

THE
JOURNAL OF MENTAL SCIENCE

[*Published by Authority of the Royal Medico-Psychological
Association.*]

No. 347 [^{NEW SERIES}
No. 311.] NOVEMBER, 1937. VOL. LXXXIII

Part I.—Original Articles.

CONVULSION THERAPY IN SCHIZOPHRENIA.

By ALEXANDER KENNEDY, M.D., M.R.C.P., D.P.M.,

Assistant Medical Officer, West Park Hospital, Epsom; lately seconded to Psychiatric
Research Unit, Maudsley Hospital.

THE following account is based on the writer's experience of convulsion treatment at centres abroad, on a review of the literature up to the present date, and on three cases recently treated at West Park Hospital, Epsom. It is published at this early stage in order to make a knowledge of the technique and literature of a method which has already proved itself worthy of extensive trial, available to a larger number of workers in this country.

Over a thousand cases have now been treated at various hospitals in Europe, and the mortality and remission-rates, especially in the catatonic type of case, compare favourably with the insulin shock treatment introduced by Sakel in Vienna in 1933 and developed in this country during the past year. The permanence of the remissions produced by this method cannot as yet be assessed.

HISTORICAL AND THEORETICAL.

In 1929 Nyiro and Jablonszky observed that cases of epilepsy in which schizophrenic features were present recovered rapidly when fits were frequent, and in 1930 Müller described two cases in which schizophrenic illnesses recovered rapidly after the appearance of spontaneous epileptic fits.

Glaus in 1931 pointed out that the combination of schizophrenia and epilepsy was a rare one, and of 6,000 schizophrenics investigated, he found only 8 who had had fits at any time of their life, and of these 4 recovered shortly after the fits appeared.

Although it is traditional in English mental hospitals that seizures of one sort or another are not infrequently found in chronic catatonic states, the writer has not been able on investigation to satisfy himself that true epileptiform convulsions have occurred in a single chronic catatonic at West Park Hospital, and in 8 cases in whose case-records seizures were reported, none had been recorded as epileptiform, and most of them seemed to have been of the nature of vaso-vagal syncope. Of 120 psychotic epileptics having frequent fits, only

one showed a mental picture at all recognizable as catatonic, though paranoid features were, of course, common enough.

Straub, on examination of 6,000 cases of schizophrenia, similarly reports that though 20 cases were said to have had epileptic fits, he could not satisfy himself as to the diagnosis, or witness a fit in a single case. Conversation with experienced mental nurses tends to confirm the fact that when seizures occur in chronic schizophrenics, they are rarely of the true epileptiform type.

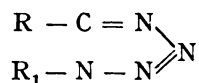
It would appear, then, that there is some antagonism between catatonic schizophrenia and epilepsy which does not allow them to occur together in anything like the number of cases that would be expected in view of the frequency of the two conditions in the general population.

It was a recognition of this antagonism that led von Meduna of Budapest, in 1934, following a series of experiments on animals, to produce epileptiform convulsions in the human subject by means of intramuscular injections of 25% camphor in olive oil. He showed that the readiness to react with a convulsion varied with the individual susceptibility, both in animals and in man, rather than with factors such as the body-weight. His first experiments in man were carried out on advanced deteriorated schizophrenics and produced little improvement in their condition, but when the method was applied to recent cases encouraging results began to be obtained at once.

The results, however, were very variable, and often severe side-effects in the form of delirium and prolonged vomiting due to the overdoses of camphor were encountered. The great bulk of the injections, their painfulness and uncertain effects led von Meduna to investigate other convulsant agents, and of these pentamethylenetetrazol has so far proved to be the most safe and reliable.

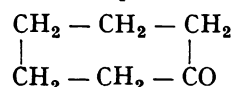
CHEMICAL.

Pentamethylenetetrazol was synthesized by Prof. K. F. Schmidt of Heidelberg, during experiments directed at the synthesis of water-soluble substances having the therapeutic properties of camphor. His efforts met with no success until a discovery made by academic workers on the dissociation of hydrazoic acid revealed hitherto unknown reactions, by which it was possible to produce from ketones compounds of the type—

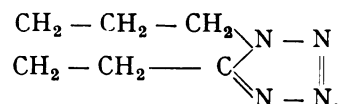


in which R and R₁ represent different organic groups of which the identity depends on the original ketone.

The basal ketone chosen by Schmidt was cyclohexanone because of its essential similarity to camphor but simpler structure :



One of the resultant compounds was pentamethylenetetrazol :



This compound is of interest in that it represents the simplest member of a series of compounds not hitherto known and of very great theoretical importance, and it was fortunate that von Meduna was able to find in it a substance having the convulsant properties of camphor without its disadvantages of insolubility and toxic effects.

PHARMACOLOGY.

A very extensive literature has accumulated on the pharmacology of pentamethylenetetrazol, which is widely used in much smaller doses by cardiologists under the names of "cardiazol" and "metrazol" (U.S.A.). Its convulsive properties in the experimental animal have been known for a long time, but their application to treatment was not discovered until von Meduna's experiments. Some of the results of earlier work, however, have a bearing on the technique of convulsion treatment.

Although no very close similarity exists between the chemical formulæ of camphor and of pentamethylenetetrazol, experiments made by F. Hildebrandt showed that it had the stimulant effects of camphor with the advantages of solubility, ready absorption and elimination, and suitability for intravenous use. He found that in large doses convulsions were produced in rabbits resembling those produced by picrotoxin. Schoen showed that in smaller doses it increases the reflexes and antagonizes the action of sedative drugs of the sulphonal and barbitone groups—a fact that emphasizes the importance of avoiding these drugs during treatment if convulsions are to be obtained with minimal doses.

Experimentally, the irritability of the "vomiting centre" is increased (Schwartz), but fortunately in the smaller doses used clinically vomiting is not common, and the writer has not seen vomiting occur within an hour of a convulsion, though it has frequently been described.

It is also a powerful stimulant of the respiratory centre, and it is probable that this is the reason for the rarity of alarming asphyxial symptoms after the apnoëic period, during the fit. Although there may be considerable cyanosis, if the airway is clear no anxiety need be felt.

The drug is a powerful stimulant to the vascular system generally, though in non-convulsant doses it does not greatly increase the blood-pressure. During a course of treatment, however, it is usual for the systolic blood-pressure between convulsions to rise day by day if recovery is going to occur. Although the large dose injected in this treatment causes the heart to beat very violently

and the great vessels to pulsate, the pulse-rate is not greatly increased even during convulsions, and is much slower than during idiopathic epileptic fits.

ABSORPTION AND EXCRETION.

Owing to its ready solubility in practically all solvents, and in lipoids, pentamethylenetetrazol is rapidly absorbed, even if given intramuscularly, and about three times the intravenous dose when given in this way will usually produce a convulsion. On account of the variability of the time before the onset of the convulsion, and of the need to watch the patient for at least an hour after administration of an intramuscular dose, and owing to the greater uncertainty as to whether a convulsion will result the writer has not employed this form of treatment, though it is given by many continental workers, including von Meduna.

The final mode of elimination after injection is as yet uncertain. It is removed rapidly from the circulation after intravenous injection. Hildebrandt finds that the speed of detoxication of the serum in an average convulsive dose is 0.85 mg./kilo/minute, and other workers confirm this (Barker and Levine).

Biehler has shown that the destruction of the drug is so rapid that two doses of 1 c.c. of a solution, injected shortly after one another, do not produce in experimental animals anything like the effect of a 2-c.c. dose, and so rapid is this destruction that even the rate of injection affects the concentration of the drug in the circulation during subsequent minutes. This rapid disappearance is one reason for the great speed with which it is necessary to inject the solution. The other reason for injecting rapidly is to ensure that as large a quantity of the drug as possible can reach the vessels of the central nervous system at the same time, after it has traversed the heart, and before it has diffused itself into the general circulation.

It may be that excretion takes place, as suggested by Biehler, into the small intestine, but a large quantity must clearly be destroyed as it cannot be recovered unchanged in the excreta. Only small quantities can be found unchanged in the urine passed after a convulsion.

The rapidity of excretion or destruction is a great advantage in treatment, as the increased excitability of the central nervous system passes off very rapidly after the convulsion is over. As will be seen, it is necessary to produce a convulsion after each injection, and if additional solution has to be injected it must be done at once, and for this reason the needle is always left in the vein until the convulsion has actually started.

PHYSICAL AND CHEMICAL PROPERTIES.

Pentamethylenetetrazol is a white crystalline powder with a faintly bitter taste; it is soluble without decomposition in most organic solvents and in water, the aqueous solution being almost neutral. A series of solutions

buffered to pH 8.0 remained at this pH after sterilization at 120° C. for half an hour, and showed no change after storage for a month.

Its presence may be detected by the production of a precipitate on addition of a saturated solution of mercuric chloride to a solution, and this is sensitive up to 0.001%. The reaction, however, is not specific, as it is given by a number of reducing substances and by some alkaloids, including quinine.

The solution gives Zwicker's reaction, i.e., if potassium bichromate be added to an acidified solution and shaken with hydrogen peroxide a blue colour is produced, which dissolves in chloroform when the latter is shaken with the solution. The test is sensitive to 0.005%, but can be made more sensitive by the addition of an acid solution of cuprous chloride, which makes it sensitive to 0.00001%. By means of these tests it was possible to detect small quantities of the drug in the urine of patients during the first hour after convulsions. It can usually be so found when a convulsion has been successfully produced and indicates that the speed of injection has been high.

The solution therefore is stable and soluble. To some extent it inhibits the growth of bacteria; v. Angerer showed that 1% and 10% solutions in saline had mild bactericidal properties. The writer, however, has found that at least 5% must be added to a broth culture to inhibit the growth of staphylococci and coliform bacilli.

PHENOMENA OF THE CONVULSION.

The usual interval between the commencement of the injection and the first sign of the convulsion is about 10 seconds. If the first signs are delayed for more than 20 seconds, the ensuing convulsions are likely to be incomplete and unsatisfactory. The fit usually comes on with great suddenness only a few seconds after the premonitory signs. These are sudden pallor, a very characteristic short cough, twitchings of the fingers and movements of the facial muscles, which give the patient the appearance of being suddenly terrified. These signs are not usually all present together, but one or more can always be seen.

Very often the terrified expression is followed by a few staring glances from side to side, dilatation of the pupils, and a cry or scream. The staring eyes then cease to move, and slowly turn upwards or deviate to one side as consciousness is lost.

The tonic state usually commences with a few twitches in the hands or feet, the hands then going into the tetanic or "accoucheur" position, or the feet plantar-flexing while the spasm rapidly spreads all over the body. Frequently one side is affected a moment before the other.

At the onset of the tonic phase in most cases the mouth opens widely, and if this moment is watched for a gag or airway can be inserted before the jaw closes.

This sudden opening of the mouth appears to be a peculiarity of the artificially induced convulsion, and accounts for the frequency of dislocation of the jaw as a complication. This occurred in one of the writer's cases.

The whole body then goes into violent opisthotonos, with the muscles quivering and tense, the face gradually becoming flushed, and the veins standing out on the neck. Respiration ceases and the arteries in the neck can be seen pulsating violently, the rate being usually about 90—rarely over 100.

The tonic state lasts from 10–30 seconds, this time varying, according to von Meduna, with the individual and not with the dosage. Other workers, however, have found the tonic state to be prolonged if more than the necessary dose be given.

The clonic stage is ushered in by short periods of relaxation, which increase in length until clonic convulsions are present. This stage lasts from 15 seconds to a minute and during it the muscles are irritable, although Chvostek's sign is absent, and the reflexes are increased and one or both plantar responses is extensor. The pupils are dilated, but may quickly contract at intervals. The pulse usually becomes more rapid as cyanosis begins to appear but rarely exceeds 120. No change can be seen in the retinal vessels at any stage of the convulsion, except possibly some widening of the veins when cyanosis is marked.

As the clonic spasms become less frequent and there are no respiratory movements, cyanosis increases and may become marked. If, however, the airway is clear, there need be no anxiety. There is sometimes an interval before respiration starts again, but if this is too prolonged a single pressure on the chest-wall with the open hand will usually start it off. The cyanosis is rarely as deep as that seen in a badly administered N_2O anæsthetic.

After the clonic stage proper, a few single convulsions may occur during the next minute and the muscles may remain irritable. If the shoulder-girdle muscles are put on the stretch by pulling on the arm, for about a minute after the clonic phase they will contract, but after this sign has gone the patient will lie still. The cough reflex soon returns, and if an airway has been put in, movements will be seen in the patient's throat.

Patients frequently micturate during the fit, and in the recovery stages they are often distressed to find that this has occurred.

Unconsciousness lasts for a variable period; in most cases 5–15 minutes, and is recovered from gradually, the patient often showing momentary signs of fear resembling those at the onset of the fit. He is invariably disorientated at first and is unable to recognize those around him, but if his contact with his environment before the convulsion has been good, he will regain his orientation in a few minutes.

The patient is usually unwilling to speak and has to be pressed to answer questions at this stage. After a few minutes of restless movements and

attempts to get out of bed he will usually curl up and go to sleep. During this short restless phase, which does not occur in all cases, the patient may wander about in an aimless fashion, and must not be let out of sight for more than a few moments.

There is no transient remission in the illness corresponding with that seen after insulin therapy, or after the administration of intravenous sodium amytal, and the patient returns after the convulsion to approximately the same state as before its induction.

After 1-2 hours' sleep the patient usually wants to get up, and will often say that he has had no food or that he is remarkably hungry; in fact, throughout the treatment appetite is always very good and tube-feeding is rarely necessary after the second convulsion, even in cases that do not recover. This observation has been made by most workers, and it has a practical application in that by a few injections cases of chronic catatonic stupor may be made to feed themselves even if they are unlikely, on account of their chronicity, to have remissions.

There appears to be no objection to patients getting up 2-3 hours after the convulsion. They will usually state that they are tired, but as a rule have surprisingly little comment to make even when recovery is practically complete.

In the majority of cases there is a complete amnesia for the period of the fit and for any abnormal behaviour which has occurred during succeeding minutes. Thus a patient who tried to climb out of the window 10 minutes after the fit went to sleep on being put to bed, and could recall nothing of the incident on the following day.

METABOLISM DURING CONVULSION TREATMENT.

A number of investigations have been done which allow of some comparison between metabolism in induced and in idiopathic convulsions. During the three-hour period following a convulsion there is a decrease in the urinary acidity, a reduction in the ammonia content, a slight increase in the phosphate content and a considerable reduction in the urinary chloride.

These findings are similar to those found in idiopathic epilepsy.

EFFECT OF NON-CONVULSANT DOSES.

Doses of 1 c.c. of the solution used in this treatment produced little in the way of subjective phenomena apart from palpitations and sometimes vertigo, but as the dose given approaches the convulsant level (4-12 c.c.), as when the earlier doses are being given in a course of treatment, the injection causes a disturbance of the patient's mental state which may last for several hours.

In mild or recovering cases this often takes the form of a severe anxiety-attack in which the patient sits up in a frightened manner, may ask those standing by not to come too near, and may give nervous glances about him as

if in fear of some unseen danger. Consciousness is not lost in these cases and the patient remembers what has happened in a vague way, and the memory is an unpleasant one, which may make him hesitate to have further injections.

In other cases, especially early in treatment, the patient may go into a state of catatonic excitement for several hours, showing inconsequent activity, being alternately erotic and aggressive, smashing crockery, stripping off his clothes, etc. This state has generally cleared up in 5 or 6 hours.

In view of the unpleasantness of non-convulsant doses, it is considered that once the dosage for the individual patient has been established, it is essential that a convulsion be successfully induced after each injection. When there is no fit the mental disturbance seems to last longer, whereas when a fit has occurred the patient usually returns to his previous state within 3 hours at the most of the injection.

TECHNIQUE.

General Purpose of the Method.

The object of the technique is to give the patient a series of epileptiform convulsions without harming him in any way, and this is achieved by giving intravenous injections of the solution to be described, in such a manner that as large a quantity of the drug as possible reaches the vessels of the central nervous system at the same moment. A series of such convulsions are given until a remission is obtained, or until it is manifest that there is no improvement.

The case selected must, of course, be a suitable one according to the criteria of case-selection to be mentioned later.

The patient is put to bed for two days and the pulse, temperature and respiration are taken 4-hourly during that period. A general physical examination is done, and, if the patient will co-operate, an exercise-tolerance test. The urine is examined on two consecutive days, and then weekly throughout treatment. The Wassermann, blood bromide and blood urea are determined and a blood-count is done if necessary. As most of the patients are stuporose, tube-feeding is often necessary, and if enough food is not being taken this should be resorted to without hesitation in order to get the patient into the best possible condition before the treatment is commenced. The blood-pressure is taken and recorded on the patient's chart with the data above-mentioned.

A diagram is next made of the veins in each antecubital fossa, so that the site of each injection can be recorded and the presence of inflammation, hæmatoma, or thrombosis marked in.

If any of the solution has been injected outside a vein, or if there is any bruising, that vein is, if possible, left alone for ten days. If thrombosis occurs, tributary veins of the thrombosed vein are avoided, in order to prevent

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mobilizing the clot. The above precautions are necessary on account of two factors ; firstly, the tendency of the solution, if allowed to be in contact with a vein for long, to cause thrombosis, and secondly, the high pressure at which the solution must be injected, as this tends to cause leakage if the lumen of the needle is not completely in the vein, with consequent paravenous inflammation and risk of thrombosis. These difficulties have been encountered by all the workers seen by the writer, and appear to be almost unavoidable in some cases. The difficulties arise in the great necessity of causing a maximum concentration of the drug to reach the central nervous system at the same moment.

Method of Preparation of the Solution.

The writer has used the 10% solution throughout his experiments, as weaker solutions made it necessary to inject inconveniently large quantities, or at an impracticably high rate. Stronger solutions have been universally abandoned since the Berne-Münsingen Congress, where several cases in which unpleasant sequelæ had occurred were described, and in addition it has been found that if this solution is not injected accurately into the vein necrosis of the surrounding tissues may follow and thrombosis of the vein is very frequent.

In order to reduce the tendency to local reactions the solution has been buffered to pH 8 by the addition of 0.1% of disodium hydrogen phosphate ($\text{Na}_2\text{HPO}_4, 12\text{H}_2\text{O}$), the formula used being :

Pentamethylenetetrazol	.	.	.	10	gram.
$\text{Na}_2\text{HPO}_4, 12\text{H}_2\text{O}$.	.	.	0.1	„
Redistilled water to	.	.	.	100	ml.

This solution is immediately transferred to rubber-capped 25 c.c. vaccine bottles made of resistive glass, soda glass being unsuitable as the pH is apt to be altered during autoclaving. The bottles are then sterilized by autoclave at 120° C. and 15 lb. to the square inch for half an hour. After sterilization samples are tested for pH as a precautionary measure, but these were never found to vary appreciably, indicating that no decomposition had taken place. A number of 5 c.c. ampoules were also supplied by Messrs. Knoll A.-G. and these were found very convenient, but some of the solution is apt to be wasted when ampoules are used, as the dose varies from time to time. As the solution is mildly bactericidal there appears to be no objection to the use of vaccine bottles provided careful aseptic precautions are taken, and their use effects a considerable reduction in cost.

Method of Giving the Injections.

When the injections are given to a group of patients at the same time, it is essential that no one patient shall see another having treatment, and for

this reason the injections were given in small rooms off a main corridor, all the cases being put to bed before the first injection was given.

It was also found advisable for patients having the treatment not to meet one another, especially in the latter stages, as in this way it was often possible to conceal from the patients that they had had convulsions, and to speak to them of the results of the injections as "a period of unconsciousness", which was useful at the stage of recovery, when most patients resented further treatment.

The injections are best given in the morning, no food having been taken except 4 oz. of glucose half-an-hour before. It is necessary to withhold all sedatives with the exception of paraldehyde and hyoscine, as when others are given it is at once necessary to give larger doses of the solution in order to produce convulsions. The writer has found that hyoscine has no inhibiting effect on the convulsions; there seems to be no objection to giving the treatment to patients premedicated with this drug, and this may prove to be a valuable method in the treatment of resistive patients.

The patient is put on a low bed or mattress in the centre of a room, the head being at the lower end of the bed so that the bed-end does not interfere with manipulations. The head is slightly raised by means of a pillow and the whole bed is covered with a mackintosh sheet and blanket. The mouth is examined for dentures.

It is absolutely essential that the needle shall not move once it is in the vein, and as it has to be left in the vein until the fit has actually commenced, the arm must be held very firmly in full extension. The patient is not held in any way, however, until immediately before the injection, as this would add to the apprehension which patients feel before the injections, in the later stages of recovery.

The syringe used is a 20 c.c. Record with an eccentric nozzle and the needle is of $\frac{5}{16}$ bore with a short bevel. Larger $\frac{11}{16}$ needles were used at first as this allowed of rapid injection without using any force, but it was found that veins were damaged more often with this size. The solution, drawn from rubber-capped bottles or ampoules, is put into the syringe before the room is entered, so that the patient does not see the syringe for more than a few seconds. 3 c.c. more than the determined dose are put into the syringe. The tourniquet used to distend the veins is a soft rubber tube, as this can be taken off more quickly than a pneumatic armlet or band and clamp.

As soon as the physician enters the room the arm is straightened out and the antecubital space painted with spirit, and the needle put into the previously selected vein. After blood has been withdrawn into the syringe the needle is pushed, if possible, about 2 cm. up the vein, so that there can be no chance of leakage at the point of entry due to the high pressure at which the solution is injected. The tourniquet is then slackened by pulling on the rubber tube, and the solution is injected as rapidly as possible up to the determined dose. The

remaining 3 c.c. are held in the syringe, and if no fit occurs within 20 seconds this is also injected.

As soon as definite premonitory signs of the convulsion appear, the needle is withdrawn as rapidly as possible. There is little doubt that if the injections are given very quickly, less of the solution is required.

The importance of obtaining a full convulsion with each injection cannot be over-estimated, as if none is obtained the patient is usually anxious and unsettled for several hours, and invariably has unpleasant memories of the event which make him less inclined to co-operate.

The assistant in charge of the mouth and the gag kneels at the head of the bed with her hands on either side of the patient's head. When she has heard the characteristic premonitory cough she waits for the opening of the mouth which usually indicates the onset of the generalized tonic convulsions, and tries to prevent the mouth from opening too wide in order to prevent dislocation of the jaw. As soon as the first shock is over she puts into the mouth a gag made up of three plywood throat spatulas bound round with bandage. This prevents the mouth from closing and obstructing respiration. After the eyes have turned up and consciousness is clearly lost a Hewitt's airway may be inserted, and this has the advantages of preventing the tongue from falling back. The airway must be removed as soon as the cough reflex returns, usually very soon after the clonic stage is over.

It is not usually necessary to restrain the patient during the convulsion, and it is best allowed to take its course unless the patient would otherwise fall off the bed. Unless the patient is in a state of excitement and actively resists treatment a single assistant may be sufficient, though two are preferable, as one can devote her attention to the arm and tourniquet and the other to the jaw and gag.

It is necessary that one nurse remain with the patient for 10 minutes after the convulsion, after which a single nurse may watch two or three patients by walking from one room to another along the corridor. In this way three or more patients may be treated with ease with three nurses, one being left behind to watch the patients after the injections are over.

On awaking from the sleep which usually follows a convulsion, patients are hungry and are allowed to eat a full lunch in bed, and to get up soon after. If co-operative, they usually soon express themselves tired and go to bed early and sleep well without a sedative. Should a sedative be required, paraldehyde is the only one permissible owing to the antagonism of most drugs to the convulsant agent.

The interval between injections varies in different clinics from 2 days to a week. When, in the recovery stages, the patient shows an alteration in mental state after each injection, e.g., excitement, this alteration passes off within 48 hours, when the patients resume their former state, and for this reason the writer gives another injection after that period, i.e., on alternate days.

After remission has occurred it is usual to give three further injections at bi-weekly, and then at weekly intervals in order to prevent relapse.

Dosage.

The dosage necessary to produce a convulsion varies from 4-16 c.c. of the 10% solution. The amount necessary to produce a fit is of considerable prognostic value, as cases in which it is necessary to give more than 10 c.c. rarely remit. With the cases described in this paper it has never been necessary to give a greater single dose than 9 c.c.

The correct dose is found by starting with an injection of 5 c.c. and giving 1 c.c. more each day until the convulsion is produced. The reason for this rapid increase is that if many injections are given without producing a convulsion, anxiety attacks and an unsettled state which is very unpleasant to the patient, may occur. Once a convulsion has been produced, it is essential that another occurs with each injection. For this reason 3 c.c. more than the determined dose are taken into the syringe so that more can be injected if there is no convulsion. The rapidity of excretion is such that this can be done with safety.

Once the patient has started on regular injections every other day it is often possible to reduce the dose by giving 5 c.c. less on each occasion until it becomes necessary to inject the 3 c.c. kept in reserve in the syringe. A chart is kept showing each dose given and its effects.

EFFECTS ON THE MENTAL STATE.

The effects on the patient's behaviour may be divided into the immediate effects brought about by each convulsion, and the total effect brought about by a series of convulsions.

The phenomena immediately following the convulsion have already been described. The patient rarely remembers much of what has happened in the period immediately after the fit. For the rest of the day in stuporose patients there is little change, except that there is usually no difficulty in getting them to take nourishment, even when they have been tube-fed before, and that the extremities, if they have been cyanosed before, are generally quite pink, and œdema rapidly begins to disappear.

Patients who can co-operate say that they are tired and sometimes complain of backache, and are usually glad to go to bed early. On the following morning the patient is almost invariably more active than before, and many of them, even those who have been in stupor, become excited and may refuse to wait to get up at the normal time and will dash out of their beds and run about, often stripping off their clothes. When they have got up they may shout, sing

and quarrel with other patients and quite often make foolish attempts at suicide or wantonly attempt to smash crockery, so that they have to be confined to bed, as they cannot otherwise be controlled. Their conversation at this stage is irrational and they show gross thought-disorder. They are very frequently hallucinated, usually aurally, but sometimes visually, and may be careless or even degraded in their habits. By the next morning the patient has usually returned to his former state, or is somewhat improved. Throughout treatment appetite is invariably good and the bowels usually act several times during the day, though severe diarrhoea is not recorded.

Owing to this tendency to overactivity, it is advisable to find occupation for the patients as soon as they are sufficiently recovered to permit of it, and they often work well on the days on which they are not having their treatment.

In more co-operative cases, a conspicuous feature is the lack of curiosity about the treatment in the earlier stages. This is later frequently replaced, as the thought-disorder improves, by a violent antagonism to it, which is, however, rarely enough to make the patient fight against the injections in a really purposeful manner, though he may refuse at first.

The effects on the mental illness itself brought about by the convulsions take place gradually, as a rule, and transient remissions such as are seen in insulin treatment and after intravenous sodium amytal are not found. von Meduna describes three types of remission: *rapid*, taking place early in the treatment and remaining permanent; *progressive*, by far the commonest type; and *intermittent*, with a series of remissions of increasing length.

Most workers have commented on the uniformity of the changes in the mental state in a great many cases, and especially on a euphoric state which often appears before recovery.

Many patients pass through several phases of schizophrenic disorder during the treatment, a catatonic stupor, for instance, developing excitement and then paranoid ideas with hallucinations, finally becoming euphoric and friendly as the remission comes on, passing in a few days through phases which might take months or years if they occurred at the usual speed of development of a schizophrenic illness.

As will be seen, two of the writer's three catatonic cases passed first into a state of excitement, in which they were co-operative and over-active, then into an anxious phase in which they seemed to dread some catastrophe and were hallucinated for hearing, and then into a euphoric-erotic state in which they welcomed the treatment unmistakably as some sort of sexual experience. Following this they thought more clearly, discussed the treatment with one another and decided that it was unreasonable, though at this time both admitted that they felt far better and attributed their improvement to the injections, and both refused further treatment, though they could always

be persuaded to take it at the last moment. The third patient changed in exactly the same way up to the euphoric-erotic stage, when treatment was abandoned ; she then relapsed completely within a few days.

It is premature to form an opinion on the permanence of the remissions produced. Many of the earlier cases have relapsed and had second courses of treatment ; others have unexpectedly remained well, as often occurs after spontaneous remissions in schizophrenia. The number of relapses in some clinics has considerably shaken the optimism with which the method was first undertaken. Even if the very high rate of recovery at first claimed is not maintained, however, the number of relapses is not sufficient to bring this rate as low as the spontaneous recovery-rate.

RESULTS OF THE TREATMENT.

Well over 1,000 cases have now been treated under well-controlled conditions by von Meduna, Angyal and Gyarfas, Klaesi, Georgi, Wahlmann, Lehmann-Facius and others, and most of this material was at the disposal of the recent Berne-Münsingen Congress. The main conclusions were :

1. Only early cases are improved. The remission-rate falls rapidly with the duration of the illness and practically no cases of over four years' duration have recovered.
2. The catatonic form makes the best response, especially stuporose cases.
3. With selected cases a complete remission-rate of over 70% can be obtained, not including partial or " social " remissions.

SELECTION OF CASES FOR TREATMENT: PROGNOSIS.

The original rules for case-selection laid down by von Meduna have stood the test of further investigation. He stated in his first paper that favourable results might be anticipated in early cases, especially if the onset of the illness is sudden and not developed gradually from an eccentric personality or superimposed on mental defect, and in cases where there is no serious psychopathic heredity. He says that remission occurs only when the individual is constitutionally able to react favourably to the treatment, and assesses this ability to react by the patient's readiness to respond with convulsions to small doses. He has also introduced a hæmatological test of his own, namely the measurement of the extent of the shift to the left of the Arneth and Schilling counts on the leucocytes during the three hours following a convulsion. There is little doubt that the response to a small dose is a good prognostic sign, but the value of the hæmatological test is still in doubt, as the shift is usually of slight extent and does not seem to be specific for induced convulsions.

Discussion as to the type of schizophrenia which reacts most favourably to the treatment has been ambiguous owing to the differing ways of describing clinical syndromes, but there is little doubt that on the classification of Kraepelin the catatonic form reacts best and the paranoid is least affected, in contrast to the results of insulin treatment.

MORTALITY.

The literature available contains reference to four fatalities during treatment. In two of these, gross disorders that had clearly been present before the treatment began were found at autopsy—aortic regurgitation and hypernephroma. The other two deaths were due to pulmonary embolism, and in view of the tendency to thrombosis of the veins it would appear that these deaths could be attributed to the treatment. If, however, precautions are taken against the formation of, and mobilization of clots, such as are described in this paper, the incidence of pulmonary embolism should be very small indeed—certainly less than that encountered after routine surgical operations.

COMPARISON WITH INSULIN SHOCK TREATMENT.

Although shock treatments for schizophrenia of various kinds, endocrine, pyretic and chemical, have appeared at intervals during the last twenty years and have failed to prove their value with large series of cases, or have proved to be of only limited application, it is remarkable that two widely differing methods in insulin shock and pentamethylenetetrazol convulsion treatment should have appeared within a year, and at once commanded attention on account of their high remission-rates in comparatively large series.

The methods are different in many respects, both in the type of case affected and the mental changes following their administration, and even the convulsions which they have in common probably differ in their origin, those following insulin being of the nature of negative release-phenomena, while those induced by pentamethylenetetrazol appear rather to represent a positive cerebral disturbance.

A few workers have studied the two methods in detail side by side, notably Angyal and Gyarfás of Budapest and Klaesi of Berne. The former have attempted to judge the remissions brought about by the two methods by the same standards, and are able to demonstrate that the type of case most benefited by each of the treatments is not the same, the stuporose cases being little affected by insulin but most influenced by convulsion treatment, while the reverse is the case with early paranoid forms.

Their most interesting observation in this connection was that in a small series of early cases treated with convulsions, a remission-rate of 44% was secured, counting only complete remissions, but when the unsuccessful cases

were submitted to insulin therapy 22% more remitted, giving a total remission-rate of 66%. This further supports the view that the two treatments act on different types of case.

The two methods, therefore, are probably mutually adjuvant in the treatment of schizophrenia as a whole, and choice between them will probably depend in the future on the clinical features of the cases, rather than on the relative ease of handling of the methods themselves.

Statistically, convulsion therapy would appear to be the safer method, the general mortality on the cases described at the Berne-Münsingen Congress being about 0.3, whereas in Küpper's series of insulin cases it was 1.5%, though, as James points out, this was at a time when the technique had yet to be improved.

In the case of insulin therapy the patient must be under close observation for a much longer period—6 hours at least—than with convulsion treatment, and the possibility of emergencies arising is much greater; in fact, serious emergencies requiring intracardiac injections, infusions and the administration of stimulants are of frequent occurrence, whereas, even with the rigid technique outlined above, the active period of the convulsion treatment is very brief.

The writer has recently had an excellent opportunity of comparing the difficulties of the two methods by seeing, on the same day, the carefully controlled insulin technique under Prof. Schneider at Heidelberg, where the physician never leaves his patients throughout the day, and has to have every means of restoration ready for the very frequent emergencies which occur, and the convulsion therapy under Dr. Lehmann-Facius at Frankfurt, where a similar number of cases were treated without incident within the space of little more than an hour.

Both methods, however, are both spectacular and dangerous, and unless a rigid technique is maintained avoidable complications are bound to occur even in the simpler convulsion treatment, and the haphazard treatment of unsuitable subjects under insufficient control can only lead to misfortune.

The idea, originated by Klaesi, that the treatments should be combined, and convulsions induced in the course of insulin coma, has received a good deal of support, but at the Berne-Münsingen Congress the general opinion was that this should be avoided on the grounds that enough is not yet known about the methods individually, and that such combination would tend to make an understanding of their mode of action more difficult.

The principal advantage of the combined treatment is that the convulsions can be induced while the patient is unconscious, and the unpleasantness which the non-amnesic patient suffers is avoided. This would appear to be the only justification for combining the treatments at the moment, but the giving of insulin and pentamethylenetetrazol on different days, as practised by James, savours of comprehensive therapy, and must lead to doubt as to which was the successful therapeutic agent, if remission occurs.

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CASE-MATERIAL.

CASE I.—E. R. E—, aged 23; single; domestic servant. Admitted as a temporary patient in a deep catatonic stupor in which she had been for about a fortnight. Remained stuporose for nine months before convulsion treatment was commenced.

Family history.—No gross psychoses among near relatives except that her mother had a menopausal depressive attack lasting three months. A healthy country family, the last generation of which had migrated to London.

Previous personality.—Always a rather quiet girl; no men friends except a tentative affair a few months before the onset of the illness. Worked well and used her leisure in a normal manner, and was not solitary. No previous breakdowns.

Present illness.—During the six months preceding the onset of her illness she had become inclined to complain, had frequently grumbled to the housekeeper about the quality of the food and had become discontented with her work; had spoken about taking up nursing, and had made arrangements to start working in a fever hospital. Two months before her admission to the observation ward, she told her sister that she felt that people would get to know that she had grumbled about the food, and that this would hinder her nursing career.

She also began to eat very little and to be grossly over-conscientious over her work, and a month later said that she had pains in her head caused by the housekeeper shouting abuse at her during the night. After this hallucinations became more prominent and she began to hear her father speaking to her, and she then, quite suddenly, went into a negativistic stuporose state and was admitted to the observation ward; being regarded as non-volitional, she was sent to West Park Hospital as a temporary patient.

State on admission.—In a deep, mildly negativistic catatonic stupor, requiring continuous hand- and occasional tube-feeding. Completely mute and incontinent of urine and fæces. Extremities cyanosed and feet swollen. No abnormal physical state apart from evidence of old tuberculosis at one apex corresponding to a history of having been treated for this when aged 16.

Progress up to commencement of treatment.—Remained in stupor for nine months, requiring every attention. Never spoke a sentence or co-operated in any way and gradually became more resistive.

Physical state at commencement of treatment.—Extremities very cyanosed. Blood-pressure 105/60. Poor air-entry at left lung-apex but no signs of active disease in X-ray. Heart-sounds normal. Exercise-tolerance test impossible on account of mental state. Urine normal. Wassermann reaction negative.

Details of treatment.—Twenty-four convulsions in all. Average dose 5 c.c. of the solution. Two injections were given without producing convulsions and an anxiety attack developed in each case. Complete amnesia for all convulsions. Last three were given at 4-day intervals, after remission was complete; others on alternate days. Total time, 8 weeks.

Progress during treatment.—After the second convulsion, spoke a little and began to feed herself. Œdema of ankles disappeared and veins in the arms became more prominent, making injection much easier. Blood-pressure 106/68.

After the fifth convulsion she became excited and said she was not going

to allow further injections. Was allowed out with her sister, who reported that she was able to converse on general topics.

After the eighth injection she became impulsive and remained so for a week, wandering about aimlessly and saying that something dreadful was going to happen.

After this she developed a paranoid trend, and for a week said that the injections were being given to hurt her heart and chest, and that these had not been properly examined. Blood-pressure 111/68. She then, five weeks after commencing treatment, began to become euphoric and rather erotic, saying that the treatment was giving her new strength, and holding out her arm asking for more injections. At this point she became volitional for legal purposes, and was able to say that she was ill, where she was, etc.

From this time onwards she developed increasing insight; was able to do useful needlework, and gradually lost all evidence of schizophrenic thought-disorder.

At the conclusion of the treatment she was made a voluntary patient and decided to stay for a short convalescent period before returning to work.

Patient's retrospective account.—She was able to remember the period of her stupor, giving the usual account of hearing everything and being unable and disinclined to do anything. She is quite unaware that she has had any fits, but knows that the injections made her unconscious. "It was always the same: I heard a buzzing in my head and felt my right arm come up. I would turn over and feel I was going to say something, and I could feel my mouth opening—and then I would wake up suddenly and find everybody gone, except the nurse at the door." She was therefore amnesic for the short period of anxiety before the fit, for the fit itself, and for the period after the fit when she used to try and get out of bed, and would answer questions put to her. She thus appeared to recover consciousness long before she actually did so.

Her blood-pressure at the conclusion was 122/74.

The above case is the only one which was eligible for treatment by von Meduna's criteria for case-selection. Her prognosis by the usual rules was probably quite good, though her illness had lasted nearly a year. Recovery was complete and she remains well.

The two cases which follow are still under treatment; they are of longer standing than the previous one and would not be considered to have a good chance of recovery according to von Meduna. Nevertheless, the first case made a considerable improvement, but relapsed completely when treatment was abandoned owing to difficulties in injecting the solution.

CASE 2.—D. L. P—, age 21, female; single; no fixed occupation. Admitted to St. Ebba's Hospital twenty months before the commencement of treatment as a case of catatonic excitement and transferred to West Park Hospital under certificate one month before.

On admission was in a mild stupor alternating with outbursts of excitement.

Family history.—This was unsatisfactory as the patient had run away from home, but several members of the family were described as unstable.

Previous personality and illness.—Was a "model child", but later was

often worried over trifles and was regarded as "hysterical", excitable and self-willed.

Five years ago had "nervous debility", and was in a mental hospital for four months in what appears to have been a catatonic state. Since then had been unable to keep in employment, and at the onset of her present illness was in a Salvation Army hostel.

Present illness.—Nothing known of the onset except that she was observed at the hostel to have foolish mannerisms, and is said to have made an attempt at suicide. At St. Ebba's Hospital she was alternately stuporose and excited, and in the latter state she was noisy and violent and had frequently to be secluded.

State on admission.—Unable to give a satisfactory account of herself. Often negativistic and impulsive. Showed marked thought disorder and often spoke unintelligible gibberish, and was evidently hallucinated for hearing. Incontinent of urine and fæces.

Progress.—Remained inco-operative and unemployable, with frequent outbursts of excitement. Was treated for pyelitis.

Physical state at commencement of treatment.—Heart and lungs normal. Blood urea and bromide within normal limits. Wassermann reaction negative. Urine shows a few pus cells and some albumin. Has intermittent glycosuria.

Details of treatment.—Eight convulsions on alternate days. Treatment then abandoned owing to difficulty in giving the injections.

Progress during treatment.—After the first two convulsions she became very excited, and could only with difficulty be kept in bed and attempted to tear up her clothing and smash crockery.

After the fifth convulsion she became euphoric, offered to do some work and made herself very useful, and after this improved steadily for a few days and was able to discuss her case. It was ascertained that she had no memory for the convulsions. At this point it became impossible to give any more injections, and within a week she relapsed completely and has shown no improvement since. Treatment has now been restarted.

CASE 3.—V. C. T—, aged 24, female; single; domestic servant. Admitted three months before treatment was commenced in a mildly stuporose state, having been confused and at times impulsive since the birth of an illegitimate child four months before.

Family history.—Two siblings are schizophrenic. Parents have lost all their money, and have come to live in an untidy flat without employment through sheer inefficiency. They deny all mental troubles in the family, but four out of five members of the family seen by the social worker have been unemployables.

Previous personality.—No previous mental illness, but has given great anxiety to her family and friends through difficulty in keeping employment, waywardness and alcoholism.

Present illness.—Sudden onset four months before commencement of treatment following the birth of an illegitimate child. During pregnancy, however, she thought that neighbours were talking about her. Three weeks after the birth of her baby she ceased to speak and took no interest in the child or in her surroundings. She sometimes became depressed and said the baby had died. She finally attempted suicide by cutting her wrist and was sent to an observation ward.

State on admission.—Lies in bed with the bed-clothes over her head and shows no interest in her environment. Smiles and giggles at intervals and will make only monosyllabic replies to questions. Refuses to eat and requires hand-feeding. Hallucinated for hearing. At times dashes suddenly out of bed without reason. Frequently incontinent of urine.

Progress.—Gradually became less accessible and more stuporose during the three months before treatment.

Physical state at commencement of treatment.—Heart and lungs normal. Wassermann reaction and blood bromide normal. No anæmia; urine normal; blood-pressure 108/70.

Details of treatment.—Twenty-nine convulsions to date. Average dose 5 c.c., given on alternate days. On two occasions on which no convulsion occurred she had very severe anxiety attacks and was unsettled for the whole day. Time taken up to the present, 11 weeks. Dislocated jaw on several occasions, but this was easily reduced.

Progress during treatment.—After the first few injections she became very excited, running out of bed and at times saying that people were going to kill her.

After 10 injections her excitement took on a euphoric tone and she announced that the injections were going to make her live for ever. There was much erotic behaviour, and she referred to the injection as if it were a sexual experience.

After 16 injections she began to work and wrote home for pocket-money and was able to spend it sensibly. She still has impulsive outbursts. Blood-pressure 112/70.

During the next two weeks she became quieter for much longer periods and was able to do sewing and write letters.

Since then her condition has fluctuated considerably and she still shows thought-disorder, though she is able to give a fair account of herself. The treatment is being continued.

Patient's retrospective account.—She is unaware that she has had any convulsions. She appears to have a very unpleasant feeling as she becomes unconscious: "I can hear myself holler out and I feel awful, as if I were sinking down and was not ever going to wake up again, but I feel all right when I wake up." She apparently recovered consciousness rapidly, but was amnesic for the period in which she appeared to be gradually orientating herself, and had no memory for the questions asked of her.

I am indebted to Dr. Norcliffe Roberts, Medical Superintendent of West Park Hospital, for permission to use case-material and publish this paper, and to Prof. Edward Mapother, Medical Superintendent of the Maudsley Hospital, London, and to Dr. W. Rees Thomas, Senior Commissioner of the Board of Control, for advice and encouragement. I wish also to acknowledge gratefully the valuable assistance I have received from Dr. J. S. Harris, Deputy Medical Superintendent at West Park Hospital, in selecting the case-material and assisting with the treatment; from Mr. R. H. Henriksen, Pharmacist at the Hospital, for assistance with the chemical aspects of the subject; and from Miss M. E. Borghorst, who very kindly translated a great deal of the literature.

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