial effect of free exchange between the cell and its environment is so easy to imagine that one forgets how far is the distance between this position which we have reached by an intuitive leap, and that from which we may some day be able to follow in full biochemical detail the processes by which the clear fire of rational thought springs from metabolic health, and the smoke of delusion from abnormality, within or without the cell.

The theory of the value of increased cell-membrane permeability seems to have a strong inherent probability, but is as yet without proof.

8. *Alteration in water and salt regulations.*

It is suggested that abnormality of water-and-salt regulation is present in schizophrenia and is corrected by the treatments under discussion. The theory was put forward at the Münsingen congress by Wilmanns¹⁴⁷; he discussed the possibility of "Hirnschwellung"; he put forward his view to explain the action not only of insulin and cardiazol but also of continuous narcosis. It is due to him to say that he stated that "darkness hovers over" our knowledge of schizophrenia, and that something more convincing may later be found to replace this tentative explanation. Accornero and Bini,² on the same occasion, reported their findings in insulin shock treatment and came to the conclusion that a change in water-salt regulation, "questions of pressure and osmosis," might explain not only many symptoms but many of the physiological events in hypoglycæmia.

This theory cannot yet be regarded as more than an attractive hypothesis.

9. *Anoxia, perhaps with consequent redistribution of cerebral blood.*

It is suggested that the fact that cells are deprived of oxygen, either by lessening the amount supplied in the circulating blood or by some other means, is somehow directly or indirectly therapeutic.

The whole question of anoxia is so bound up with that of tissue respiration that it seems to be hair-splitting to separate them, but again for the sake of clearness of conception we make a distinction where there is not much difference.

The supply of oxygen to the cell depends on many things. It depends inter alia upon the presence of oxygen in sufficient amount in the inspired air, upon an adequate circulation to carry it to the

brain, and upon the activity of the respiratory enzyme in the cell without which oxidation cannot take place.

Before going further with this topic, it will be well to define anoxia. As will be seen when Loevenhart's important work is discussed, one cellular phenomenon (in this case inability to use oxygen), may be regarded in different ways by different workers. Some will say that a cell which cannot *use* oxygen supplied to it is suffering from anoxia; others will take the view that whatever the cell may suffer from in such a condition, it cannot properly be called "anoxia," since there is no lack of oxygen supply in the local blood-stream.

To make clear the sense in which we use the term "Anoxia," we shall quote some paragraphs from Samson Wright's text-book,¹⁵² for much of his discussion of this subject is relevant to theories of the action of insulin and cardiazol as well as to those of older therapeutic methods, upon the brain. We use the word with his meaning.

Anoxia then, according to Wright, may be divided into types, as follows :—

"1. *Anoxic type* where the *tension* of oxygen in the arterial blood is lower than normal, and consequently the hæmoglobin is not saturated with oxygen to the normal extent.

2. *Anæmic type*.

3. *Stagnant type*.

4. *Histotoxic type*: the tissue cells are poisoned, so that they are unable to make effective use of the oxygen supplied to them.

Histotoxic anoxia occurs in poisoning by *cyanide* which interferes with tissue oxidation by paralysing the respiratory enzyme, described by Warburg, and prevents it from oxidising cytochrome. As the combination of respiratory enzyme and cytochrome probably constitutes the essential oxidizing system of cells, it can be readily understood why tissue respiration is arrested. Narcotics also depress oxidation. . . . In the presence of narcotics cytochrome remains oxidized and does not become reduced by the other cell constituents."

The first of the treatments which may be mentioned under the heading of anoxia is that of Loevenhart, Lorenz, and Waters,⁸⁴ which raised so many hopes in 1929. By giving their patients a mixture of oxygen with anything up to 30 or 40 per cent. of carbon dioxide to breathe, they produced results closely resembling those which may follow the modern treatments, but unfortunately the effects did not last longer than "two to twenty-five

minutes." Some quotations from their paper will serve to show how close is the parallel between their observations and those of today.

"A catatonic patient will relax and some spontaneous movements may occur . . . the limbs may become completely flaccid . . . pallor passes off and there is a flushing of the face and hands . . . the skin becomes moist . . . the ocular movements are purposeful . . . patients may sit up suddenly and look about in an apprehensive manner . . . from that time on it is possible to hold a clear and in many instances intelligent conversation. When psychic function is so increased, a marked change in the facial expression is noted. Those patients having a smirk or silly grin lose it, and those exhibiting an apathetic expression change to an animated expression apparently characteristic of the individual. Muscular movements of the extremities are purposeful and adequate. This response may last from two to twenty-five minutes or more in patients that had previously been markedly stuporose and wholly inaccessible. In some cases the patient responded quite like a talkative psychotic person, expressing many bizarre delusions. If no more gaseous mixture is given, the patient gradually returns to his former condition" . . . "in some cases the lapse is remarkably sudden, so that a sentence begun is left unfinished" . . . "occasionally, in certain cases in which high concentrations of carbon dioxide were used, a phase of definite motor stimulation was encountered. This may amount to mere twitching and jerking of the extremities or may consist of powerful contortions, not convulsive in character but more in the nature of strong tonic contractions. In some instances the motor stimulation somewhat resembled cerebral convulsive seizures. In one case of great excitement and excessive motor stimulation, pure oxygen given for from one to two minutes caused this state to pass off entirely, and left the patient showing only the marked psychic stimulation which we were striving to produce."

Such effects as these have often been produced by many means in the past, by physical illness, by the administration of anaesthetics, by protein shock, by the shock of sudden unexpected bereavement or of violent attacks by other patients, and in former times by sudden immersion in water, spinings, beatings and other drastic methods which were then reputable therapeutic procedures. But while such things have undoubtedly produced remissions, these have been so capricious in their occurrence and often so brief in their duration that many attempts have resulted in but few successes. The failure of these methods is the basis of much understandable scepticism about modern methods.

Loevenhart's work now emerges in rather a new light. One may begin to hope that the hounds of research have run their fox to earth in those rocks where, years ago, what seemed like a false scent was abandoned.

One very interesting point is that Loevenhart's investigations developed out of work on respiratory stimulation by sodium cyanide, which produced a transient change in the mental state. Here again is a link with "Histotoxic anoxia," as defined by Wright, though the American investigators looked at it from rather a different angle; they say "It is obvious that oxygen want is not responsible for the reaction, because the reaction can be produced by sodium cyanide, in which oxygen is present in abundance but

the cells cannot utilize this oxygen. Oxygen want, however, is one method of producing reduced oxygen fixation, and thus can bring about the reaction. Carbon dioxide, we believe, interferes with the utilization of oxygen in somewhat the same manner as hydrocyanic acid, but a much larger quantity of it is required to produce the same degree of reduced oxygen fixation." They go on to relate the increased oxygen fixation to depression and reduced oxygen fixation (up to a point) to increased psychic activity, basing their theory on the view that total cell-energy tends to be constant, being made up of recuperative activity on one hand and functional activity on the other. It need not be said that a great deal of work on oxidation and tissue respiration has been done since Loevenhart and his colleagues published their paper.

In cardiazol treatment the arrest of respiration during the fit and the severe cyanosis bring the possibility of cerebral anoxia into the foreground.

In insulin treatment the matter is different; in hypoglycæmia, when the point is reached at which the cells have parted with much of their glucose, they are unable to remove oxygen from the cerebral blood. It may or may not be justifiable to call this a condition of "histotoxic anoxia," but in effect one is sufficiently close to the other at least to deserve mention under a common heading.

An interesting small point may be quoted from a recent note in the British Medical Journal, by Maddox,⁸⁵ on "An unusual manifestation of hypoglycæmia" in a patient, claiming to be "the world's champion diabetic athlete" who developed a very definite aphasia. "He appeared to understand everything that was said to him and in his hearing, and at times could say 'Yes' and 'No'; but usually, as he attempted to put two words together, he would only succeed in reiterating 'xx double x.' About twelve hours after its onset the aphasia began to improve and passed off gradually." Aphasia is of course a well known phenomenon in therapeutic hypoglycæmia, but usually passes off in a few minutes. This patient had had a "slight aphasia turn" twelve months previously, of one hour's duration.

Dr. Maddox makes a comment for which this case is quoted here :

"Apparently the degree of hypoglycæmia was low enough to injure his cortical cells to such an extent that it required nearly twelve hours for them to recover, even though bathed in a plasma containing a sufficiency of glucose. The analogy with certain instances of cerebral anoxæmia . . . for example carbon monoxide poisoning . . . is close."

The view taken by Loevenhart in 1929 as to the effect of oxygen reduction on the cells has been quoted. Anoxia may be seen from another standpoint, however. It is possible that anoxia in one part of the brain may result in, or at least, be associated with improved oxygen supply to some other part, or that a general anoxia may be followed by a reaction in the form of a salutary increase of oxygen

supply or of oxygen intake. Professor Golla, in a sentence, quoted with his permission from a discussion on the psychopathology of schizophrenia, said "I have a kind of suspicion that these disorders are conditioned by an anoxæmia of the cortex dependent on disturbance of some lower centre," an interesting opinion in the present context.

The theme is one which might be greatly expanded; enough has been said however to show the importance of anoxia in its direct or indirect effects, so far as present knowledge and opinion will carry us.

10. *Alteration of tissue respiration.*

It is suggested that improved tissue respiration is responsible for the improvement in mental function.

Only expert biochemical work can decide the relationships and the validity of this and the preceding theory, but, for reference, some investigations may be mentioned here which bear more directly upon intimate cell-metabolism than upon the clinical manifestation of anoxia already discussed.

Physiological textbooks, for instance, that of Samson Wright¹⁵² quoted above, describe the mechanism of tissue oxidation, a mechanism which is much too complex for us to attempt to summarize.

Jowett and Quastel,^{60, 61} in a series of studies on narcotics and tissue respiration, expressed the view that narcosis is due to a depression of oxidation in the nervous system of glucose and other substances and described the effect of varying the substrate as well as the effects of the concentration of the drug, of time, and temperature, and of potassium and calcium values.

Himmwich, in discussion⁵³, remarked that :

"Apparently the brain, under hypoglycæmia, ceases to maintain its normal oxygen consumption" . . . the evidence to date seems to indicate that the brain can oxidize only one foodstuff, carbohydrate, and that when carbohydrate is removed as the result of the low blood-sugar, the brain is temporarily deprived of its energy requirements . . . "just where this observation fits into the amelioration of the condition of schizophrenia is still to be solved."

Demole^{15, 16}, whose work has already been quoted, ends one of his papers with the remark "The therapeutic action of the pancreatic hormone in dementia præcox appears to be attributable to its influence on oxybiotic intracellular processes."

The rôle of other endocrines in this process is mentioned by many. The substances concerned are,¹⁶ inter alia, "thyroxin, adrenalin, pituitrin, the anterior pituitary thyrotropic hormone and the products of protein hæmolysis."

Most workers who have studied the physiology of cardiazol convulsions and of hypoglycæmia touch upon oxidation to some extent, but Freudenberg³⁴ has gone into the point specifically in

his work on the use of Vitamin B₁ and B₂ in insulin shock treatment.

The formation and destruction of intermediary substances in tissue respiration has been mentioned (p. 33). Some workers, notably Küppers⁷⁵, lay particular stress on this factor in formulating theories as to the mechanism of the treatments.

The theory that improved tissue respiration is the most important therapeutic factor is attractive, but is so closely bound up with other theories that, until we have fuller biochemical knowledge, the question as to the degree of emphasis to be laid on it is more academic than practical.

11. *Psychological stimulus or help.*

It is suggested that the real basis of hypoglycæmic shock treatment and of cardiazol convulsion treatment is psychological.

This theory appears in three forms, first, that the nervous changes per se have a profound psychological effect; second, that the determination, effort, and optimism of the doctors and nurses are the major influence in treatment; and, third, that deliberate psychotherapy is necessary to achieve good results.

As to the nervous changes per se, some hold that the "life and death struggle" of the drastic treatments or the sense of dread induced particularly by cardiazol, are effective, a theory which is a revival of the old "fear treatment" which hardly seems justified in the light of the failure of the old methods to produce good results. Others, particularly working on Freudian lines, see in the treatments a means of release of unconscious conflict. In so far as the patient appears to be unconscious at the time when his nervous system is most threatened and often has amnesia for the events of the treatment, it is difficult to square this theory with analytical practice in patients not under the influence of drugs, where consciousness of the material evoked is essential. That there is, however, a very considerable disturbance is often to be deduced from the behaviour of patients. Steinfeld, in discussion in America, quoted a patient who said "I don't want to become any better. I should like to remain in this stage where I feel just like a little child. Please don't give me any more of those treatments. It disturbs my whole life." The Freudian aspect of treatment was discussed by Jelliffe⁴⁸ at a meeting in 1937.

There appears to be little doubt that the outlook and personality of the staff, apart from any deliberate psychotherapy, have a great influence on the outcome of treatment. As Briner⁹ remarks "Chemical means alone cannot cure schizophrenia." Workers of experience insist on the need for thorough and determined treatment, and on the value of the will and effort put by the

physician into treatment, whether by insulin, cardiazol or prolonged narcosis. As to this Roemer¹⁵ makes the remark "Doctors who in decades of professional work have become oversceptical and consequently tend to therapeutic nihilism are as unsuited for this work as uncritical enthusiasts who have not the necessary knowledge and the clinical psychiatric experience at their disposal."

On the need for psychotherapeutic help of one kind or another during treatment there is such general agreement and emphasis, that to deal fully with it one would need to refer to almost every paper concerning with treatment, whether written by Sakel, von Meduna, Müller and other well known workers, or by those whose experience is comparatively limited; from most continental countries, from America, and from Australia come similar expressions of opinion. Indeed, to expect a patient to go through the experience of treatment or even, if that were possible, to allow him to come to himself without any knowledge of the treatment, in the environment of a mental hospital, with the dislocation of his life behind him and the contact with psychotics around him, and to expect him to deal unaided and unadvised with himself in that situation would be as unreasonable as to expect someone on whom a major operation has been successfully performed to get up and fend for himself without any nursing or care in convalescence.

One or two believe that the help should be on analytical lines, particularly during the actual period of hypoglycæmia, but most are of opinion that encouragement and reassurance are more valuable and that deep probing is actually harmful. This last view has long been held by Sakel. The help given by von Meduna takes the form of interviews, arranged whenever possible between the patient and himself after every five treatments, so that he may reassure and advise the convalescent. Speaking personally to us, he emphasized the value of these interviews and mentioned the comparative failure of cardiazol where no care was taken to protect the patient from the sight and sound of other patients in convulsion, and where no deliberate psychological help was afforded.

The drugs provide a stimulus, and create an opportunity, but every resource of sound psychotherapy, and régime and occupation should be mobilized to prevent a lapse into the psychosis and to keep the patient hopefully on the forward path. One of the most impressive arguments for this side of the work was provided by the nurses, male and female, whom we saw in English hospitals and whom we asked to tell us how treatment helped their patients. "It wakes the patient up and lets you get at him." "It brings her to you, as it were, and you can talk to her and interest her and do something for her." "After they have had treatment you can get near them," are remarks which reinforce the emphasis placed by the medical staff on the need for active help. In discussing insulin and cardiazol, Ellery²³ writes "I am of

the opinion that neither agent is entirely responsible for the remission achieved, but that each serves to bring the patient, by means of shock as profound as that of impending death, into touch with those around him to the extent that he can, through individual and personal attachment to his physician, be brought into contact with reality."

A word may be said on the outlook of the patient after treatment. Morse⁹⁹ quotes Glueck who, he says, divides recovered patients into two groups, one with a distinct emphasis on the virtues of repression and an attitude that the past was best buried, and the other with a definite preference for the so-called working-through and re-integration." Talk with patients after treatment confirms that view; one meets many who do not recollect the events of their illness and do not want to recollect them, and others who are interested to speak of their experiences. There is a proportion, too, who feel that they have gained through the illness and its treatment, and who thereafter feel steadier and more able to understand their environment and to deal with it than at any previous time. Some of this, after giving cardiazol, has to be discounted as symptomatic of the euphoria induced by the drug, but there is no doubt that in many cases it is very real, and is confirmed by the relatives and friends; it occurs, of course, in some patients who recover without any of the modern drug treatments.

TENTATIVE VIEWS WHICH RESULT FROM A CONSIDERATION OF MANY THEORIES.

As has been said by von Meduna,⁹⁶ treatment is certainly twofold, it has a biochemical aspect and a psychological aspect; though said of cardiazol it is equally true of insulin therapy.

A consideration of the biochemical theories which have been discussed leads us to the expected conclusion that no one event will probably prove to be alone in therapeutic importance. A restored pH balance or a freer metabolic lability, better vegetative system function, improved permeability, with more normal water and salt regulation and better tissue respiration are all items which seem to hang together inevitably, and in the production of these conditions convulsion or anoxia with possible increase of oxygen elsewhere in the brain or in the originally anoxic portion of the brain at a later period are factors which appear to be very important.

Along with all this the need for psychological help and encouragement is recognised everywhere, a fact which, in this new sphere of insulin and cardiazol therapy, affords yet again evidence for the interdependence of body and mind and gives reason for the adoption of a broad psychiatric outlook, which appreciates both chemical and psychological methods of attack upon psychosis.

PART V.

RESULTS.

DIAGNOSIS AND SELECTION OF CASES.

The methods of diagnosis and choice of cases for treatment must be considered before there can be any real assessment of results or any useful comparison of results as between one country and another. Herein lies, as in the past, a grave difficulty, which was discussed in an earlier report.¹⁴⁸ We are still without any means of precise diagnosis in many cases, though it seems possible that in time biological standards may be set up to define the borders within which certain groups of patients (perhaps in accordance with our present psychological and behaviour classifications), may be included for purposes of discussion and record. The Lehman Facius test,^{80, 81} if it proves on wider trial to be sufficiently applicable, may give one of these standards.

Though the difficulty of diagnosis is known to us all, it may be useful to quote some of the remarks made at the Münsingen Congress under this head to show how it is appreciated on the Continent.

Müller,¹⁰² in his introductory lecture, said that in spite of the attention given to this subject by such a man as Bleuler, we were still uncertain as to what belonged essentially to the basic schizophrenic process, and what to superstructure; there were the greatest differences in the concept of specific schizophrenia in different schools and countries, to recall, for instance, only "the work of Kleist and the divergence of the French and Dutch schools from our Swiss concept of schizophrenia."

On this, Rubenovitch¹¹⁶ of Paris was very definite in discussion. He said:

"Schizophrenia, for us at Saint Anne's, is not a disease but a terminal syndrome, an ending. In other words, the Swiss school classes as schizophrenia mental states which we consider spontaneously curable, and which are to us cases of confusion, attacks of depression or of excitement with dissociation, or outbursts of delirium. Our point of view obliges us to refuse to accept without previous examination, the assessment of remissions obtained mainly in cases which have not lasted longer than six months. That takes away nothing from our confidence in Sakel's method."

In Vienna, Frankfurt and Budapest we were impressed by the great emphasis on the need for prompt treatment, beside which the question of diagnosis was relatively unimportant. Dussik verbally expressed an opinion, much the same as that which he has written¹⁹ to the effect that . . . insulin treatment should be begun as soon as the diagnosis is established, if it were possible even on the first day in hospital; "in future, cases would probably be treated without waiting for the end of every diagnostic doubt, because we can cut down to weeks confused cases which would probably otherwise last for months."

Kleist spoke to us of the need to treat restless acute confused cases at once, to cut short the psychosis in order to save life. Von Meduna⁹⁷ regards his treatment as of proven value for schizophrenics in their earlier stages, though he hopes that it may be found useful in other types of disorder as time goes on; he describes his 'diagnosis of schizophrenia as according to the teaching of Bleuler, but he does not lay much stress on this, for he believes that prompt treatment may save life and reason in a patient with acute confusion and excitement, where physical health is beginning to be undermined. He said to us . . . "The important thing is to get the cases treated, without waiting to establish a certain diagnosis."

Müller¹⁰³ writes to much the same effect with reference to insulin treatment.

Marzynski,⁸⁷ writing on insulin treatment in Poland, says that the treatment is used for undoubted schizophrenics and for those whose symptoms have a schizophrenic colouring, and that of course diagnosis cannot be regarded as incontrovertible in quite recent cases whose illness has only lasted a few days or weeks.

Brousseau¹⁰ also discussed diagnosis in early cases.

The result of it all is that the clinician, in deciding on the value of the treatments, is forced back upon observation of cases he has himself previously known. Here evidence is strong; there can be few who, having seen insulin or cardiazol adequately used, have not come across cases in which the diagnosis was quite undoubted, and would be undoubted by clinicians of any school, and in which the outlook appeared hopeless until treatment produced one of these remarkable improvements or apparently complete recoveries which are leading so many to persevere in this therapeutic campaign.

REMISSIONS APART FROM THE USE OF INSULIN AND CARDIAZOL.

In former times diagnosis was made on the Kraepelin conception of dementia præcox; there was less admission of comparatively mild cases to hospital, and the regime and outlook was in many ways different from that which is usual now. Nevertheless, most of our estimations of "spontaneous" remissions, and of remissions under treatment without the drugs with which we are concerned, have hitherto been drawn from those days.

It is interesting to consider some modern views on such remissions,⁸² and in particular those based on investigations done with the definite aim of finding standards of comparison for the remissions claimed by insulin and cardiazol workers.

Whitehead¹⁴⁶ has written "A comparative study of present results and those obtained from hypoglycæmic treatment." He says that by present methods (by which he means those other than insulin or cardiazol therapies) cases with a duration of less than

6 months show 50 per cent. improvement and 22 per cent. recovery. Cases with a duration of from 6 to 18 months show 38 per cent. improvement and no recoveries; cases with a duration of over 18 months showed 25 per cent. improvement and no recoveries. He describes these results as "parallel to but only half as good as" the results reported for hypoglycæmic treatment as far as percentage improvement is concerned, and says the recovery rate reported from hypoglycæmia is far ahead of that from other methods, but that it is exceptionally difficult to reach accurate conclusions as to recovery.

A careful paper was written by Fromenty,³⁷ on 271 cases (from which were eliminated cases not observed in the hospital service, and others with delirium, puerperal onset, or chronic hallucinatory psychosis). This work, entitled "*Les rémissions dans la schizophrénie; statistiques sur leur fréquence et leur durée avant l'insulinothérapie,*" contains tables showing details; the main conclusion is that 15 per cent. of cases show "complete and permanent remissions" after a variable number of schizophrenic attacks. The criteria of diagnosis are very much more rigid than those applied to the selection of cases for insulin and cardiazol treatment; we do not know what percentage of cases would remit under these treatments, if the group treated corresponded with that of Fromenty.

Another work on similar lines, but with a smaller series, is that of Faurbye.²⁷

He made a study of spontaneous and institutional remissions in a mental hospital in Denmark, on patients with simple or catatonic dementia præcox, whose illness, though comparatively recent, had brought them to hospital at least a year previously. Of 72 cases, he had 40 remissions, with 30 discharges. He says his remissions, 42 per cent., were under-estimated, as some might remit who had not yet done so. The catatonic group did best. He commends his results as a corrective to over-optimism about special methods. He quotes Lange, who has 77 remissions in 100 cases.

Ederle²² has made a comparison in a series of cases, treated and untreated. He notes that 70 per cent. of the treated cases, however, were recent. Insulin was used.

He gives the following figures :—

	Remitted.	Improved.	No change.
Treated (69 cases)	... 38 per cent.	32 per cent.	30 per cent.
Untreated (147 cases)	... 3 per cent.	26 per cent.	71 per cent.

Interesting as all these investigations are, they are not yet enough to give us a solid basis for comparing remissions in cases treated by older methods with those treated by the new. Whitehead with 92 cases and Faurbye with 72, are working with small

numbers. The group chosen by Fromenty is not comparable with the groups chosen for insulin or cardiazol treatment by most workers, and Ederle's treated and untreated cases are not strictly comparable, because the first group contained a higher proportion of early cases.

The following estimates of remission under older methods were also put forward during 1937:—

Pullar Strecker¹³⁶—"23.6 per cent. could be looked on as spontaneous remissions" (of 40 per cent. total remissions under treatment, in 500 Swiss cases).

Sakel¹²⁰—"The figures for spontaneous remissions according to different authors range from about 5 to 25 per cent."

Mason Smith¹²⁸—"Spontaneous recoveries are less than 10 per cent."

Müller¹⁰², quoting others—"Spontaneous remissions in recent cases are not over 30 per cent."

Maier⁸⁶—"We ought not to forget the 30 to 40 per cent. of spontaneous remissions."

Steck¹³⁰—"At Cery, cures or very great improvements are now obtained in some 43 per cent. of cases of schizophrenia."

Klaesi⁶⁶ (Bern): "60 social remissions, or very great improvements, in 100 cases, without any insulin, are frequent."

Briner⁹, at the same Congress, Münsingen, and from the same clinic, gives this figure also. He writes, "Of cases of schizophrenia admitted to the Bern clinic from 1933 to 1935 with a duration of illness of less than a year, about 60 per cent. could be discharged as social remissions or greatly improved; among them was a large series of results of continuous narcosis." It is very interesting to find, as will be seen later, that his results with cardiazol are much the same.

It will be seen that the range of figures quoted by various authors as to spontaneous or other remission without insulin or cardiazol is from 5 to 60 per cent.

RESULTS AND THEIR CLASSIFICATION.

Writers differ considerably in their way of stating these. At the top of the scale in almost every form of record is "Complete remission," about which there is no serious argument, though of course there are sceptics who are unwilling to apply such a term to any case, on the ground that there is no such thing as recovery, in an exact sense. Most clinicians are content, however, to regard a patient as having had a complete remission when he himself and his physician can find no sign of mental disorder in him, and when he is fit for his work.

The next step, or steps, bring a host of terms: "social remission," "incomplete remission," "partial remission," "greatly improved," "substantially improved," "improved," "improved, fit for discharge," "improved, not fit for discharge" and "fit for employment." It is in attempting to compare results expressed in these varying terms that the chief difficulty lies, more especially in records in which the phrase "complete remission" is omitted altogether and one of the others substituted.

Next comes "unimproved," "unchanged," or "uninfluenced," and if those words could be taken at their face value there would not be much difficulty of comparison here. Unfortunately, however it seems necessary to follow the practice of those who want to pitch the assessment of favourable results low rather than unfairly high, and who therefore include under one of these headings cases which have undergone improvement not great enough to warrant their discharge from hospital (on the reasonable basis that an improvement, which is not enough to bring the patient up to the discharge threshold, cannot fairly be recorded in any of the real "improved" groups.) The patients to which particular reference is made here are a considerable source of satisfaction to their doctors, nurses, and relatives, and often their own interest in life appears to be substantially increased; they are those who before treatment were mute, totally indifferent, hopeless and needing every care and attention, including sometimes tube-feeding, and who after treatment become responsive, orderly, able to care for their own bodily needs, and employable in hospital, though still quite insane and unfit for discharge. Classed by some "improved, not fit for discharge," they are grouped by von Meduna and others in the "unimproved" category, and called, for purposes of discussion among doctors "Institution remissions."

The following scheme is adapted from the translation given by James, Freudenberg, and Cannon⁵⁸ of the classification used by Müller. Its usefulness as a standard scheme used by many Continental workers, would not be spoiled by the modifications (shown in brackets) introduced to meet the needs of those who find the original inadequate, for if the main headings remain intact the main results can be compared. Subheadings enable the observations to be recorded more precisely. The addition of the fifth heading, shown for the rare occasions on which it would be required, makes no essential difference to the usefulness of the scheme as a whole.

1. *Complete remission*.—This category represents complete disappearance of schizophrenic symptoms, with normal affective relationship, full insight, and ability to return to the normal sphere of work.

2. *Incomplete remission*.—This category includes patients who are able to work but with persistence of any one of the psychic symptoms described under 1.

3. *Partial remission*.—Patients in this category are able to resume work; symptoms remain without interfering with their daily life.

4. *Unimproved and requiring hospital care*.

(a) Institution amelioration.)

(b) Unchanged.)

(c) Worse.)

(5. *Died.*)

Whatever the position may be in future as to classification it will be seen that it is now very complicated. The difficulty of doing justice to published results in any brief account is increased by the fact that many workers have studied a short series of cases in great detail, others have studied large series taken broadly, and results have been analysed according to the duration of illness expressed in various ways, according to the various clinical types of disorder, and according to the extent of treatment expressed in months, weeks or days, or reckoned by the number of injections, of comas, or of fits.

With so much material and so much divergence of outlook we have not found it practicable to set out all the results which have come before us in a table or diagram (which could only be comprehensive at the cost of being incomprehensible), nor does it seem desirable to record in wearisome detail even the main findings of so many workers.

We shall content ourselves therefore with putting forward :—

1. The outlines of results from a few large series of published cases.
2. Outlines of results from England.
3. The percentage of relapses, according to various authors.
4. The results of treatment by the two drugs in various clinical types of case.

1. OUTLINE OF RESULTS FROM A FEW SERIES OF PUBLISHED CASES.

Insulin results.

Müller¹⁰², 495 cases.

Duration.		Percentage of full or social remissions.	Improved.	No change
Under 6 mo. ...	...	59·1	82·9	17·1
Up to 1 yr. ...	...	57·2	78·4	21·6
1 to 2 yrs. ...	...	27·3	61·4	38·6
Over 2 yrs. ...	...	11·3	43·5	56·5
		40·4	66·7	33·3

“ In general the insulin remission is qualitatively superior to the spontaneous remission.”

*Day and Niver*¹⁴.—58 completed cases, 25 full remissions, 12 back to work, 14 moderate improvement, 7 improved.

*Roemer*¹¹⁵.—100 cases (25 male and 72 female); 32 no change; 50 improved (of whom 17 not fit for discharge; 21 fit for discharge, 12 fit for work); 18 full remissions.

*Benó*⁵.

Duration of illness.	Social remission.	Im-proved.	Dis-charged.	Relapsed.	Died.
1 to 6 mo. ...	77·27	18·18	90·90	4·54	—
6 to 18 mo.	9·09	45·45	36·36	9·09	2·05
Over 18 mo.	14·28	42·85	35·07	21·42	—

*Frostig*³⁹.—23 new cases, of whom were :—

20 complete remissions, 1 incomplete remission, 1 negative,
1 died. Complete remissions in this group were 86·9 per cent.

30 old cases, of whom were :—

7 complete cures, 3 incomplete cures, 5 partly improved, 15 not improved.
Complete remissions in this group were 23·3%. The percentage of complete and incomplete cures—i.e. all cases able to live in social life, is about 60%.

*Pollak*¹¹², reporting on patients treated by physicians in America under Sakel, records :—

275 patients. Recovered 24·4 per cent. Much improved 17·8 per cent. Improved 7·6. "Hypoglycæmia appears to cause an improvement in 40 per cent. to 70 per cent. of cases. It is not a home or office treatment."

Enke gives the following table which embodies some well-known reports :—

" Author.	Full remissions.	Improved.	No change.	Remarks.
Dussik and Sakel. } 70 per cent. to 75 per cent.		88 per cent.	—	Recent cases.
Dussik and Sakel. } 19·6 per cent. to 26·4 per cent.		—	—	Old cases.
Von Pap Ederle	38·9 per cent. 33·3 per cent.	33·3 per cent.	33·3 per cent.	
Küppers Friedlander	54 per cent. 3/14,	11/14		

Hutter and Langfeld are against treatment."

Langfeld's series of cases was small^{77 78}.

*Marzynski*⁸⁷ has published tables embodying information about a series of individual patients, recording as to each sex, age, duration of illness, duration of treatment in days, results immediately after treatment, on day of discharge, and at latest report, as well as the stage at which improvement began. This very interesting and informative work is too detailed to quote.

We realise that these figures are confusing. We have quoted them because we thought it desirable to give readers some actual

examples of the results put forward by experienced workers, results from which they may, incidentally, appreciate the obstacles which have prevented us from reducing these figures to any kind of simple statement.

Cardiazol results.

*von Meduna.*⁹²

Published results.—In cases under 6 months there is an 80 per cent. to 90 per cent. probability of remission. In cases older than one year, the probability sinks rapidly until, in cases over 4 years, remission can no longer be secured.

*Verbally (1937)*⁹⁷.

All cases, remissions ... 45 per cent.
Subacute cases (half to one year) ... 50 per cent.
Recent cases (up to half year) ... 75 per cent.

Dr. von Meduna has recently (1938) with great courtesy sent for our use a copy of a table of results contributed by the doctors of 29 American hospitals.

The figures (total) are :—

Total cases.	Acute Cases.				Subacute Cases.				Chronic Cases.				Complications.		
	Remitted.	Improved.	Unimproved.	Total.	Remitted.	Improved.	Unimproved.	Total.	Remitted.	Improved.	Unimproved.	Total.	Limb Fractures.	Mandible Dislocations.	Infections.
1244	120	39	24	183	69	38	55	162	89	38	1	128	27	27†† Numerous.	28

Full remissions in acute and subacute cases ... 59·7 per cent.

Full remissions in chronic cases ... 10 per cent.

Improved and remissions total in all cases ... 59 per cent.

Angyal and Gyarfás (quoted by Kennedy)⁶² had 44 per cent. success; resistive cases were given insulin and an additional 22 per cent. remitted, making 66 per cent. in all. "The two methods are therefore mutually adjuvant in the treatment of schizophrenia as a whole."

Scheuhammer and Wissgott,¹²⁴ treating 30 cases, had 13 complete or almost complete remissions. They say "old cases are hopeless." They had 69 per cent. remissions, which they say is "considerably over the figure of spontaneous remissions."

*Briner*⁹, already quotes in relation to remissions following treatment without insulin or cardiazol, obtained 59 per cent. of

cases discharged improved or in social remission, in a series of under one year's duration of illness.

His paper contains much interesting clinical observation; in relation to the general topic of remissions as we are now considering them, his final paragraph is particularly striking. He writes:

"In spite of all scepticism and reserve it may be said that convulsion treatment according to von Meduna is a very important advance. Whoever has himself worked at the bedside and seen how patients, who were given up as hopeless and alternated back and forth between the continuous bath and the observation dormitory, have been apparently cured, and become people enjoying life and fit for work, will not doubt any more about the value of the treatment." There could not be a better example than this of the way in which clinical experience outweighs statistics in the minds of those actually dealing with patients.

Insulin and Cardiazol results compared.

One of the most valuable papers on this subject was given by Küppers⁷⁵; we quote from a version of it kindly lent to us by von Meduna.

The paper is based on 128 replies to a questionnaire sent to mental hospitals in Germany. Of these 50 per cent. used cardiazol and insulin, 20 per cent. used cardiazol alone, and 30 per cent. used only insulin. The cardiazol treatment was preponderantly used in old cases, insulin in recent cases. Full remissions reached 53 per cent. with cardiazol and 30 per cent. with insulin; the differences, in his opinion, are not to be taken too seriously because he thinks that the statistics on cardiazol are not so stringent as those on insulin. In illness of over two years' duration cardiazol gave full remission in 2 per cent. and insulin in 7 per cent. Taking spontaneous remissions into account, in the speaker's opinion, the percentage of remissions actually to be ascribed to the treatment is 20 to 30. In comparison with results achieved before the introduction of the new method, the advance lies less in a raising of total percentage of cures (40 to 60 after the new methods, as opposed to 30 to 50 after the older ones) but more in the fact that whereas formerly discharge followed in about 8 months, now it came as soon as three or four months. This represented a great saving in maintenance.

Cook,¹³ on the basis of various reports, gives insulin remissions as 39 to 70 per cent. and cardiazol remissions 44 to 91 per cent.

Kraus⁶⁸ stated that he had as yet seen less striking results from cardiazol than from insulin.

Pullar Strecker¹³⁷ has written an interesting paper in which he compares insulin and cardiazol treatments clinically and statistically.

From his table of results, based on the figures of Müller, Meduna, Briner, Angyal and Gyarfás we quote the totals only :—

	Number of Cases.	Complete and Incomplete Remission.	Complete, Incomplete and Partial Remission.	Unimproved.
Insulin - -	495	200 (40·4)	330 (66·7)	165 (33·3)
Cardiazol -	265	99 (37·4)	156 (58·9)	109 (40·1)

We have been struck both here and abroad by the fact that those who are successful with either treatment tend to achieve comparatively poor results with the other, until they have had time to develop familiarity with and confidence in the management of both. Many are familiar with insulin because it was first in the field; others have begun with cardiazol because of its comparative simplicity of technique, and few clinicians are as yet in a position to give us impartial views on both treatments as seen in the same hospital by the same observer.

Insulin and cardiazol combined.

Good results are reported by the various methods which have been described, but they are as yet too few for statistical consideration.

Patients made worse by treatment.

This appears to occur in so few cases that as a clinical risk it is negligible. After insulin, "Some remissions, like some spontaneous remissions, seem more stupidly euphoric than before" (Humbert and Friedmann)⁵⁷. Cardiazol which fails to produce fits "leads to at least a temporary worsening in the clinical picture" (Georgi)⁴². "In hopeless cases, treatment with cardiazol or insulin may accelerate the progress of the illness" (Küppers)⁷⁵. "In a few negative cases, we thought that treatment speeded up the course of the illness" (Kronfeld and Sternberg)⁶⁹.

2. OUTLINE OF RESULTS IN ENGLAND (*Cardiazol and Insulin*).

The following, the most comprehensive survey of results in this country, is quoted from "A Year's Experience of Insulin Therapy in Schizophrenia" by James, Freudenberg and Cannon, given before the Psychiatric Section of the Royal Society of Medicine.⁵⁹ They write :—

"By the kindness and courtesy of members of the British Psychiatric Insulin Society we are able to present a summary of

a further 94 cases, which added to our own makes a grand total of 118, out of which number, one patient died. The figures have been given to us by Dr. Finiefs, of the Three Counties Hospital; Dr. Hunter Gillies of the West Ham Hospital; Dr. Hamilton of the Bethlem Royal Hospital; Dr. Larkin of the West Ham Hospital; Dr. Russell of St. Bernard's Hospital; Drs. Siegheim and Grace Watson, whose work has been done at Millbrook House.

To these generous colleagues and to their Superintendents we would tender our very grateful thanks. By their kindness we are enabled to give this Section a table of results which would have taken any one of us alone some years to collect. Cardiazol combined with insulin has been used by most of our colleagues.

<i>Duration of Symptoms.</i>	<i>No. of Cases.</i>	<i>Complete and Social Remissions.</i>		<i>Un- improved.</i>
—	—	<i>Cases.</i>	<i>Per cent.</i>	—
Cases under 6 months ...	22	19	—	3
Cases from 6-12 months	18	15	—	3
Cases from 12-18 months	9	5	—	4
Cases over 18 months ...	69	22	—	47
	118	61	51.7	57

Average duration of treatment = 64.6 days.

In the table appended we have not adhered to the Müller categories, but summarised results in one column as Complete and Social Remissions, thus grouping together Müller's Complete, Incomplete and Partial Remissions. Further, we do not think that the small numbers in each group of cases justify the use of percentages. We have therefore shown the total percentage only of all groups treated, from those of less than 6 months' duration up to those of long standing, even up to 12 years. The joint percentage of Complete and Social Remissions works out at 51.7 per cent. which may be compared with a table quoted by Müller (1937) and compiled from 381 Swiss cases treated for a sufficient period. His figure is 52.5 per cent. It is worth noting that in this table of our united cases, in those groups in which the psychosis had lasted up to 18 months, a total of 49, only 10 remained unimproved, or, put another way, 39 out of 49 recent cases are at home and working.

We submit that if generous allowance be made for differences in diagnosis and estimation of results, these figures are still ahead of spontaneous remissions, and other methods of treatment. It remains to be seen how durable these remissions will prove."

It is interesting to see that the average duration of treatment in these cases was over 64 days.

Cardiazol.

In the introduction to this report we have said that we thought it too early to give figures from some of the hospitals visited to see Cardiazol treatment. As an example, however, of the kind of results obtained by some of those who are carrying out treatment we may quote, with the permission of the Medical Superintendent, the experience described to one of us at a statutory visit to Newport Mental Hospital, Monmouth, where five patients had then been treated. The first failed to improve. In the second, treatment had to be abandoned owing to difficulty in finding suitable veins. A third who had been dull, mute, and indifferent became talkative and destructive but showed no essential improvement. The remaining two were discharged recovered; one of them had been in the hospital for three years and for a considerable time had been described in some such words as "demented and lost to his surroundings." His discharge followed after a course of 8 injections. A recent letter from his wife contains the words:—"he is keeping very well and very happy to be able to enjoy his work again after so long."

RELAPSES.

3. PERCENTAGE OF RELAPSES, ACCORDING TO VARIOUS AUTHORS.

Insulin.

Author.	Duration of illness.	Result before relapse.	Per cent. relapsed.	Note.
Frostig ³⁹		Complete remission -	14·8	
Müller ¹⁰²	Up to 6 mo.	Full or social remission -	6·8	} On 495 cases.
"	"	Improvements - -	—	
"	6 mo. to 12 mo.	Full or social remission and improvements.	8·3	
"	Over 1 yr. -	" "	13·1	
Beno ⁵	Up to 6 mo.	—	4·54	
	6 to 18 mo.		9·09	
	Over 18 mo.		21·42	

Dussik²⁰ remarks "There are of course relapses but these are few."

Cardiazol.

The following, from Dr. von Meduna,⁹⁷ is by courtesy of Dr. J. H. Pameijer of Holland, by whom the information was given to us.

"Out of his 230 discharged cases he had 14-18 cases of relapse" (he had not the exact figure at hand). "They were all re-admitted and treated again by cardiazol," the result was that all but 5 of

these relapsed cases recovered. The point of time at which the relapses occurred was not constant nor did they depend on the completeness of the remission or on the duration of illness before the first cardiazol treatment. For this sort of conclusion the number of relapse cases was too small."

Taking both together.

Küppers,⁷⁵ summarising answers from 158 hospitals and not distinguishing between insulin and cardiazol says:

"Relapses, about 4 per cent., are not of much importance."

TYPE OF ILLNESS.

4. TYPE OF ILLNESS AND RESPONSE TO TREATMENT.

The following summaries of results by various authors may be of interest:—

Schizophrenia.

Authors.

Pullar Strecker¹³⁶ - -
Palisa and Sakel¹⁰⁷ - -
Müller¹⁰² - -

Angyal and Gyarfás⁶² -
Humbert and Friedmann⁵⁷ -
Kronfeld and Sternberg⁶⁹ -
Briner⁹ - - -

Paranoid cases.

Findings.

React best to insulin.
Show a step-like progress.
Give a specially good response particularly if the illness is not over one year's duration; after that their response sinks rapidly.
They should be treated by insulin.
They react best of any type, to insulin.
They do wonderfully well, or not at all.
They react badly to cardiazol if they are old-standing cases; if they are of hypochondriacal colourings with bodily delusions, they do excellently.

Catatonic Excitement.

Pullar Strecker¹³⁶ - -
Palisa and Sakel¹⁰⁷ - -
Müller¹⁰² - -

To insulin they react nearly as well as paranoids; if the duration is over 6 months the catatonics do best and the paranoids next. They do not do well with cardiazol.
They show an irregular improvement with insulin.
The results with insulin are good; these cases do not fall in response after one year so rapidly as the paranoids do.

Catatonic Stupor.

Pullar Strecker¹³⁶ - -
Kennedy⁶² - -
Angyal and Gyarfás⁶² - -
Palisa and Sakel¹⁰⁷ - -
Müller¹⁰² - - -
Briner⁹ - - -
Press¹¹³ - - -

} They do best with cardiazol.
Improvement with insulin is in phases, not gradual.
They react less well with insulin than paranoids and catatonics.
With cardiazol, mild stuporose cases did very well; mute resistive stuporose cases did very badly.
With insulin our best results were obtained in stuporose and agitated catatonics.

Schizophrenia.

Authors.	Findings.
Humbert and Friedmann ⁵⁷	Agree generally with Press.

*Catatonic Stupor.**Hebephrenia.*

Scheuhammer and Wissgott ¹²⁴ .	They respond least well to insulin.
--	-------------------------------------

Dementia Simplex.

Angyal and Gyarfás ⁶²	-	Should be treated with cardiazol.
Briner ⁹	-	This type did not do well with cardiazol.

Conditions other than Schizophrenia.

Some work has been done on this⁸ but is not enough to summarise here.

General remarks on type of case and response to treatment.

On the whole the impression is gained that insulin is the drug of choice for paranoid cases, while cardiazol is best for stuporose cases. The hebephrenics and simplex cases are the least responsive to either treatment. For types other than those just mentioned, the treatment chosen will depend on the view of the physician, but cases which fail with one method may respond either to the other, or to both in combination. The following, not included in the table above, may be quoted. "Paraphrenics did not react very well to cardiazol" (Briner)⁹. "Cases with manic depressive colouring often react poorly to insulin" (Müller)¹⁰². "We saw our best results with insulin in catatonics of the 4th and 5th decade with depressive colouring, the prognosis of which is usually bad. Catatonics often have dry shock" (Sakel)¹²⁰.

It has been seen that stuporose cases do well with cardiazol. If that point is added, the following paragraph from Kronfeld and Sternberg⁶⁹ (written with reference to insulin treatment), seems to us to give a good statement of the findings of many workers with either drug.

"We came to the conclusion that treatment hastened remission in the remitting type of case, and in many cases mobilized a tendency to remission which might otherwise have remained latent. Though early cases do tend to remit, those remitting with insulin are notably more. In a few negative cases we thought that treatment accelerated the progress of the illness. The more lively the affective reaction in a depressive-hypochondriacal case, the better the result. Second attacks may be treated with success. Good results in cases over two years are rare. The type of onset gives more help in prognosis than the symptom picture; productive types with hallucination and delusion do specially well."

PART VI.

CONCLUSIONS.

1. Cardiazol treatment has few contra-indications. It is simple and for physically healthy people it is without serious danger.

2. Insulin treatment has been modified so as to improve the management of complications.

3. The physiological changes in both treatments have been much studied; the rationale of improvement is not yet understood.

4. The two drugs are not mutually exclusive but may be used separately, alternately, or in combination. Cases which fail with insulin may respond to cardiazol and vice versa.

5. Results are encouraging but the well-known difficulties of statistical evaluation have not been solved.

6. Cardiazol appears to be best for stuporose and insulin for paranoid cases; other types may respond to either.

BIBLIOGRAPHY.

- ¹ ACCORNERO, F., Ricerche istopatologiche sperimentali sullo shock insulinico. Schweiz. Archiv.* 93-94.
- ² „ „ e BINI, L., La insulina-shock-terapia nella Clinica Neuropsichiatrica di Roma. Schweiz. Archiv.* 145-148.
- ³ ANGYAL, L., Über die verschiedenen Insulinschocktypen und ihre neuropsychopathologische Bedeutung. Arch. f. Psychiat. 106. 662-680 1937.
- ⁴ BEIGLBÖCK, W., und DUSSIK, K. TH., Zur Physiologie des hypoglykämischen Schocks bei der Behandlung der Schizophrenie. Schweiz. Archiv.* 38-44.
- ⁵ BÉNO, N., Observations et résultats de 52 cas de traitement de psychoses par l'insuline. Schweiz., Archiv.* 149-153.
- ⁶ BERGLAS, B., und ŠUSIĆ, Z., Über die Hypoglykämie-Chokbehandlung der Schizophrenie. Psychiat-neurolog. Wochenschr. 39. 599-602. Nov. 1936.
- ⁷ BRAUNMÜHL, V., (in discussion). Schweiz. Archiv.* 231-233.
- ⁸ BRESLER, J., Insulin in der Psychiatrie. Psychiat-neurolog. Wochenschr. 39.14-15. Jan. 1937.
- ⁹ BRINER, O., Ergebnisse der Konvulsionstherapie an der psychiatrischen Klinik in Bern. Schweiz. Archiv.* 118-121.
- ¹⁰ BROUSSEAU, A., La thérapeutique convulsivante de la schizophrénie. Encéphale 1. 287-291. May 1937.
- ¹¹ BÜCKMANN, Beri-beri in der Hypoglykämie-therapie der Schizophrenie. Nervenarzt 10. 8. 412. 1937.
- ¹² CAMERON, D. E., and HOSKINS, R. G., Experiences in the insulin hypoglycemia treatment of schizophrenia. J. A. M. A. 109. 16. 124. 1937.
- ¹³ COOK, L. C., Cardiazol convulsion therapy in schizophrenia. Proc. Roy. Soc. Med. xxi. 567-577. April 1938.
- ¹⁴ DAY, G. W., and NIVER, E. O., Insulin hypoglycemia in the treatment of schizophrenia. Texas State J. Med. 33. 236-242. July 1937.
- ¹⁵ DEMOLE, V., Demence précoce, Hypoglycémie, Insuline, Vitamine B. Schweiz. Archiv.* 44-48.
- ¹⁶ „ „ (in discussion). Schweiz. Archiv.* 227.
- ¹⁷ DRABKIN, D. L., and RADVIN, I. S., Mechanism of convulsions in insulin hypoglycemia. Am. J. Physiol. 118. 174-183. Jan. 1937.
- ¹⁸ DUENSING, F., Darf der Cardiazol-Krampfanfall diagnostisch verwertet werden? Munch. med. Wochenschr. 84. 1011-1015. June 1937.
- ¹⁹ DUSSIK, K. TH., Dreieinhalb Jahre Hypoglykämitherapie der Schizophrenie. Ergebnisse und Fragestellungen. Schweiz. Archiv.* 182-186.
- ²⁰ „ „ Jahreskurse für ärztliche Fortbildung. Lehmanns. Berlin. May 1937.
- ²¹ „ „ (verbally).
- ²² EDERLE, W., Über unsere seitherigen Erfahrungen mit der insulinschockbehandlung der Schizophrenie. Zeitschr. f. d. ges. Neurol. und Psychiat. 158. 442-448. 1937.
- ²³ ELLERY, R. S., Schizophrenia and its treatment by Insulin and Cardiazol. M. J. Austral. 552-564. Oct. 1937.
- ²⁴ ENKE, W., Arzneimittelbehandlung in der Psychiatrie. Fortschritte d. Neurol-Psychiat. 9. 225-249. June 1937.
- ²⁵ ERB, Über die Möglichkeiten der kombinierten Insulin-Cardiazol Behandlung der Schizophrenie. Klin. Wochenschr. 16. 50. Dec. 11, 1937.
- ²⁶ ESSER und KUHN, Cardiazol Vergiftung, tödliche (Selbstmord). Vergiftungsfallen, 4. Lieferung 9. Vogel, Berlin. 1933.

* Schweizer Archiv. für Neurologie und Psychiatrie. Ergänzungsheft zum Band xxxix. Die Therapie der Schizophrenie. Füssli, Zürich. 1937.

- ²⁷ FAURBYE, Norsk. med- Tidskr., Feb. 6, 1937. (Abstract in B.M.J. I. 65. April 24, 1937.
- ²⁸ FINIEFS, L. A., Induced epileptiform attacks as treatment of schizophrenia. *Lancet*. 2. 131. July 1937.
- ²⁹ „ „ Significance of fits in the insulin therapy of schizophrenia. *Lancet*. 1. 371. Feb. 12, 1938.
- ³⁰ FORSTMAYER, W. M., Untersuchungen über die Permeabilität der Blut-Liquorschranke bei der Schizophrenie und deren Beeinflussung durch die Insulinschocktherapie. *Schweiz. Archiv.** 95-97.
- ³¹ FRANKE, G., Zur Frage der epileptiformen Anfallsbereitschaft im Insulinchok. *Psychiat-neurolog. Wochenschr.* 39. 63-65. Feb. 1937.
- ³² FREUDENBERG, R., Zum Verhalten des wahren Blutzuckers während des Insulinschocks. *Schweiz. Archiv.** 98-100.
- ³³ „ „ Zur Verwendung von Vitamin B und Nebennierenrinden-präparaten bei der Insulinschocktherapie. *Schweiz. Archiv.** 215-216.
- ³⁴ „ „ Über die verwendung von Vit. B₁ und B₂ bei Insulinschocktherapie der Schizophrenie. *Wien Klin. Wochenschr.* 50. 535-536. April 1937.
- ³⁵ „ „ (In discussion). *Schweiz. Archiv.** 216.
- ³⁶ „ „ Insulin Therapy: a review with special reference to the mechanism of cure. *Jl. M. Sc.*, lxxxiv. 348. 165. Jan. 1938.
- ³⁷ FROMENTY, L., Les rémissions dans la schizophrénie; statistiques sur leur fréquence et leur durée avant l'insulinothérapie. *Encéphale* 1. 275-286. 1937.
- ³⁸ FROSTIG, J. P., (German) Vorläufige Richtlinien für die Hypoglykämiebehandlung bei Schizophrenie nach Dr. Sakel. *Ars medici.* Vienna. 1937.
- „ „ (English) Sakel's pharmacological treatment for schizophrenia. *Arch. Neurol. and Psychiat.* 39. 2. 219. 1938.
- ³⁹ „ „ Erfahrungen mit der Insulintherapie bei Schizophrenen unter besonderer Berücksichtigung der klinischen Probleme. *Schweiz. Archiv.** 153-157.
- ⁴⁰ „ „ (In discussion). *Schweiz. Archiv.** 228-229.
- ⁴¹ „ „ PERSYKO, J., and PERSYKO, H., Der Blutzuckersenkungsquotient. Beitrag zur Frage der Insulinsensibilisierung. *Schweiz. Archiv.** 157-160.
- ⁴² GEORGI, F., Krampfproblem und Insulintherapie. Berücksichtigung klinischer und humoralpathologischer Gesichtspunkte. *Schweiz. Archiv.** 49-55.
- ⁴³ „ „ und STRAUSS, R., Krampfproblem und Insulintherapie. Besondere Berücksichtigung des von Meduna angegebenen Verfahrens. *Schweiz. Archiv.** 55-64.
- ⁴⁴ „ „ (In discussion). *Schweiz. Archiv.** 233-234.
- ⁴⁵ GIES, Erfahrungen mit 58 insulinbehandelten Schizophrenen. *Psychiat-neurolog. Wochenschr.* 39. 201-205. May 1937.
- ⁴⁶ GILLIES, H., Convulsive Therapy in Schizophrenia. *Lancet*. 2. 131-132. July 1937.
- ⁴⁷ „ „ Hypoglycæmic therapy in psychoses. *B.M.J.* 1. 254-1255. June 1937.
- ⁴⁸ GLUECK, JOLLIFFE, SAKEL, WORTIS et al. Discussion in *Jl. Nerv. and Ment. Dis.*, summarised in *Psychiat-neurolog. Wochenschr.*, 39. 21. 254. 1937.

* Schweizer Archiv. für Neurologie und Psychiatrie. Ergänzungsheft zum Band xxxix. Die Therapie der Schizophrenie Füssli, Zürich. 1937.

- ⁴⁹ GOLLA, MANN, MARSH, MORRIS and ROWE, (several papers) on urinary reaction, urinary acidity and respiratory regulation in psychoses. *Jl. M. Sc.* lxxiv 306. 425. Jan. 1928.
- ⁵⁰ GROSS, M., (In discussion). *Schweiz. Archiv.** 213-215.
- ⁵¹ HADORN, W., Insulin und Kreislauf. *Schweiz. Archiv.** 64-68.
- ⁵² HAMILTON, J. G., After-shock in treatment of schizophrenia. *Lancet.* 2. 16. Nov. 6, 1937.
- ⁵³ HIMMICH (in discussion of papers of Cameron and Rymer), *J.A.M.A.* 109. 16. 1253.
- ⁵⁴ HIMSWORTH, H. P., Dietetic Factor determining glucose tolerance and sensitivity to insulin of healthy men. *Clin. Sc.* 2. 67-94. Sept. 1935.
- ⁵⁵ HIRSCHMANN, J., Über Insulinbehandlung bei schizophrenie. *Psychiat.-neurolog. Wochenschr.* 39. 13-14. Jan. 1937.
- ⁵⁶ HIRSHFELD, S., HYMAN, H. T., and WAGNER, J. J., Influence of Velocity on response to Intravenous Injections. *Arch. Int. Med.* 47. 259-281. Feb. 1931.
- ⁵⁷ HUMBERT, F., et FRIEDEMANN, A., Critiques et indications des thérapeutiques de la schizophrénie. *Schweiz. Archiv.** 125-158.
- ⁵⁸ JAMES, G. W. B., FREUDENBERG, R., and CANNON, A. T., Insulin shock treatment of schizophrenia. *Lancet.* 1. 1101-1104. May 1937.
A Year's Experience of Insulin Therapy in Schizophrenia. *Proc. Roy. Soc. Med.* xxxi 6. 578. April 1928.
- ⁵⁹ " " " " " "
- ⁶⁰ JOWETT and QUASTEL. The effects of ether on brain oxidation. *Biochem. Jl.* xxi. 7. July 1937.
- ⁶¹ " " " " " " The effects of narcotics on tissue oxidation. *Biochem. Jl.* xxxi. 565. 1937.
- ⁶² KENNEDY, A., Convulsion therapy in schizophrenia. *Jl. M. Sc.* 347. lxxxiii. 42. 1937.
- ⁶³ KERR, S. E., and GHANTUS, M., Carbohydrate metabolism of brain; effect of varying carbohydrate and insulin supply on glycogen, free sugar and lactic acid in mammalian brain. *J. Biol. Chem.* 116. 9-20. Nov. 1936.
- ⁶⁴ " " " " " " Carbohydrate metabolism of brain; on origin of lactic acid. *J. Biol. Chem.* 117. 217-225. Jan. 1937.
- ⁶⁵ KLAESI, J., (in discussion) *Schweiz. Archiv.** 225-226.
- ^{65a} KLEIST, Professor, staff of, verbally.
- ⁶⁶ KNOLL, LTD., Cardiazol. Ludwigshafen 1937.
- ⁶⁷ KRAULIS, W., Der protrahierte Schock in der Insulinbehandlung der Schizophrenie und Ergebnisse der Therapie in Riga-Lettland. *Schweiz. Archiv.** 219-221.
- ⁶⁸ KRAUS, VAN DER MEULEN and ROMBOUTS. Die Behandlung der Schizophrenie nach von Meduna. *Nederlandsch. Tijdschrift voor Geneeskunde.* 33. 3931. 1937.
- ^{68a} KRAUS, Komplikationen bei der Cardiazol-Behandlung nach von Meduna. *Psychiatrische en Neurologische Bladen.* Jan.-Feb. 1938. 81-83.
- ⁶⁹ KRONFELD, A., and STERNBERG, E., Erfahrungen mit der Insulinschocktherapie bei der Schizophrenie. *Schweiz. Archiv.** 187-194.
- ⁷⁰ KRÜGER, L., Beitrag zur Frage der Schizophreniebehandlung nach von Meduna. *Psychiat.-neurolog. Wochenschr.* 38. 135-137. March 1936.

* Schweizer Archiv. für Neurologie und Psychiatrie. Ergänzungsheft zum Band xxxix. Die Therapie der Schizophrenie Füssli, Zürich. 1937.

- ⁷¹ KUBO, K., Ergebnisse der Hypoglykämieschockbehandlung der Schizophrenie. Schweiz. Archiv.* 194.
- ⁷² KULKOW, A. E., WEILAND, W. J., and KAKUSINA, B. E., Über die humoralen Veränderungen bei der Behandlung der Schizophrenie mit der Dauernarkose, Gemisch nach Cloetta. Schweiz. Archiv.* 194-204.
- ⁷³ KÜPPERS, E., Die Insulinbehandlung der Schizophrenie. Deutsch med. Wochenschr. 63. 377. 1937.
- ⁷⁴ „ „ Der Hypoglykämische Zustand in der Selbstbeobachtung. Schweiz. Archiv.* 160-163.
- ⁷⁵ „ „ Die Insulin- und Cardiazol Behandlung der Schizophrenie. Psychiat-neurolog. Wochenschr. 52. 597. 1937.
- ⁷⁶ LANCET. Annotation. Inducing fits for diagnosis. Lancet. 2, 699. 1937.
- ⁷⁷ LANGFELD, G., Insulin shock in Schizophrenia. Psychiat-neurolog. Wochenschr. 38. 483. 1936.
- ⁷⁸ „ „ Effect of large doses of insulin in schizophrenia. Nord. med. Tidskr. 12. 1833-1843, Nov. 1936.
- ⁷⁹ LARKIN, E. H., Insulin shock therapy of schizophrenia B.M.J. 1. 747-749. April 1937.
- ⁸⁰ LEHMAN-FACIUS, H., und GERHARDT., Über die Schock und Fieberbehandlung der Schizophrenien. Medizinische Klinik. 35. 1937.
- ⁸¹ „ „ Liquoruntersuchungen bei destruktiven Erkrankungen des Nervensystems, besonders bei der Schizophrenie. Zeitschr. f.d.ges. Neurol. und Psychiat. 158. 109-115. 1937.
- ⁸² LEWIS, A. J., Prognosis in schizophrenia. Lancet, 1. 339-341. Feb. 1935.
- ⁸³ LIGTERINK, Schwierigkeiten bei der Konvulsionstherapie (Dutch) Psychiatrisk en Neurologische Bladen. 4. Juli-Aug. 1937.
- ⁸⁴ LOEVENHART, LORENZ, and WATERS, Cerebral stimulation. J.A.M.A., 92. 1. 880. March 1929.
- ⁸⁵ MADDOX, An unusual manifestation of hypoglycæmia. B.M.J., 1. 1170. 1937.
- ⁸⁶ MAIER, H. W., (In discussion) Schweiz. Archiv.* 224-225.
- ⁸⁷ MARZYNSKI, M., Ergebnisse der Insulinschockbehandlung der Schizophrenie. Schweiz. Archiv.* 168-173.
- ⁸⁸ VON MEDUNA, L., Über experimentelle Kampferepilepsie Archiv. f. Psychiat. 102. 333-339. 1934.
- ⁸⁹ „ „ Versuche über die biologische Beeinflussung des Ablaufes der Schizophrenie. Zeitschr. f. d. ges. Neurol. und Psychiat. 152. 235-262. 1935.
- ⁹⁰ „ „ Die Konvulsionstherapie der Schizophrenie Psychiat-neurolog. Wochenschr. 37. 317-319. July 1935.
- ⁹¹ „ „ New methods of medical treatment of Schizophrenia. Gyógyszat. Abstract in Arch. Neurol and Psychiat. 35.
- ⁹² „ „ Die Konvulsionstherapie der Schizophrenie. Marhold, 1937.
- ⁹³ „ „ Allgemeine Betrachtungen über die Cardiazoltherapie. Schweiz. Archiv.* 32-38.
- ⁹⁴ „ „ Die Bedeutung des epileptischen Anfalls in der Insulin und Cardiazolbehandlung der Schizophrenie. Psychiat-neurolog-Wochenschr. 39. 331-334. July 1937.
- ⁹⁵ „ „ (In discussion). Schweiz. Archiv.* 233.
- ⁹⁶ „ „ Über die häufigsten Fehler bei der Konvulsionstherapie. Psychiat-neurolog. Wochenschr., 8 and 9, 1938.
- ⁹⁷ „ „ (Personal communication).

* Schweizer Archiv. für Neurologie und Psychiatrie. Ergänzungsheft zum Band xxxix. Die Therapie der Schizophrenie Füssli, Zürich. 1937.

- ⁹⁸ MOLONY, C. B., and HONAN, M. S., An unusual complication of insulin shock (hypoglycaemic) therapy. *Jl. M. Sc.* lxxxiii. 347. 630. Nov. 1937.
- ⁹⁹ MORSE, R. T., Insulin shock therapy; critical review. *Jl. Kansas Med. Soc.* 38. 248-253. June 1937.
- ¹⁰⁰ MORSIER, G. DE., GEORGI, F., et RUTISHAUSER, E., Etude expérimentale des convulsions produit par le Cardiazol chez le lapin. *Schweiz. Archiv.** 144.
- ¹⁰¹ MORSIER, G., et BERSOT, H., Les troubles cérébraux dans l'hyperinsulinémie provoquée. *Schweiz. Archiv.** 101-108.
- ¹⁰² MÜLLER, M., Die Insulin-therapie der Schizophrenie. Einleitendes Referat. *Schweiz. Archiv.* 9-21.
- ¹⁰³ (In discussion). *Schweiz. Archiv.** 226-227.
- ¹⁰⁴ NICOLAJEV, V., Über eine besondere Gliaveränderung nach wiederholten Insulinschocks im Tierversuch. *Schweiz. Archiv.** 205.
- ¹⁰⁵ „ „ und WERNER, R., Zur Erfolgsprognose der Insulinschockbehandlung und zur Deutung des Heilungsvorganges (Untersuchungen über Schrankenpermeabilität). *Schweiz. Archiv.** 206-208.
- ¹⁰⁶ PALISA, CH., and FLACH, A., Das Erwachen aus dem Hypoglykämischen Schock. *Schweiz. Archiv.** 69-76.
- ¹⁰⁷ „ „ und SAKEL, M., Zur Phänomenologie des Hypoglykämischen Zustandsbildes bei behandelten Psychosen. *Monatschr. für Psychiatrie und Neurologie* 96. 12. 1937.
- ¹⁰⁸ PALISA, CH., (In discussion) *Schweiz. Archiv.** 229.
- ¹⁰⁹ PARFITT, D. N., The Neurological and Psychological effects of hypoglycaemia. *Proc. Roy. Soc. Med.* xxxi. 2 187. Dec. 1937.
- ¹¹⁰ PETRIE, A. A. W., Hypoglycaemic treatment of schizophrenia; some impressions. *Jl. M. Sc.* lxxxiv. 348. 156-159. 1938.
- ¹¹¹ PFISTER, H. O., Die Neuro-vegetativen Störungen der Schizophrenien und ihre Beziehung zur Insulin- Cardiazol- und Schlafkurbelbehandlung. *Schweiz. Archiv.** 77-83.
- ^{111a} PLATTNER, P., und FRÖLICHER, E., Zur Insulinschockbehandlung der Schizophrenie. *Zeitschr. f. d. ges. Neurol. und Psychiat.* 160. 735.
- ¹¹² POLLACK, B., Present status of treatment of Schizophrenia. *Med. Times, New York* 65. 403-408. Aug. 1937.
- ¹¹³ PRESS, M. L., Rémissions après traitement insulinique. (Contribution au problème des rémissions dans la schizophrénie). *Schweiz. Archiv.** 173-178.
- ¹¹⁴ REITMANN, F., Zum Frage der Insulinschockwirkung. *Psychiat-neurol. Wochenschr.* 5. 1938.
- ^{114a} REESE, H. H., and VEER, A. V., Protamine Zinc Insulin; its unsuitability for hypoglycemic shock therapy. *Arch. Neurol. and Psychiat.* 39. 2. 212. Feb. 1938.
- ¹¹⁵ ROEMER, H., Die neuen Behandlungsmethoden der Schizophrenie, und der Anstaltsbetrieb. *Schweiz. Archiv.** 164-167.
- ¹¹⁶ RUBENOVITCH, P., (In discussion). *Schweiz. Archiv.** 216.
- ¹¹⁷ RUSSELL, L. W., Hypoglycaemic shock in treatment of schizophrenia. *Lancet, I.* 747-749. March, 1937.
- ¹¹⁸ SAKEL, M., Neue Behandlungsmethode der Schizophrenie. Vienna and Leipzig, 1935.
- ¹¹⁹ „ „ New treatment of schizophrenia. *Am. J. Psychiat.* 93. 829-841. Jan. 1937.
- ¹²⁰ „ „ Das Wesen und die Entstehung der Hypoglykämiebehandlung der Psychose. *Schweiz. Archiv.** 21-32.
- ¹²¹ „ „ (In discussion). *Schweiz. Archiv.** 229-230 and 237-238.

* Schweizer Archiv. für Neurologie und Psychiatrie. Ergänzungsheft zum Band xxxix. Die Therapie der Schizophrenie. Füssli, Zürich, 1937.

- ¹²² SAKEL, M. Zur Bedeutung des epileptischen Anfalles als therapeutischen Faktors in der medicamentösen Schocktherapie der Schizophrenie. *Deutsch. Klin. Wochenschr.* 37. 16. 1277-1282. 1937.
- ¹²³ SALM, H., Benommenheitszustände im Anschluss an die Insulinschockbehandlung der Schizophrenie. *Munch. med. Wochenschr.* 84. 1046-1048. July 1937.
- ¹²⁴ SCHEUHAMMER, P., und WISSGOTT, L., Erfahrungen mit der Cardiazolbehandlung der Schizophrenie. *Psychiat-neurolog. Wochenschr.* 39. 286-288. June 1937.
- ¹²⁵ SCHMID, H. E., Beiträge zur Histophysiologie des Insulins. *Schweiz. Archiv.** 109-117.
- ¹²⁶ „ „ L'Histopathologie du choc insulinaire. *Ann. méd-psychol.* 2. 94. 658-664. Nov. 1936.
- ¹²⁷ SCHÖNMEHL, Provokation von epileptischen Krampfanfällen Munch. *med. Wochenschr.* 83. 721-723. May 1936.
- ¹²⁸ SMITH, H. M., Hypoglycemic shock therapy. *Jl. Florida. M.A.*, 24. 11-20. July 1937.
- ¹²⁹ SOLLMANN, T., Reactions to Intravenous Injections. *Manual of Pharmacology*, 5th Edition. 478. Saunders.
- ¹³⁰ STECK, H., und BOVET, H., Resultate auf dem Gebiet der Insulintherapie in Cery von 1929-1937. *Schweiz. Archiv.** 117-118.
- ¹³¹ STEINFELD, J., Insulin shock therapy in schizophrenia. *J.A.M.A.* 108. 91-92. Jan. 1937.
- ¹³² STIEF, S., Der Wirkungsmechanismus der sogenannten Konvulsions-therapien mit besonderer Rücksicht auf die Insulinschockbehandlung. *Psychiat-neurolog. Wochenschr.* 39. 225-229. May 1937.
- ¹³³ STORCH, A., (In discussion) *Schweiz. Archiv.** 235.
- ¹³⁴ STRECKER, H. PULLAR, Die Insulinbehandlung der Schizophrenie. *Munch. med. Wochenschr.* 83. 649-650. April 1936.
- ¹³⁵ „ „ Erfahrungen mit der Insulinbehandlung in England. *Schweiz. Archiv.** 178-179.
- ¹³⁶ „ „ Recent advances in Insulin treatment. *Jl. M. Sc. lxxxiv.* 348. 146-155.
- ¹³⁷ „ „ A comparison of insulin and cardiazol convulsion therapies in the treatment of schizophrenia. *Lancet.* 1. 371. Feb. 12. 1938.
- ¹³⁸ TEENSTRA. (In discussion.) *Psychiatrische en Neurologische Bladen* 4. Juli-Aug. 1937.
- ¹³⁹ TEGLEBJAERG, H. P. S., Investigations on epilepsy and water metabolism. Levin and Munskgaard. Copenhagen 1936.
- ¹⁴⁰ TELATIN, L., Su alcune variazioni biochimiche durante lo shock insulinico. *Schweiz. Archiv.** 221-224.
- ¹⁴¹ THUMM. (In discussion.) *Schweiz. Archiv.** 229.
- ¹⁴² TORP, H., Mental and Neurological changes after Hypoglycaemic coma in case of schizophrenia. *Norsk Mag. f. lægvidensk.* 93. 760. 1932.
- ¹⁴³ WECHSLER, Z., Über den Einfluss der Hypoglykämie auf die Blut-Liquorschanke in Tierversuch. *Psychiat-neurolog. Wochenschr.* 39. 230-232. May 1937.
- ¹⁴⁴ WEGIERKO, J., Le léger choc insulinaire comme facteur hypnotique et analgesique. *Paris. med.* 1. 365-367. April 1937.
- ¹⁴⁵ WESPI, H., Vorläufige Mitteilung über Beobachtungsergebnisse von vegetativen Funktionen bei der Insulinschockbehandlung Schizophrenen. *Schweiz. Archiv.** 83-93.

* Schweizer Archiv. für Neurologie und Psychiatrie. Ergänzungsheft zum Band xxxix. Die Therapie der Schizophrenie. Füssli, Zürich. 1937.

- 146 WHITEHEAD, D., Prognosis in dementia præcox; comparative study of present results and those obtained from hypoglycemic treatment. *Psychiat. Quart* 2. 83-390. July 1937.
- 147 WILLMANS, K., (In discussion) *Schweiz. Archiv.** 227-228.
- 148 WILSON, I. G. H., A study of hypoglycemic shock treatment in schizophrenia, H.M.S.O. London, 1936.
- 149 WORTIS, J., Cases illustrating treatment of schizophrenia by insulin shock. *Jl. Nerv. and Ment. Dis.* 85. 446-456. April 1937.
- 150 " " Sakel's hypoglycemic treatment of psychoses; history and present status; Collected Abstract. *J. Nerv. and Ment. Dis.* 85. 581-595. May 1937.
- 151 " " Common acne and insulin hypoglycemia. *J.A.M.A.* 108. 971. March 1937.
- 152 WRIGHT, SAMSON. *Applied Physiology.* Oxford. Medical Publications. 5th Edition. 1934.

* *Schweizer Archiv. für Neurologie und Psychiatrie. Ergänzungsheft zum Band xxxix. Die Therapie der Schizophrenie* Füssli, Zürich. 1937.

INDEX.

	PAGE
Accornero	29, 35
ADRENALIN	18, 20, 22, 28
AFTER-SHOCK	19, 21
ALKALI	18
ALKALOSIS, in hypoglycæmia	24, 27, 33, 34
Andrews	17
Angyal	3, 30, 50, 55, 56
America, work from	5, 50
ANOXIA or ANOXÆMIA	35, 36, 39
Arlesey, Mental Hospital at	3
AVITAMINOSIS	31, 34
BIOCHEMISTRY OF TREATMENTS	26, 30, 42
Beiglböck	22, 23, 26, 27, 34
Benedek	3
Béno	16, 22, 49, 54
Berglas	23
Bersot	29
Bexley, Mental Hospital	3
Bini	35
BLADDER, in cardiazol treatment	10
BLOOD-PICTURES, in treatments	30
BLOOD-PRESSURE	26
BLOOD SUGAR	26, 30
Braunmühl	16, 18, 55
Briner	40, 46, 50, 55, 56
BRONCHOPNEUMONIA	23
Brousseau	44
Bückmann	18
Cannon (<i>see</i> James)	17, 20, 47, 52
CAFFEIN, in status	21
CALCIUM, in failure to wake	18, 21
CAPILLARY FUNCTIONS, in treatments	26
CARDIAZOL and its substitutes	5
CARDIAZOL treatment	5
CARDIAZOL with insulin	24
CARDIOVASCULAR SYSTEM, in treatments... ..	12, 13, 23
CATATONIA, response to treatment	55, 56
CEREBRAL VESSELS and cells, in the treatments	23
CEREBRO-SPINAL FLUID	28, 29
Co ₂ breathing of	18, 20, 21, 36
COMA, onset and estimation of	16, 19
Conclusions	57
CONFUSED CASES, treatment of	44
Consulate, British, in Frankfurt	3
CONTRA-INDICATIONS to Cardiazol... ..	13
Cook	9, 12, 51
CORTEX, in hypoglycæmia	30
CYANIDE	36, 37

	PAGE
Day	15, 24, 28, 34, 38
DEATHS and the treatments	6, 13, 14
DEMENTIA SIMPLEX, response to treatment	56
Demole	33, 34, 39
DIAGNOSIS of cases for treatment	43
DIET and insulin sensitiveness	16, 17
DIFFICULTIES of cardiazol treatment	11
DIGITALIS	23
DISEASED CELLS, elimination of	31, 32
DISLOCATIONS, with cardiazol	11, 12
Dobozy	13
DOSAGE of cardiazol	5, 25
„ of insulin	14, 16
Dowden	3
Drabkin	29
DURATION of cardiazol treatment	7
„ of insulin treatment	16
Dussik, frequently throughout.	
EARLY TREATMENT, importance of	43
Ederle	45, 49
ELECTROCARDIOGRAPH	13, 23, 26, 31
ELIMINATION OF CARDIAZOL	7
Ellery	41
Enke	49
EPILEPSY and cardiazol	5, 12
EPILEPTIFORM ATTACKS in hypoglycæmia	21, 25, 27, 33
Erb	25
EUPHORIA, with cardiazol	10
EUPHYLLIN	22
EXHAUSTION after treatment	21
EXCITEMENT, treatment of	25, 55
FAILURE to wake, in hypoglycæmia	20, 28
Faurbye	45
Fiala	3
Finiefs	10, 18, 22, 33, 53
FITS, and cardiazol	7, 9, 10
„ and hypoglycæmia	21
„ as therapeutic agents... ..	32
FLUSHING, with cardiazol	8
Forstmeyer	29
Fox	15
Freudenberg	18, 20, 27, 28, 39, 47, 52
FREUDIAN aspect of treatments	40
Friedemann	11, 55, 56
Friedlander	49
Fromenty	45, 46
Frostig	15, 16, 21, 49, 54
GASTRIC ANALYSES	27
Georgi	21, 25, 26, 27, 29, 30, 52
Gies	19, 21
Gillies	9, 21, 22

	PAGE
Ghantus	29
Gross	26
Goodmayes, Mental Hospital at	3
Glaus	5
Glueck	42
GLUCOSE and hypoglycæmic shock treatment	20, 22, 28
GLYCOGEN in brain	29
Golla	39
Gyarfas	3, 50, 55, 56
HALLUCINATIONS, with cardiazol	11
Hamilton	21, 33
HEBEPHRENIA, treatment of	25, 56
Himmwich	29, 39
Himsworth	17
HIPPUS, during treatment	30
Hobson	12
Honan	28
Humbert	11, 55, 56
Hutter	49
HYPOGLYCÆMIC shock treatment	16, 31, 32
" " " standardisation	15
" " " combined with cardiazol	16
" " " interruption in	19
" " " duration of	16
" " " modifications in	19
INJECTIONS, cardiazol	7, 9
INSULIN and cardiazol	14, 24, 51
" makes of	17
" secretion of... ..	28
" sensitisation to	16
INTERMEDIARY substances and fits	40
INTERRUPTION of hypoglycæmia	19, 20
Jablonsky	5
James	17, 20, 47, 52
JAWS, gaping of	31
Jowett	39
Kakusina	31
Kennedy	31, 50, 55
Kerr	29
Klæsi	46
Kleist	3, 43, 44
Klemperer	15
Knoll	5, 9
Küppers	20, 24, 30, 40, 49, 51, 52, 55
Kulkow	31
Kubo	19
Kraulis	16
Kraus	51
Kronfeld	22, 52, 55, 56

	PAGE
Langfeld	49
Larkin	53
LARYNGOSPASM, in hypoglycaemia	22
Lax	13
Legation, British	3
Lehman-Facius	43
LOBELINE	12, 21
Loevenhart	36, 37, 38
Lorenz	36, 37, 38
LUMBAR PUNCTURE in treatment	21, 24
LUMINAL	21
LYMPHOCYTOSIS	27
Maddox	38
Maier	46
MANIC DEPRESSIVE mood and treatment	56
Marzynski	20, 44, 49
Maudsley Hospital	34
von Meduna, frequently throughout.	
MENSTRUATION, and cardiazol	13, 14
METABOLIC CHANGES and hypoglycaemia	24, 26
METHYLGLOXAL and convulsions	33
METRAZOL	5
Molony	28
MORPHINE in treatment	11, 21
Morse	42
Morsier	29, 31
MORTALITY in treatments	20
Müller, frequently throughout.	
Münsingen, Congress at	4, 25
MYOCLONIFORM COLLAPSE	21
NARCOSIS, prolonged	41
Nederlandsche Vereeniging voor Psychiatrie	4
NEUROLOGICAL FINDINGS	30
Newport, Mental Hospital of	54
Nicolaev	29
Niver	15, 24, 29, 34, 48
NURSES and treatment	11
Nyirö	5
ŒDEMA of lungs	22, 23
OLIGURIA	24
OXYGEN fixation and cerebral function	38
OXYGEN in treatment	18, 21, 22
Palisa	3, 30, 55
Pameijer	54
von Pap	49
PARANOID cases, response to treatment	55
PARAPHRENIA, response to treatment	56
Pfister	32
PERMEABILITY of cell membranes	29, 35

	PAGE
pH in the treatments	18, 34
PHYSICAL DISEASE and cardiazol	13, 14
PHYSICAL EXAMINATION, need for	10
PHYSIOLOGICAL CHANGES in the treatments	26, 30
Pollack	49
Pötzl	3
Press	55
PROTAMINE INSULATE	17
PROTRACTED SHOCK... ..	16
PSYCHOSIS accelerated by treatments	52
PSYCHOLOGICAL aspect, psychotherapy	32, 40
PULMONARY, embolism, œdema, thrombosis	9, 11
PUPIL CHANGES in treatment	30
Quastel	39
QUININE in hypoglycæmia	19
Radvin	29
RECOVERED CASES, outlook of	42
RED-CELL COUNT in treatments	27, 30
Reitmann	3
RELAPSES	54
REMISSIONS without the treatments	44
„ hastened by treatment	56
RENAL DISEASE and cardiazol	13
RENAL PERMEABILITY and insulin	24
RESISTANCE to the drugs	8, 16, 17
RESPIRATORY DISEASES and the treatments	12, 13, 22
„ „ Enzyme	34, 36
RESULTS of treatment	4, 43, 46, 48, 50, 51
Roemer	41, 48
Rombouts	10, 11
Rubenovitch	30, 43
Russell	53
SAFETY of cardiazol treatment	13
Sakel, frequently throughout.	
Salm	21, 29
SALYRGAN in treatment	24
Scheuhammer	50, 56
Schmid	30
Schweizer Archiv. für Neurologie	4
SCOPOLAMINE before cardiazol injection	11
SCREENS and cardiazol treatment	10
SELECTION of cases for treatment	43
SENSITIZATION to the drugs	8, 16
SHOCK	30
Siegheim	53
SKIN and hypoglycæmia	24
Smith	46
SMOKING and treatment	19
SPEED SHOCK	8
STAFFING for treatment	10
STATUS epilepticus	21
Steck	15, 46
Steiner	5

	PAGE
Steinfeld	21, 40
Sternberg	22, 52, 55, 56
Stief	24, 29, 31, 32
Straus	5, 30
Strecker	16, 21, 22, 46, 55
STROPHANTHIN	22, 23
STUPOR, treatment of	25, 55
SUCTION to remove saliva	19
SUGAR POTENTIAL	27
SUMMATION treatment	11, 24, 45
Susić	23
TACHYCARDIA	26
Teglbjaerg	17
THANKS for help	3
THEORIES of treatment	26, 31, 42
TISSUE RESPIRATION	32, 39, 40
Tokay	29
TOLERANCE to cardiazol	8
„ to insulin	17
TRANSFUSION in hypoglycæmia	19
TUBERCULOSIS and cardiazol treatment	13
TURNING-POINT in hypoglycæmia	27
TYPE OF ILLNESS and response to treatment	55
UNCONSCIOUSNESS, history of, and cardiazol	14
UNPLEASANTNESS of cardiazol	11
URINARY alterations, with cardiazol	31
Van der Meulen	10
VEGETATIVE SYSTEM, changes in	31, 32
VEINS, difficulty in finding	11, 22
„ obliteration of	11
„ thrombosis of	13
VENESECTON, uses of	21, 22
VITAMIN B	33, 34, 40
WATER and salt regulation... ..	35
WATER into stomach in hypoglycæmia	21
Waters	36, 37, 38
Watson	53
Wechsler	29
Weiland	31
Werner	29
Wespi	27, 30
West Park, Mental Hospital at	3
Whitehead	44, 45
Willmans	35
Wissgott	50, 56
Wortis	24
Wright	28, 36, 39

