OBSERVATIONS ON CONVULSION THERAPY WITH TRIAZOL 156.*

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ANY TAKERS?

"A new hope has arisen for sufferers in a treatment introduced by Dr. von Meduna of Budapest. He injects a drug which induces fits and causes convulsive shocks." —*Evening Standard.*

From *Punch*, June 8, 1938.

Pace Mr. Punch, we know that there are plenty of takers, and anyone who uses convulsion therapy soon becomes convinced that much good is achieved in one way or another. Moreover, it has become evident that the treatment is not applicable to schizophrenia only; some striking results are seen in depressive states and in atypical paranoid and obsessional cases. This matter is dealt with at length in Dr. Cook's paper. These results, together with the comparative ease of application of the treatment, suggest that it will inevitably be tried out on a very large scale indeed.

Now certain consequences follow from this, which it would perhaps be well to face at this stage. One is that when large groups of patients are being dealt with by a form of treatment in which the same all-or-nothing reaction is produced in all cases, individualization of treatment becomes difficult if not impossible. This is bad for the patient, to whom situational and psychological factors mean much in attaining a good recovery; it is equally bad for the psychiatrist, for whom the treatment may become a mere routine of injections. This need for individualization of treatment has also been stressed by workers with insulin therapy, and several attempts have been made to introduce modifications, and to fit these to particular types of illness.

Moreover, the attitude of the public must be taken into consideration. At present this is favourable; there is a definite demand for the "new treatment" or "treatments", especially for established and chronic cases. But should it become the general impression that entering a mental hospital or clinic means, almost automatically, having to undergo epileptic seizures, we may see an increased reluctance to arrange for the admission of early cases.

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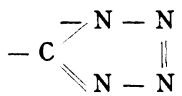
Besides, we cannot absolutely guarantee that convulsion therapy is innocuous. Apart from such complications as fractures, to be dealt with later in this paper, and cardiac changes such as are described by Drs. Dick and McAdam, we have to bear in mind the possibility that repeated convulsions may induce some measure of intellectual deterioration similar to that seen in ordinary epileptics. Though the risk may be well worth taking in severe and chronic cases, it becomes a matter of some importance when dealing with patients who are as yet intellectually well preserved, especially if the nature of their work demands that their intellectual powers should remain intact. Mader has actually described such an effect, though he finds that the mental dullness and impairment of memory pass off in the course of a few months.

Hitherto convulsion therapy has been conducted almost exclusively according to the original technique of Meduna, and there has seemed little possibility of devising alternative methods. As compared with insulin, it has been stigmatized as crude, inelastic and inadaptable to individual requirements. In the work in which we have been engaged during the last three months, we have throughout had in mind the possibility of removing this reproach to some extent.

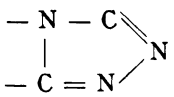
In a preliminary note published in the *Lancet* we gave a brief account of a new drug, triazol 156, which we have used as a convulsant agent in substitution for cardiazol, and which we have found to possess certain practical advantages. The smaller dosage required, and the suitability of the drug for intramuscular and even, as we have since found, for oral use, have made it possible for us to attempt some modifications of treatment. In the short time we have worked with the drug, we have been able to go only a very little way in this direction, and but for the choice of this subject for discussion at the present meeting, we should not have ventured on publication until much later. At the same time, however, we have made a start on some investigations for which the use of the new drug appeared to give opportunities. We have felt justified, therefore, in including some mention of quite tentative work in this paper, as a contribution to the exchange of ideas which is the object of this symposium.

PHARMACOLOGY OF TRIAZOL 156.

Triazol 156 is only remotely related to cardiazol; whereas the tetrazol ring, as seen in cardiazol, consists of four N atoms with a single C atom, the triazol ring has three N and two C atoms, thus:

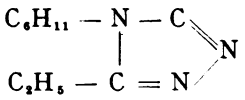


Tetrazol



Triazol

The particular member of the series under discussion has the two side-chains cyclohexyl (C_6H_{11}) and ethyl (C_2H_5) ; its chemical name is 4-cyclohexyl 3-ethyl 1-2-4-triazol, the complete formula being—



The makers, Messrs. C. H. Boehringer Sohn, Nieder-Ingelheim-am-Rhein, Germany, have issued it at various times under the names of "T156", "Triazol-Ingelheim", and "Azoman". As, however, its trade name in this country is still undecided, we are referring to it throughout simply as "triazol".

Behrens, Dinkler and Woenckhaus reported at length on the properties of this substance, which they had selected as the most suitable after testing over a hundred compounds of the series.

In animal experiments they found a marked effect on respiration, which became more rapid and deeper ; the effect was much more pronounced when the respiratory centre had previously been depressed by such a drug as morphine. The effect was produced with only one-tenth the dose required with cardiazol.

There was a slight fall in temperature ; a rise in blood-pressure, which the authors are satisfied is of central origin ; no effect on the isolated heart. Subcutaneous and intramuscular injections produced no local damage to the tissues. Toxic doses induced convulsions in all experimental animals.

The clinical trial of the substance was carried out on patients suffering from various forms of narcotic poisoning, and it was found to act as a powerful antidote. The authors were particularly concerned to test its action when given subcutaneously or intramuscularly in order to produce a slower and more lasting effect, and they found the drug satisfactory when given in this way. They recommend a dose of 0·1 to 0·2 grm. in narcotic poisoning, or one of 0·05 to 0·075 grm. when given as a cardio-respiratory stimulant.

Behrens and his co-workers used the drug, in the same way as cardiazol has been used, as a means of diagnosis in suspected epilepsy, fits being brought on in epileptics with an unusually small dose. They had not, however, considered its theraputic use as a substitute for cardiazol in convulsion treatment.

Use of Triazol in Convulsion Therapy.

Our first experiments were begun in March of this year on patients who were already undergoing treatment with cardiazol, and since then we have treated 45 cases, with a total of over 500 convulsions.

In describing the methods we have used and the effects produced, we are assuming that the reader is acquainted with the technique of treatment with cardiazol, as it has been described by Kennedy, Cook, and Nightingale, and we will therefore touch principally on the differences observed in using triazol.

General Scheme of Treatment.

The orthodox treatment by spaced single convulsions was carried out in the same way as with cardiazol. Intravenous injections were given generally every three or four days. Intramuscular injections were used either when the patient had poor veins, or for experimental purposes. The injections were generally given between 11 and 12 in the morning, the patient having had a light breakfast at 8 a.m. We saw no difference of note in cases where the patient was treated fasting.

We give the treatment in a dormitory with a single row of beds, reserved for the purpose. Screens are placed between the beds, and no patient comes in for treatment until all disturbing sounds from the last patient treated are over. Routine premedication with atropine is used to prevent vomiting.

Sclerosis of the veins, often a troublesome obstacle to treatment with cardiazol, has never occurred with our triazol cases. This is probably because the solution is less irritating to the tissues. In the few instances in which some solution was spilled outside a vein, the latter remained patent and presented a normal appearance by the time the next injection was due.

Dosage.

As was mentioned above, the dose of triazol is much smaller than that of cardiazol. A convulsion can be induced by approximately 0·05 grm. given intravenously, instead of the 0·5 grm. (5 c.c. of 10% solution) needed with cardiazol. The makers supply a 5% solution in ampoules containing 1 c.c. or 2 c.c.; up to now the substance has not been available in bulk solution.

In our series the smallest dose needed to induce a fit was 0·7 c.c. of this 5% solution; the largest dose was 2·8 c.c. The former dose, however, was only effective in two debilitated patients, and the largest doses were only reached by patients who acquired tolerance in the course of their treatment. The smaller range of 1·2 to 1·6 c.c. covers the great majority of initial doses.

Our practice, therefore, is to start with a dose of 1·4 c.c. in the case of a man of average build, using smaller doses for patients below normal weight, and commencing with no more than 0·6 c.c. where the patient appears much debilitated.

If the initial dose fails to produce a fit, a supplementary dose may be tried, as explained below; or else the dose may be increased by 0·1 c.c. each day until a fit occurs. If no symptoms at all are observed, so that it is obvious that the initial dose was much too small, an increase of 0·2 c.c. is permissible.

The action of triazol is somewhat slower, and its excretion probably less rapid than that of cardiazol. Whereas with cardiazol it is usually recommended that the rather bulky injection should be given as rapidly as possible in order to ensure a sufficient concentration in the brain, this is quite unnecessary with

triazol. Of course, owing to the much smaller quantity used, the injection will in any case be completed sooner with triazol.

As the induction period is longer than with cardiazol, one should wait at least a minute before deciding that a convulsion is unlikely to occur. With cardiazol, in such failed cases, it has now been found safe to repeat the injection, giving the same or a slightly larger dose. With triazol this must not be done. Only a small supplementary dose is given, about one-third to one-half the original dose. Thus, if a dose of 1·4 c.c. has failed to produce a fit, one might give an extra dose of 0·5 or 0·7 c.c. The severity or otherwise of the symptoms induced in the absence of the fit will generally give some guidance as to the size of the supplementary dose required. If this is too large, the patient may have a second fit, generally about 5 to 10 minutes after the first one. This, however, does not appear to be harmful in any way, so that it is perhaps better to be bold rather than cautious in estimating the supplementary dose. These supplementary doses are generally effective if given up to two minutes after the original injection.

If the full dose is repeated in the way usual with cardiazol the patient will have a batch of fits, probably four or five. This subject of multiple fits will be considered in more detail later on.

As with cardiazol, a number of patients show increased tolerance to the drug, and the dose may have to be gradually increased during the course of the treatment.

For intramuscular use the dose averages from one and a half times to twice the intravenous dose. In most cases it is possible to do at least one or two intravenous injections first, and to work out the probable intramuscular dose from these. Thus, if the intravenous dose is found to be 1·5 c.c., intramuscular injections may start at 2·5 c.c. If, however, the patient has no injectable veins, and it is desired to give intramuscular injections from the start, it would be safer to begin with only 2 c.c. or less, according to the build and condition of the patient. The relation between intravenous and intramuscular dosage is not constant however; in one of our cases there was a difference of only 0·2 c.c. between them.

It is important to remember that changes in tolerance, generally a diminution, occur after the treatment is discontinued. If, therefore, the treatment has been suspended for a time for any reason, it is not safe to resume it with the same dose as was being used just before the interruption; it is necessary to start afresh with the usual small initial dose. Failure to realize this will lead to an overdosage, resulting in multiple convulsions.

Convulsive and other Phenomena.

With a full dose of triazol a complete major fit ensues, similar to that seen with cardiazol. Some features special to triazol need mention, however.

The pre-paroxysmal or induction phase is longer, lasting generally for from

20 to 40 seconds. During this phase the subjects show very varied reactions. In some the passage into the tonic stage is extraordinarily smooth and silent; in others the onset is much more dramatic and may be accompanied by a typical epileptic cry. Some patients remain silent, and only show their subjective sensations by a frown or a smile; others are able to describe their feelings in a few words; others appear panicky or else euphoric. On the motor side the patient may remain motionless until his fit, or may have more or less violent myoclonic jerks. These phenomena are better observed in the prolonged induction phases obtained by intramuscular injections, and will be referred to in greater detail later.

One pre-paroxysmal phenomenon, the characteristic *cough* almost constantly observed just before a cardiazol convulsion, hardly ever occurs with triazol.

At the onset of the convulsion itself there is often a rapid movement of flexion of the limbs, followed by an equally rapid and very powerful movement of extension. In a number of instances there is a powerful movement of rotation of the arms and thighs also.

Incontinence of urine has been seen in only one patient of our series, and incontinence of fæces has not occurred at all. Seminal emissions, on the other hand, are relatively common.

At the end of the fit respiration appears to be restored more readily and smoothly than with cardiazol. There is hardly any apnœic period, and we have never found it necessary to press on the chest-wall as is commonly done when using cardiazol.

Post-Paroxysmal Symptoms.

After the fit recovery is usually rapid, but here again a variety of reactions may occur. These correlate fairly well with the pre-paroxysmal symptoms, and will be discussed later.

Vomiting was a common and troublesome symptom, coming on from ten minutes to half an hour after the fit. It occurred in patients who had had no food in the morning as well as those who had had breakfast three hours before the injection. We now give all patients $\frac{1}{100}$ gr. of atropine hypodermically about an hour before the injection, and this has completely abolished what to some was a distressing feature of the treatment.

Fractures.

Fractures and dislocations are the most important of the complications that may occur with convulsion therapy, and as we were unfortunate enough to have two instances of fracture in our series, we attempted a search of the literature for previously published cases, in order to arrive at some estimate of the extent of the risk. It soon became evident, however, that the published cases only represent a proportion of the accidents that have actually occurred.

A census of such occurrences, taken by the Inspector of Mental Hospitals for Holland, reveals that their number, while small, cannot be regarded as negligible. The more severe injuries which we have found recorded, and all of which occurred with cardiazol, are fractures of the neck of the femur, including one bilateral case (Kerstens); various fractures of the humerus, again including one bilateral case (Kraus); fractures of the scapula (Briner); dislocations of the shoulder and of the jaw. The last complication is generally regarded as so common and of so little importance as to be almost a normal feature of the treatment, but we have not seen it in any of our cases. In a few recorded instances some disease of the bone was found to account for the fracture (e.g., Perthes' disease or Paget's disease); in others there was no evidence of any bony change.

Our own cases both had fractures of the neck of the femur, and in one the fracture was bilateral.

CASE 1.—Male, aged 41. In hospital for three years, suffering from an atypical psychotic state, with mixed confusional and schizoid symptoms. At the commencement of his treatment he was in a dull, bewildered state, scarcely accessible. His left knee was ankylosed from an old war wound.

He improved from the commencement of his treatment, and became accessible and more active, while his mood changed to one of contentment. At first he appeared to have amnesia for events in his life subsequent to his boyhood, but later this cleared up.

After the eleventh injection he complained of pain in the left thigh, and was found to have a fracture of the neck of the femur. He was transferred to a general hospital for operative treatment. The X-ray picture showed no evidence of bone disease round the site of the fracture.

CASE 2.—Male, aged 35. In hospital for three and a half years, but had had a previous attack four years earlier. A mental defective with a superadded psychosis originally described as depression. On admission was miserable and plaintive, and intensely hallucinated; he had periods of great agitation. He went downhill and became increasingly stuporose when not agitated, refused food and lost 2 st. in weight. After a year he improved physically, but showed no mental change. A similar cycle occurred in the following year, and again he regained his lost ground, his weight rising to nearly a stone more than on admission. No clear evidence of disease was found at any time, and his physical state was satisfactory at the time of commencing treatment. His mental state was one of semi-stupor.

After his first fit he complained of pain in the lower abdomen and thighs, and examination, confirmed by X-ray, revealed fractures of the neck of the femur on both sides. There was no evidence of bone disease.

He was later transferred to a general hospital for operative treatment, and a double osteotomy was performed. He died the next day. At the post-mortem nothing abnormal was found, except for a marked hypoplasia of the heart and smallness of the organs generally. There was no sign of disease in the bones.

In the first case it seems probable that the ankylosis of the knee, by impeding the normal movement of flexion of the hip during the fit, was the main cause of the fracture. We feel, therefore, that all cases presenting abnormalities of this kind should be excluded from the treatment.

The second case is more difficult to account for. Fractures are said to occur more frequently in patients who have been kept in bed for long periods, and

this was the case here. On the other hand his diet had throughout included extra milk and eggs and he had been taking cod-liver oil and malt, so that he is unlikely to have suffered from a vitamin deficiency.

Since these occurrences we have made a practice of turning down the bed-clothes and supporting the patient's hips during the convulsion, but we are unable to say whether fractures can be prevented by any such measures.

Intramuscular Injections: Prolonged Inductions and Twilight States.

When triazol is injected intramuscularly in the doses described above a fit follows after an interval, generally of between ten and twenty-five minutes. To some extent the length of the induction depends on the doses given. But if the dose is increased beyond the amount which produces a fit in about ten minutes a second fit will probably follow, while if the dose is reduced so that more than twenty-five minutes elapse without a fit, the probability is that none will occur.

During the induction phase pre-paroxysmal reactions are seen, the nature of which varies with each patient. Whereas with intravenous injections these are necessarily brief, being soon terminated by the fit, after intramuscular injections they show themselves to perfection and can be studied at leisure.

If a subconvulsant dose is given by either route, the same kind of reaction is seen, but instead of leading up to a fit, the reaction increases in severity for a variable period, which naturally is much longer after an intramuscular injection, and then gradually passes off.

In general, these reactions may be described as consisting of variable degrees of disturbance of consciousness, constituting a " twilight state ", psychomotor changes, changes of mood, and involuntary movements in the form of myoclonic twitchings or jerks. The individual differences in the clinical picture are, however, most striking; each patient appears to have his own type of reaction, and in nearly all cases this remained constant for each, varying if at all only in degree. A study of these reaction types seemed likely to throw some light on epileptic phenomena in general; as we are dealing here with a single exciting stimulus, the individual differences may confidently be ascribed to factors within the subject, for which it might be possible to find biochemical concomitants.

In observing the degree of consciousness during these twilight states, we made use, where the patients were sufficiently co-operative, of several simple tests. The patient was asked at intervals to count, to recite the alphabet, to do simple additions and multiplications. We found the topical method of the spelling bee particularly useful; the patient was given a word to spell just within his capacity, and at short intervals after the injection he was asked to recall the word and to spell it again. Disturbance of consciousness was shown by difficulty and later failure in recalling the given word; by mistakes in spelling, followed later by

complete inability to spell, and later still by failure to understand what was required; often there was perseveration from previous tests. In the more severe twilight states there was complete inaccessibility and stupor verging on coma.

We have found it possible to classify these reactions into groups showing sufficient resemblance among themselves to constitute definite reaction types. At present we distinguish four such types, which we designate the *placid*, the *restless*, the *myoclonic* and the *petit-mal* types.

1. *Placid type.*—A patient of this type shows little obvious disturbance. He lies quietly in bed, and there is little to be seen beyond frequent blinking of the eyelids. The mood is expressed by occasional frowning or smiling. When questioned as to his sensations he makes some brief reply, such as "All right, thanks", or "A bit dizzy". Disturbance of consciousness sets in after a variable interval; in some it can be detected within the first few minutes, and very soon the patient is stuporose and inaccessible and remains so until the onset of the fit; in a few cases there is hardly any impairment, and the patient though quiet and unwilling to converse, is able to respond to all tests throughout the induction, the fit finally occurring quite suddenly and with no premonitory signs.

2. *Restless type.*—A general increase in psychomotor activity sets in soon after the injection. The patient sits up in bed, turns about, constantly changes his position, and generally makes attempts to get up. He becomes talkative and often whistles or sings. The mood may be one of euphoria, with laughter and all the signs of high spirits. Other patients show some anxiety and helplessness, and there is frequently a childish clinging to the doctor or nurse; sometimes this takes on an erotic colouring. The patient's speech and movements may express his psychotic symptoms, and there may be a revival of delusional material which in the patient's normal state may have been in abeyance. Stereotyped phrases may be repeated in a perseverating manner, and the picture may closely resemble that of a catatonic excitement. Co-operation is generally absent in the later stages of this condition, but disturbance of consciousness may be traced by the usual tests in the early stages. A few myoclonic jerks are seen in the last few minutes, and the excitement is interrupted at its height by the onset of the fit.

3. *Myoclonic type.*—In this type myoclonic jerks begin very soon after the injection, and continue at close intervals during the whole induction. Consciousness, on the other hand, may be retained almost until the onset of the fit. It is very striking to watch such a patient, in good touch with his surroundings and able to answer questions, spell correctly, etc., while his activities are being interrupted every few seconds by a vigorous jerk of the whole body. This twitching appears to cause him no distress; often he is unaware of it, and replies "Nothing" when asked what has just happened; at other times he reports casually that he has just had "a jump" or "a jerk", but attaches no

importance to it. Apart from this he may describe some dizziness, as in the "placid" type. Towards the end of the induction, consciousness is lost, the myoclonic jerks become more frequent, and finally they merge into the major fit.

4. *Petit-mal type*.—This reaction has only been seen in one patient. It resembles the myoclonic type in that minor epileptic manifestations begin early, but instead of twitchings they take the form of momentary losses of consciousness, which interrupt the patient's stream of thought. If engaged in conversation, or in performing one of the tests, his speech suddenly trails away into meaningless sounds, his eyes become fixed and staring and he sinks back in bed momentarily. At first the loss of consciousness is so momentary that he is able to pick up the thread of his thoughts, resuming his counting or recital of the alphabet at the point where it was interrupted; later he becomes unable to do this, but goes back to 1 or to the beginning of the alphabet; later still he fails altogether to resume his previous activity. Occasionally, in addition to the interruptions of consciousness, this patient has twitchings as well, and this has become more frequent in the course of the treatment.

These, then, are what we consider to be the main reaction-types. We have, however, a few patients who are less typical, and are for instance to some extent intermediate between placidity and restlessness, the one or the other predominating on different occasions. In a single case we have seen a complete change of type, the patient, previously strongly myoclonic, reacting as a restless type, although the treatment had been identical on the two successive occasions.

These reactions have an obvious parallel in the phenomena seen in certain stages of insulin treatment, either preceding the coma, or immediately after the patient has been awakened by a glucose feed (compare Opalski's "hypokinetic", "hyperkinetic" and "fitty" types), though it does not follow, of course, that they have the same origin.

As was mentioned in a previous section, the state of the patient after the fit correlates approximately with the type of reaction shown by him during the induction. Thus the "placid" patients tend to remain quiet and perhaps sleep for a time after the fit, whereas those of the "restless" type generally continue so on regaining consciousness. The restlessness may even increase, and often takes the form of urgent requests to be allowed to get up, or of actual attempts to do so. Usually this state subsides within half an hour, but occasionally it passes into a more lasting reactivation of psychotic symptoms, similar to that described after cardiazol convulsions.

The "myoclonic" and "*petit-mal*" types generally show no symptoms after the fit, except that on a number of occasions myoclonic twitchings have continued for some time.

With subconvulsant doses exactly the same reaction types are seen, and the same sequence of events occurs in each individual. Recovery takes place

gradually, but the whole process does not take much longer than if a fit has occurred. The fit, therefore, does not cut short the effect of the drug—a fact of some interest, since it is often supposed that epileptic fits have a detoxicating effect. So far as the patient's affective and psychomotor states are concerned, the fit appears only as an incident in the course of a twilight state induced by the drug.

We have made a number of attempts to prolong the twilight states resulting from subconvulsant doses by injecting further small doses at intervals determined by previous experience of the same patient. A short prolongation can readily be obtained, but after the second or third supplementary dose a number of patients have a fit. However, in a few cases we have succeeded in prolonging the twilight state for nearly three hours, with no apparent ill-effects to the patient.

Multiple Fits.

We have already alluded to the induction, by an overdose of triazol, of multiple fits. Our knowledge of this action of the drug was obtained in the first place accidentally, through resuming treatment, after interruption, with the same dose as was used previously. In this case the dose in question was 4·5 c.c. given intramuscularly. The patient had three strong fits within ten minutes without regaining consciousness. Further fits followed, but at gradually lengthening intervals, up to a total of nine within an hour. Luminal was given intramuscularly to a total of 9 gr., but it seems doubtful if this helped in any way to bring about the cessation of the seizures. Between the first few fits the pulse was feeble and intermittent; later, however, it became regular and full. Consciousness was fully regained shortly after the last fit, but the patient remained semi-stuporose for the greater part of the day; this may have been an effect of the luminal. There was a rise of temperature in the evening. No further ill-effects were observed.

The immediate effect on the patient's mental condition was so good that we have deliberately induced multiple fits in other cases. The therapeutic value of this procedure will be discussed later; here we are dealing only with the phenomena observed. We have given doses that have induced sequences of four or five fits, and have found it possible to predict fairly accurately the number of fits that would ensue from a given dose.

On each occasion we have observed that the spacing of the fits follows the same rule, namely that from the beginning the interval between the fits increases in length. Thus, the second fit may occur five minutes after the first, the third after ten minutes, the fourth after twenty and the fifth after thirty. The rule is, moreover, the same whether the drug is given intravenously or subcutaneously. It seems to us of some significance in regard to the mechanism of epileptic fits in general that there should be just this sequence. With a full concentration of the drug in the blood one might have expected either an exceptionally strong

fit, or a succession of fits at brief and equal intervals. Further experiments seem to be required however, before one could hazard any interpretation of the phenomenon.

Oral Administration.

Recently we have begun to try the effects ot triazol given by the mouth. We have succeeded in inducing fits by oral administration of a little over twice the intramuscular dose, and about four times the intravenous dose. Smaller doses produced typical twilight states. We are, of course, unable to say at this stage whether this ratio of doses will prove to be the general rule.

Patients' Attitude to the Treatment: Amnesia.

In our experience with cardiazol we had a number of patients who, after a time, objected more or less strongly to the treatment. This agrees with the experience of almost all other authors. Again we found, in agreement with several recent papers on the subject, but contrary to Meduna's original views, that there seemed to be no relation between the patient's attitude and the occurrence of "failed" fits. We were, however, especially interested in the patients' expressed reasons for their objection. These fell into three groups:

1. Some patients complained of a terrible experience immediately after the injection. "I get an awful feeling of fear" was one of the most explicit descriptions given. "Terrible agony all over" was complained of by another patient, who will be mentioned again later.

2. In others the complaint was of pains in the limbs, back or head persisting after recovery from the fit. Patients were particularly insistent on pain in both arms, mainly around the site of the injections, but not specially severe on the side where the last injection had been given.

3. Lastly, there were patients who were unable to give any grounds for their dislike of the treatment. When questioned, they replied evasively, saying that they were better now and did not require any more, or that they wanted to go home now. These patients appeared to retain a vague unpleasant memory of their experience, which was not clear enough for anything more explicit.

There were, of course, also patients who never raised any objection to the treatment, including some who had amnesia for the whole procedure.

With triazol we have a definite impression that amnesia is more often complete, and that fewer patients retain unpleasant memories. Ot the three grounds for objection described above, the first and second have been virtually abolished. The patients who show reluctance to triazol—and they are few—are practically always of the third, evasive group.

The difference was well shown in the case of the patient already referred to,

who had described agonizing feelings immediately following cardiazol injections. With triazol he was unable to recollect the injection at all: "You came and stood by the bed, and someone put a band round my arm, and then I got a headache which is still there now." He now objected to treatment on account of the headache, but admitted that this was quite different from his sensations with cardiazol.

Even patients who have undergone a twilight state without a fit, and are of the "restless" type, may show a satisfactory amnesia for what at the time seems a severe experience. As has been mentioned above, some patients show euphoria, and this may be carried over into the waking stage, so that what recollections the patient has are entirely pleasant. But even where this is not so and the patient during his treatment appears to be in distress, the subsequent recollection is often *nil*, or at the most comparatively trivial ("going under" or "feeling dizzy").

There is still, we feel, a good deal to be learnt about patients' subjective sensations. Thus one patient, when given triazol intravenously, invariably described sensations as of an electric shock, and was able to report the moment of onset of these sensations before losing consciousness and having his fit. He always remembered these sensations afterwards, though he did not consider them bad enough to want to refuse treatment. After an intramuscular injection, however, which produced a prolonged twilight state with severe myoclonic jerks, he expressed himself as particularly satisfied, and said that he much preferred to take his treatment in that way.

Our conclusion is that triazol is superior to cardiazol in its acceptability to patients, but that it is not perfect in this respect. Possibly further research may lead to the introduction of a convulsant giving perfect amnesia in all cases.

Biochemical and Other Investigations.

The introduction of convulsion therapy has opened up new fields of investigation into epileptic phenomena. These possibilities are increased by the use of triazol, for in the first place we are able, by intramuscular or oral administration, to produce a slow-motion picture of the onset of an epileptic fit; and again, by using subconvulsant doses, to distinguish between those effects which are bound up with the paroxysm and those which are independent of it.

As indicated above, we have been specially interested in the possibility of biological differences corresponding to the clinical differences between the reaction-types. Numerous biochemical investigations which have been carried out on epileptics obviously require to be repeated in this connection. As a beginning, we selected three investigations in which some preliminary results might be expected in the limited time available before this meeting. We are including our findings to date in this paper, but are not yet in a position to draw definite conclusions.

Blood Sugar.

Estimations of blood sugar in connection with cardiazol convulsions have been made by Georgi, by Sorger and Hofmann, by Maurer and his co-workers, and by A. Harris.

Georgi's findings are the best known, and have been extensively quoted. He states that "in the pre-paroxysmal phase the level rises, except in *petit-mal* attacks, when it falls. The intraparoxysmal level shows the effect of a compensatory mechanism ('*Gegenwirkung*' or contrary action), except again in *petit-mal*. After the paroxysm there is a significant rise"; and again, "in every case but one the change during the paroxysm was in a direction opposite to the change that preceded it". He says further that "when no convulsion took place similar but quantitatively less significant shifts were noted".

On the basis of these blood-sugar findings, and of other biochemical investigations, Georgi concluded that "the patho-physiological processes which lead to the epileptic attack after large doses of cardiazol coincide fully with those which we may observe in the first phase of insulin treatment", and other authors have accepted this as signifying that the fits are due to a temporary hypoglycæmia, and as confirmation for their belief that all forms of shock therapy act in much the same way.

It appears, however, that what Georgi called his "intra-paroxysmal" specimens of blood were actually collected "about the end of the clonus, shortly before or after the first deep breath". It seems to us that this stage should really count as post-paroxysmal, and we find it difficult to believe that the finding of a fall in blood sugar at this stage is any proof that the fit has been caused by a hypoglycæmia (or rather by an intracellular change expressing itself as a hypoglycæmia).

Sorger and Hofmann and also Maurer and his co-workers confined themselves to post-paroxysmal specimens of blood, and their results are hardly relevant for our present purpose.

Our own investigations refer to the effects of triazol, and it remains to be seen whether the results would hold good for cardiazol as well.*

Twelve patients undergoing treatment were selected; they included representatives of all four reaction-types. An ordinary sugar-tolerance curve was done on each patient and was ascertained to be within normal limits in all cases. Each patient was then investigated by taking serial specimens after doses of triazol given intravenously (convulsant), intramuscularly (convulsant), and intramuscularly (subconvulsant). Most cases had more than the minimum three investigations, and altogether we have records of 56 investigations on the 12 cases.

As regards the convulsant doses, we found it almost impossible, in agreement with Georgi, to obtain blood from the finger during the tonic stage.

* Since writing this, we have made several control observations, using cardiazol on the same patients, and have obtained the same results.

However, we have had no difficulty in obtaining blood from the lobe of the ear, and after the first few attempts all our specimens were taken in this way. The fits last long enough to make it possible to take at least one specimen in the tonic and one, sometimes two, in the clonic stage. Owing to the longer induction period with intravenous triazol, we have also been able, in most cases, to obtain one, sometimes two specimens before the onset of the fit. Specimens have also been taken immediately after the fit and thereafter at lengthening intervals.

With intramuscular injections the specimens were taken at about five-minute intervals at first, more frequently when the fit appeared to be approaching, and thereafter as with the intravenous cases. With the sub-convulsant doses we proceeded in the same way, noting one of the estimations as corresponding to the maximum effect of the drug.

The table shows some typical readings, and a few characteristic curves are also shown graphically in the charts. In these graphs, in order to show side by side the effects of intravenous and intramuscular administration, we have not adhered to a single time-scale. The time of injection and the time of the convulsion have been taken as fixed points, and the pre-paroxysmal readings have been distributed between these. For the non-convulsant readings we have charted the point of maximum effect as equivalent to the convulsion. This method gives a clearer picture of the general shape of the curves, though this may also be deduced from the control graph provided for Case C.S— (Chart 2) in which the time-scale is accurately shown.

Our findings differ materially from those obtained by Georgi, using cardiazol. We found considerable variation in the shapes of the curves, and these differences correspond to some extent with the type of reaction shown by the patient. In cases belonging to what we have called the " restless " type, the blood-sugar level shows a single rise of between 0·2 and 0·5 mgrm. %, followed by a fall. The maximum point of the rise may occur during the convulsion, or may precede or sometimes follow it (Table, Cases F.G— and R.N—; Charts 1, 2 and 4, Cases C.S— and W.J—). The curve is essentially of the same shape whether the rise has been rapid after intravenous or slow after intramuscular injection. With a non-convulsant dose the same rise occurs, and may reach as high a level as with a convulsant dose. Here again the maximum level may be reached before, during or shortly after the maximum of clinical symptoms. We were unable to find any evidence of a reversal of the curve during the fit, except that, as has just been said, in some cases the highest point of the curve had already been passed when the fit began. In fact, our general impression is that the fit is an irrelevant incident as far as the blood sugar is concerned, it being impossible to deduce from reading a curve at what stage the fit has occurred or whether one has occurred at all (Chart 4).

In the " placid " cases, in general, the graph shows very little change in the blood sugar, there being irregular rises or falls, generally of not more than 0·2%

CASE B. D—.

Date.	Time.	Blood sugar.	Clinical state, etc.
June 11, 1938	11.46	·10	Before injection.
	11.54	·09	
	12.00	·10	
	12.05	·10	No fit. Confusion only. Silent,
	12.15	·11	inaccessible, negativistic;
	12.20	·11	later repeating religious
	12.28	·11	phrases.
	12.35	·11	
June 29	11.32	·15	Before injection.
	11.34	·14	Intravenous injection.
	11.35	·13	During fit.
	11.36	·13	
	11.37	·14	
	11.38	·13	
	11.39	·12	
July 2	11.28	·11	Before injection.
	11.35	·10	
	11.40	·11	As on June 11.
	11.43	·10	
	11.44	·09	
	11.45	·10	During fit.
	11.46	·10	
	11.50	·10	
	12.11	·11	
July 6	11.20	·08	Before injection.
	11.36	·09	As above; negativistic; few twitchings.
	11.46	·09	During fit.
	11.47	·11	
	11.50	·11	Slight restlessness after fit.
	12.00	·11	
July 15	11.40	·11	Before injection.
	11.47	·12	
	11.50	·11	During fit.
	11.51	·11	
	11.52	·11	
	11.53	·11	
	11.59	·11	
	12.08	·12	
	12.18	·13	

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CASE B. D—. *Continued.*

Date.	Time.	Blood sugar.	Clinical state, etc.
July 26	11.45	·09	Before injection.
	11.50	·10	
	11.51	·10	No fit ; confusion only ; usual
	11.53	·11	type of reaction at first.
	11.55	·11	
	11.59	·12	Talkative; somewhat euphoric;
	12.03	·11	confusion only.
	12.10	·11	
	12.34	·10	

CASE J. F—.

May 25, 1938	11.30	·13	Before injection.
	11.40	·13	Placid ; increasing confusion ;
	11.47	·11	rare twitchings.
	11.53	·13	Fit.
	12.36	·13	
June 7	11.10	·11	Before injection.
	11.28	·10	
	11.30	·11	Same reaction, with slight
	11.31	·11	euphoria.
	11.33	·11	
	11.34	·11	
	11.35	·10	During fit.
	11.36	·11	
	11.37	·12	Some restlessness after fit.
	11.41	·13	
June 29	11.30	·11	Before injection.
	11.40	·12	
	11.45	·09	Same reaction.
	11.46	·12	
	11.47	·13	During fit.
	11.48	·13	
	11.50	·12	
	12.10	·12	
July 4	11.57	·11	Before injection
	12.13	·11	During fit.
	12.14	·11	
	12.15	·11	
	12.16	·12	Restless after fit.
	12.24	.14	
	12.35	·12	

CASE F. G—.

Date.	Time.	Blood sugar.	Clinical state, etc.
June 2, 1938	11.40	·10	Before injection.
	11.44	·10	
	11.47	·11	Much restlessness; fumbling;
	11.49	·11	getting out of bed.
	11.51	·13	
	11.58	·15	During fit.
	12.04	·14	
June 11	11.25	·09	Before injection.
	11.20	·11	
	11.32	·11	
	11.33	·11	
	11.35	·11	
	11.36	·12	During fit.
	11.38	·11	
	11.49	·16	
June 20	11.40	·11	Before injection.
	11.48	·12	Quiet at first; "better"; "all right". Then sitting up, fumbling, coughing, restless.
	11.51	·18	
	11.55	·15	During fit.
	11.56	·15	
	12.10	·12	
July 6	11.40	·13	Before injection.
	11.48	·14	Not so much restlessness, but
	12.00	·15	fumbling and picking nails.
	12.02	·14	During fit.
	12.03	·14	
	12.05	·15	
	12.10	·15	
	12.20	·13	

CASE R. N—.

July 13, 1938	11.53	·09	Before injection.
	11.55	·10	Intravenous injection.
	11.56	·11	During fit.
	11.57	·10	
	11.58	·10	
	12.00	·09	
	12.02	·09	
	12.06	·10	
	12.15	·10	

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CASE R. N—. *Continued.*

Date.	Time.	Blood sugar.	Clinical state, etc.
July 16	12.06	·09	Before injection.
	12.25	·09	Too long an interval was allowed before first specimen was taken. There may have been changes during this time.
	12.27	·08	During fit.
	12.28	·08	
	12.30	·09	
	12.35	·11	
	12.40	·09	
	12.45	·09	
July 26	12.14	·11	Before injection.
	12.20	·11	
	12.25	·13	During fit.
	12.26	·13	
	12.30	·12	
	12.40	·12	

Between injection and fit: confusion marked, restlessness, whistling, irrelevant talk.

(Table, Cases B. D—, J. F—). In one of the cases, however, irregular fluctuations were seen, which showed no consistency, and which we were unable to correlate with the clinical picture.

The single case of the "*petit-mal*" type showed a fall in blood-sugar level on each occasion, though not usually a very marked one (Chart 3, Case J. L—). This is interesting in view of Georgi's finding of a fall "in cases of *petit-mal* attack", though of course our use of the term "*petit-mal* type" does not designate the same thing. Here again, however, we found no evidence of a contrary action during the fit.

The findings in the "myoclonic" type were more irregular and inconsistent, resembling the atypical case of the "placid" group mentioned above. Possibly in these cases the alterations in the sugar level are complicated by the effect of the prolonged muscular movements.

The secondary rise coming on some time after the paroxysm, which previous authors have found almost invariably, was seen in a fair proportion of our cases, but not in all, possibly because the estimations were not continued over a sufficiently long time. Marked rises were seen in connection with post-paroxysmal restlessness.

It might be suggested that the primary rises are really due to the emotional condition of the patient, in particular to his anxiety and apprehension, and are not an effect of the drug at all. Against this we have the fact that several

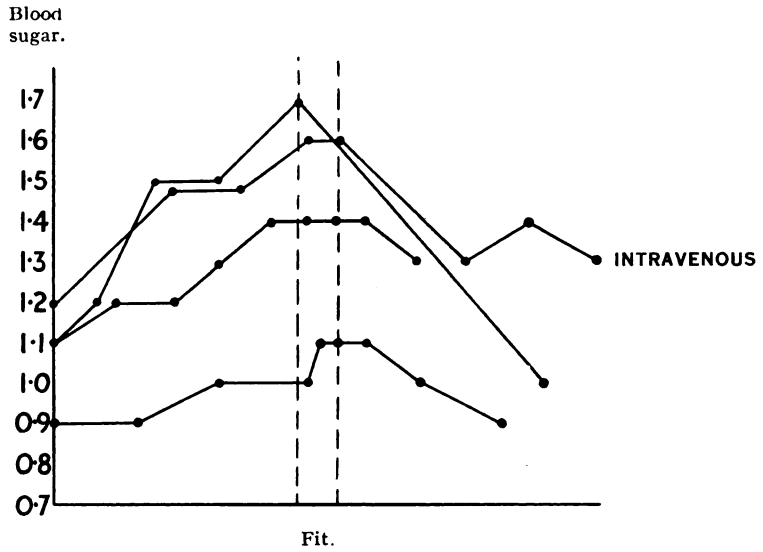

CHART 1.—Case C. S—. "Restless" type. For explanation of method of charting see text. All injections intramuscular except where otherwise stated. Space between vertical dotted lines indicates fit.

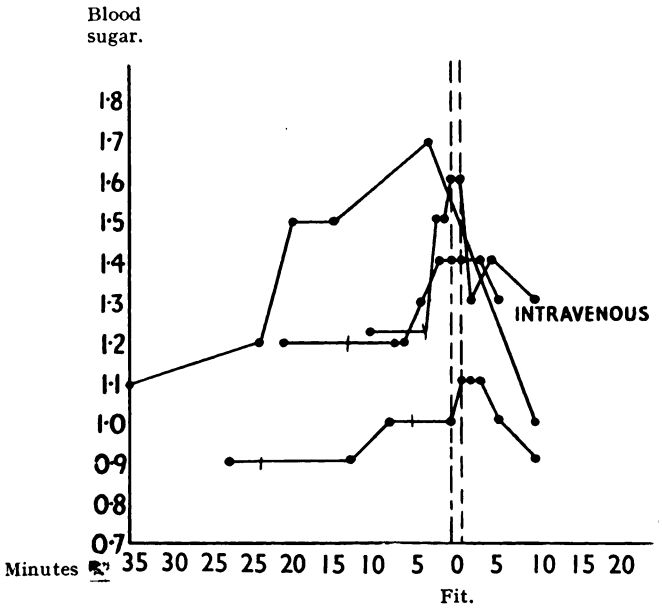

CHART 2.—Case C. S—. Same as Chart 1, but with time intervals correctly shown. They are reckoned backwards and forwards from the fit.

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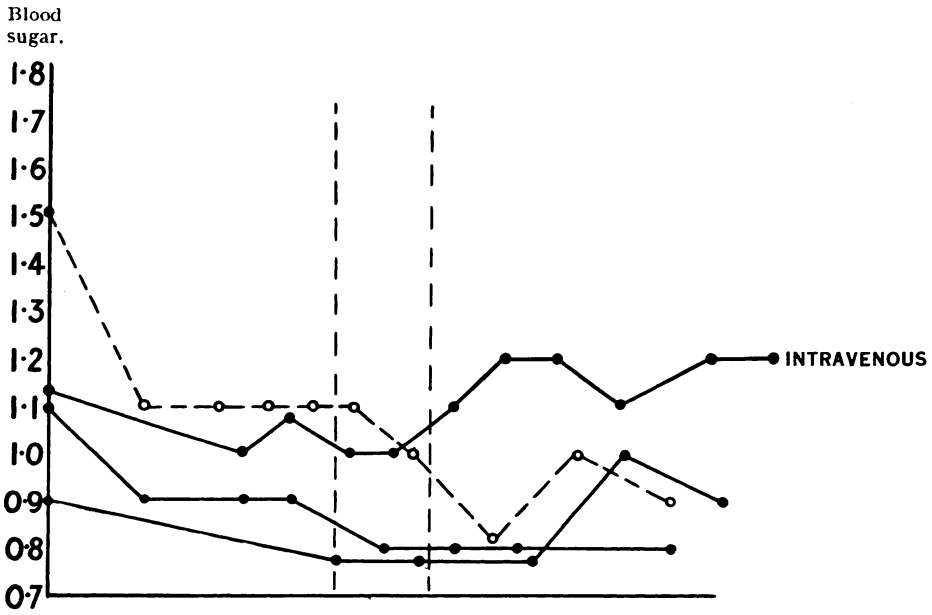

CHART 3.—Case J. L—. "*Petit mal*" type, charted as in Chart 1. Space between vertical dotted lines represents the fit or height of confusion. Continuous line = with fit. Dotted line = without fit.

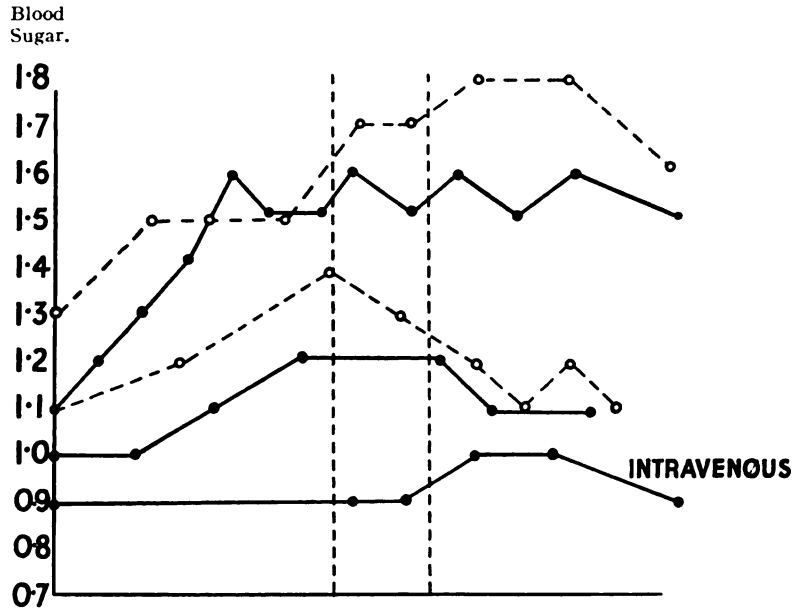

CHART 4.—Case W. J—. Case showing varying degrees of restlessness. The height of curve depended on this, but was independent of the occurrence or not of a fit. Charted as in Charts 1 and 3.

patients who expressed apprehension or were obviously uneasy at the time of their injection showed a normal sugar level ; further, the apprehensive mood in a number of patients passed into mild euphoria as the induction proceeded.

Our general conclusions, then, on this point may be summarized as follows :

There is no evidence, as far as triazol is concerned, that the fits or disturbances of consciousness are produced by " hypoglycæmia ". Such changes in the blood-sugar level as occur are independent of the fit and are not due to muscular exertion (except possibly where there is prolonged myoclonus), nor are they due to emotional changes. There seems to be a correlation between the shape of the blood-sugar curve and the " reaction-type ", and it is reasonable to suppose that the same vegetative changes which govern the sugar level are also factors in determining the patients' reaction.

Serum Proteins.

The importance of a rise in the serum protein level and of a disturbance of the normal albumen-globulin ratio in epilepsy has been emphasized by Frisch. He finds that in epileptics there is a rise in total protein, with a relative increase in albumen. This is in contrast to the findings in all conditions in which processes of cellular " destruction " are taking place, such as tuberculosis, cachexias and inanition states of various origin, etc., in which the ratio is altered in favour of the globulins. He finds that after subjecting dogs to either starvation or intoxication by ricin, either of which causes a rise in globulin, the dogs become relatively insusceptible to electrically induced convulsions. These findings may possibly have a bearing on the suggested antagonism between epilepsy and schizophrenia which formed the original basis of convulsion therapy.

In epileptics Frisch finds that the preponderance of albumen increases continuously in the interval between the fits, and falls immediately after a fit has occurred.

It seems of importance, therefore, to determine whether a similar rise occurs in the triazol induction phase, whether the magnitude of the rise correlates with the occurrence or not of a fit, and whether there is any correlation with the patient's reaction-type.

Up to now we have only been able to obtain estimations on a very small number of cases (4 patients examined once and 2 twice). The findings for total protein were not consistent. In regard to the albumen-globulin ratio, there was a rise in 2 cases of the " restless " type and in the single case of the " *petit-mal* " type ; a fall in 2 cases, both of the " placid " type ; no change in 1 patient of the " myoclonic " type. Two of the patients were examined on two occasions each, with and without a fit respectively, and showed the same result on each occasion. We refrain entirely from drawing any conclusions from these first few observations.

Blood-Pressure.

Blood-pressure estimations have been made on a number of patients during the induction stage, and at intervals during the course of their treatment.

During the prolonged induction following intramuscular administration the pressure remains unchanged as long as there is no twitching or other signs of increased muscle tone. Thus, patients of the "placid" and "*petit-mal*" types show a constant reading during the greater part of their induction.

The findings immediately after the fit vary considerably. The readings seem to depend on a number of factors, the relative influence of which it is difficult to assess. Besides the completeness of muscular relaxation during the estimation, and the amount of muscular effort before, during and after the fit, there is the direct influence of the drug to be considered; according to animal experiments, this is more pronounced if the respiratory centre has been depressed—for instance by morphine.

A brief fall appears to occur immediately after the fit, coinciding with the muscular relaxation and deep breathing, in some cases followed by a rise lasting for half an hour or more. In other patients the pressure is already heightened by the time the pulse becomes palpable again at the end of the "blue" stage of the fit.

During the course of their treatment a number of patients show a gradual rise, amounting to between 20 and 30 mm. Similar observations have been reported with cardiazol. We are not yet in a position to say how long this raised level persists after the termination of the treatment.

Experiments with Vaso-Dilators.

Among theories brought forward to explain the mechanism of epileptic seizures, that of vaso-motor spasm has figured prominently for many years, and it has recently been re-stated in relation to cardiazol convulsions by Reitmann. In experiments on rabbits, Reitmann succeeded in cutting short convulsions induced by cardiazol by means of inhalations of amyl nitrite. Köst produced similar results in patients under treatment. He gave an inhalation of amyl nitrite just before the intravenous injection, with a second dose immediately afterwards. This manœuvre inhibited the fit in every schizophrenic case, but failed to do so in epileptics, and Köst believes that this can be used as a diagnostic test.

It seemed to us that the prolonged induction stage after intramuscular triazol, especially in a patient of the "myoclonic" type, would afford a good opportunity of re-testing the effect of vaso-dilators. In such a patient one might expect amyl nitrite to produce, if the theory were well founded, an immediate

cessation of the myoclonic jerks, together possibly with a more remote effect in preventing the onset of the major fit. It would also be of interest to ascertain at what stage in the induction the effect, if any, could best be produced. In these investigations we have had the advantage of Dr. Reitmann's collaboration. For technical reasons a decisive experiment is not easy to carry out; we have actually succeeded in obtaining the expected result in one or two cases, but only by using large doses of amyl nitrite, which produced dangerous toxic effects.

Modifications of Treatment.

Returning to the therapeutic aspect of our work, we are now in a position to give a brief account of the modifications of treatment which we are trying out.

The most obvious modifications that suggest themselves for any form of drug treatment are reduction or increase in dosage, and the devising of means for prolonging the action of the drug. Modifications on these lines have been suggested and introduced for insulin therapy. In the case of convulsion therapy, alterations in dosage mean the induction, on the one hand, of twilight states without the occurrence of a fit, or, on the other hand, of more than one fit at a time.

1. *Subconvulsant doses.*—It has hitherto been emphasized that in giving cardiazol treatment a fit should be aimed at on every occasion, on the grounds that, should a fit not occur, an anxiety state would be produced, with retention of distressing memories and a consequent bad psychological effect. The "failed fit", in fact, was regarded as something definitely harmful. More recent authors, however, have reported that they were unable to find any correlation between anxiety and resistance to treatment and the occurrence of "failed fits". This has also been our experience with triazol. Moreover, as we have already shown, with triazol amnesia is in any case more often complete, and recollections less often unpleasant. Occasionally patients have shown a definite preference for the subconvulsant doses, given intramuscularly. We are satisfied that the induction of twilight states in this manner has no harmful effect.

Can we go further and suggest that a course of more or less prolonged twilight states, induced by subconvulsant doses, might have a therapeutic effect? If it should appear that the fits really constitute no more than a side-action of the drug, and that its actual therapeutic action lies elsewhere, then it would be rational to suppose that in some cases at least a dose slightly below the convulsant level might be equally beneficial, especially if its action could be prolonged.

The action of a single intramuscular dose has generally passed off within

an hour. By giving small supplementary doses it can be prolonged up to two or sometimes three hours. Triazol given by the mouth will also, it seems, produce a more prolonged twilight state. The length of action of the drug can therefore be varied should indications be found for doing so.

Several of our cases have been given subconvulsant treatment at a majority of their injections, and some of these have shown improvement, but we have still to produce a single case treated throughout by this method and ending in recovery. A single successful case would in any event mean very little, but more significance might attach to success with a relapsing case that had previously been shown to be amenable to orthodox convulsion treatment. We hope to have an opportunity of treating such a case shortly.

The suggestion put forward in this section is therefore unsupported by any definite results, and remains as part of a programme for future work.

2. *Multiple fits.*—Here we are on slightly surer ground. Whether we believe that fits are essential to the treatment or not, it is reasonable to suppose that some patients might benefit by a more intensive action of the drug, or a greater degree of shock, than is represented by a single convulsion. The question is whether such treatment can be given with safety. Our observations, given in an earlier part of this paper, show that an increased dose of triazol does not lead to *status epilepticus*, but to a definite number of fits spaced out at increasing intervals, and that four or five fits can be induced at one time without any apparent ill-effects, except that the patient may remain somewhat dull and retarded on the day after the treatment.

As to the therapeutic effect, we have the following observations :

The patient mentioned previously, in whom a sequence of nine fits was accidentally induced, showed a greater improvement after this than after any single convulsion.

Another patient, who had previously had a course of cardiazol with some success but had relapsed, and on whom an ordinary course of triazol was having no effect whatever, was given an increased dose, producing four or five fits, on three successive occasions at intervals of a week. He showed marked improvement after each treatment, though he relapsed towards the end of each week. Treatment at more frequent intervals was not considered justifiable in view of his general physical state.

A third patient is a schizophrenic of a relapsing type, the relapses, without special treatment, generally lasting from six to eight weeks. On two occasions these relapses were cut short by four injections of triazol, each producing a single fit. At his next relapse he was given a larger dose, which was followed by four fits. This resulted in an immediate improvement, and no further treatment was needed to maintain him in a state of temporary remission.

It seems, then, that multiple fits may have a place in treatment, in cases, for instance, who fail to benefit from single-fit treatment, or in acute or resistive patients in whom an immediate effect would be desirable.

Results of Treatment.

As regards results of treatment, we have little to add to what was said in our original communication. Our series is too small for any figures to be of value in making a comparison between triazol and cardiazol. This must be left to those who dispose of a larger material, including more early cases. Moreover, the published figures for cardiazol are already so divergent that an exact statistical comparison would hardly be possible. We believe however that, using triazol by the orthodox technique, similar results can be expected to those obtainable with cardiazol. We have had a fair number of dramatic improvements, some leading to discharge; other patients benefited more gradually; some have relapsed, and a few have shown a change of phase only, always in the direction of a more active type of psychosis.

Summary of Advantages of Triazol 156.

In our first communication we summarized the advantages of triazol 156 as follows: the lessened unpleasantness of the treatment to the patient; the smaller dosage, and the ease with which failure to induce a fit can be rectified by a supplementary dose; the elimination of venous sclerosis; and the possibility of intramuscular use in cases where intravenous injections are impracticable. To-day we would add that oral administration promises to be as practicable as injection; and further that with triazol, modifications of treatment are possible, of which we have suggested two forms. Should these or other modifications prove of value, it would be a real step towards that individualization of treatment to which we referred at the beginning of this paper.

Finally we believe we have shown that the use of triazol affords opportunities for numerous investigations into both schizophrenic and epileptic phenomena, a few of which we are now pursuing, while others we hope may be taken up by other workers.

We have to thank Dr. G. A. Lilly for permission to make use of the clinical material; Dr. S. A. Mann for carrying out the serum protein estimations; and the pathological assistants and nursing staff at Cane Hill Hospital for their help. The manufacturers of triazol 156 have continued to supply us with the substance for our clinical trials and experiments, and to them also our thanks are due.

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