Occasional Note.

TRIAZOL *v.* CARDIAZOL.

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Introductory.

This communication, notwithstanding its title, does not pretend to be anything in the nature of an exhaustive comparison of the respective merits of triazol and cardiazol in the convulsion therapy of schizophrenia.

That comparison has already been adequately drawn by Walk and Mayer-Gross in a preliminary report on the use of triazol 156, published in the *Lancet* (1) and in a later, more elaborate paper in the *Journal of Mental Science* (2).

These workers were the first to use triazol for producing fits in the convulsion therapy of schizophrenia, and it was as a result of reading their original report in the *Lancet* that we began to use this drug in August, 1938, not as a substitute for cardiazol in every case under treatment, but side by side with it, so that we had two small series of cases simultaneously receiving convulsion therapy with the two substances.

Although neither series was sufficiently large to warrant the drawing of statistical conclusions of any particular value, we nevertheless feel that an account of some complications encountered in individual cases and a description of some minor divergencies from the classical findings of Walk and Mayer-Gross may be of interest, more particularly as we note that cyclohexyl-ethyl-triazol, under the trade name of "azoman", has now been put on the market, and consequently is likely to come into more general use in this country.

Cardiac Complications.

Our first case was chosen because of its catatonic features, and triazol therapy was instituted more in an attempt to ameliorate the nursing difficulties incidental to the catatonia than in the hope of achieving a successful therapeutic result on the psychosis proper. It was that of a male, aged 30 years, with a history of nearly four years' duration of psychosis which had progressed to a condition of resistive stupor, with absolute mutism and persistent refusal of food. We have to admit that such a chronic patient, who had been confined to bed and tube-fed over a long period, was not the most ideal subject for the treatment. The main interest lies in the dramatic effect of a few injections of triazol on the catatonia, and on the cardiac muscle.

Treatment was commenced on August 17, 1938, by the tentative intravenous injection of 1·5 c.c. of a 5% solution of triazol. He had a major fit within twenty seconds, which left him very collapsed, and was followed by a second rather less severe seizure some fifteen minutes later. After this he was very shocked, practically pulseless, with sighing respiration and restlessness, great pallor, etc. He was able to swallow sips of neat whisky, and rallied on the administration of strychnine and digitalin.

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On recovery he was quite accessible mentally, and gave a lucid description of the intense weakness, coldness, feeling of tightness round the heart, præcordial pain, abdominal discomfort and other anxiety feelings he had experienced following his recovering consciousness after the first and second fits.

The really dramatic sequel, however, to this, his first and probably somewhat excessive dose of azoman was the way in which he began to take food voluntarily in the afternoon and continued to do so next day; this, after three years and eight months of uninterrupted tube-feeding.

In spite of these definite warnings that his myocardium was not all that it might have been, we were very reluctant to discontinue the treatment there and then, more especially as it seemed to be having such beneficial results on his mental condition. Accordingly, six days later, when his heart-muscle appeared to have recovered its tone, and to be again in a reasonably good condition, he was tentatively given 1 c.c. of azoman. This had to be supplemented by ·3 c.c. as it failed to provoke a fit after a reasonable interval. A good fit thereupon resulted, but was again followed by much shock and collapse, which was this time also promptly controlled by strychnine and digitalin.

He had meantime been taking all his meals well and mentally become more pliable and accessible, so it was decided that he could just about tolerate weekly injections provided they were graded down to the very minimum necessary to provoke a major fit.

Consequently, seven days later, he was given a third injection—of 1·2 c.c. This resulted in the most satisfactory fit so far, with comparatively minor after-effects. A note was made that strychnine and digitalin seemed to control the unsatisfactory heart-action which followed the fit in a satisfactory manner, and, it was thought, should form a routine feature of future therapy in his case.

On the next day, however, his heart was beating at the rate of only 34 per minute, and a definite re-duplication of the first sound was elicited between the apex-beat and the sternum. These signs clearly showed the presence of heart-block, and, of course, resulted in our discontinuing the treatment forthwith.

He has now quite recovered from the heart-block, and has improved appreciably both mentally and physically, and, seeing that he has since taken all his meals well, it may perhaps be claimed that the therapy has justified itself.

Dick and McAdam have reported a somewhat similar cardiac complication which occurred equally early in the course of cardiazol therapy (3).

This patient displayed great anxiety and apprehension in connection with the reception of his second and third injections, but, although this emotional re-awakening was in interesting contrast to his stuporose state prior to the first injection, we cannot legitimately claim it as an exception to the rule that triazol does not provoke the antipathy towards the injections so often found with cardiazol. We realize that the anticipatory terror, in this case, was more likely due to the definite subjective sensations of a cardiac origin which the patient was able to describe to us so vividly, and which appeared to have many of the attributes of an attack of angina pectoris.

Another apparently healthy male adult in our triazol series, who tolerated his first two injections splendidly, disappointed us by developing a distressing præcordial pain after the third dose of 1 c.c., and, as this symptom persisted for several hours, and was accompanied by tachycardia and extra-systoles, with evidence of enlargement of the heart, the treatment had, perforce, to be discontinued. This was all the more unfortunate as even these few injections had resulted in a marked mental improvement.

From the point of view of possible cardiac complications a third case is particularly interesting. It seems to indicate that such complications are more likely to arise from medication with triazol than with cardiazol. The patient was a robust married woman of 25 years. She was started on cardiazol therapy on January 2, 1939, and had four injections of this drug without the slightest suspicion of any ill-effects on the heart-muscle. There was the greatest difficulty, however, in getting into her veins, and, entirely on this account, it was decided to employ

triazol intramuscularly. The first injection was uneventful. While the second produced a satisfactory fit in fifteen minutes, she was noticed to be very pale after it, and the pulse-rate presented rather disturbing features. Five minutes after the injection the rate was 104 per minute; ten minutes after the injection it was 120 per minute; and immediately after the fit it dropped to 96, and the heart showed some extra-systoles. It rose again in a few minutes to 104, and five minutes after the fit, with the patient fully conscious, the pulse-rate was again 120 per minute. This fluctuating type of tachycardia persisted for thirty minutes after the seizure was completely over, and thereafter there appeared such definite signs of myocardial weakness that we decided against further convulsion therapy.

We have, perhaps, been rather unfortunate in the myocardia possessed by some of the patients we chose for treatment, but, apart from this aspect of the matter, the frequency with which we found pulse-rates of over 100 per minute as long as thirty minutes after the injection of intravenous doses of triazol was striking. By contrast we have never found tachycardia to persist for longer than eight minutes after a cardiazol fit, this being pretty much in keeping with Meduna's observation that "the pulse usually returns to normal within five minutes after the attack" (4).

This important difference in action of the two drugs deserves to be stressed, and is doubtless due to the slower rate of excretion of triazol. The length of time taken by a convulsant dose of triazol to be excreted would appear to be at least half an hour after an intravenous injection, and, during this time, the heart is beating at a much accelerated rate in the great majority of cases. For this reason alone we are convinced that triazol is more likely to bring out any hidden weakness of the myocardium, and to lead to cardiac complications, than is cardiazol. For that reason, too, we have now come to regard cardiazol as the medicament of choice for convulsion therapy in any case where there appears to be the least reason to suspect the integrity of the heart-muscle. From every other point of view we have formed a strong predilection in favour of triazol.

Cardiazol and Triazol Contrasted in the Same Patient.

One of our patients received 31 injections of cardiazol with 30 fits, and this course, after an interval of eleven days, was followed by 24 injections of triazol, resulting in 24 fits.

She was aged 25, and had been ill for four years prior to treatment. She had been intermittently refusing her food over a period of eight months, and was in a condition of deep catatonic stupor. On April 29, 1938, she had had an epileptiform seizure, after which she had improved a good deal temporarily—took her food voluntarily, and did some work in the garden. This phenomenon suggested that she might be a suitable subject for convulsion therapy.

The first injection of cardiazol, given on July 22, 1938, partially aroused her from her stuporose state, so that she spoke rather freely and rationally. The day after the third dose she was able to occupy herself at sewing and reading, she wrote a good letter to her mother, and partook of all her meals.

These improvements were only temporary, however, and she relapsed into catatonic stupor in a day or two. Nevertheless she improved steadily with subsequent injections up to the twenty-first, given on September 16, 1938, and she was then much better mentally, and capable of doing good work in the Occupation Therapy Department, going to church, and occasionally into town to the cinema.

So far she appeared to have complete amnesia for the period of the seizure, and never showed the slightest fear or apprehension about the injections. Thereafter she developed a very obvious dislike and fear of them, and used to start screaming as soon as she saw the needle. This was quite independent of the occurrence of a "missed" fit—actually the one and only "missed" fit was a result of the twenty-fifth injection, given on September 29.

The net result of 31 injections of cardiazol, producing 30 fits in this patient, was that she made a very considerable improvement during the course of the treatment,

but relapsed completely soon after its cessation. She had improved a good deal physically, however, and menstruated for the first time for a year.

On October 28, 1938, a course of azoman injections was begun, and an opportunity was afforded of making some comparisons between the action of this drug and cardiazol given over a long period in the same patient.

The dosage necessary for fit-production varied between the narrow limits of 1·3 and 1·5 c.c. of the 5% solution.

The induction phase was generally longer than with cardiazol, varying between forty and ninety seconds. Exceptionally the twenty-third fit supervened four seconds after completing the injection of 1·5 c.c.

On one occasion, when the onset of the seizure was delayed for the unusually long interval of ninety seconds, powerful clonic movement of the limbs were noted before the seizure proper commenced. This phenomenon was never observed with cardiazol.

We may mention here that induction phases of as long as four minutes have been experienced in a patient we are at present treating with triazol.

In keeping with the longer pre-paroxysmal phase, and doubtless because of the less rapid destruction and excretion of the drug, the return to normal after the fit was invariably much longer than with cardiazol.

Rigidity of the extensors and internal rotators of the limbs, persisting for several minutes after the clonic movements of the third stage of the fit had completely ceased, was repeatedly observed in this and other patients with triazol, never with cardiazol.

Confused " twilight " states of twenty minutes' duration were quite common after the seizure was entirely over.

Post-paroxysmal restlessness and excitement were a feature of triazol therapy, which contrasted with the quiet demeanour when cardiazol had been used. The restless and excited state exhibited by this patient after a triazol fit reminded one forcibly of a similar condition often found in the pre-comatose phase of insulin shock.

Myoclonic twitchings of varying degree, never seen after cardiazol, were a frequent post-paroxysmal finding in this patient. After the twenty-fourth fit, strong spasms of the sterno-mastoid muscles repeatedly occurred so that the head was jerked forward in rather a distressing manner. This condition persisted for twenty-five minutes, and led us to discontinue the therapy at this stage, as it was feared that some more lasting form of cerebral irritation might be resulting from the long series of seizures.

It was hoped that the anxiety phenomena associated with injections of cardiazol in this patient might be absent when triazol was substituted, but, after eight injections had been given without any signs whatever of dislike or apprehension, she stated, after the ninth injection, that she hated them because they caused such an unpleasant sensation of fear soon after they were administered. This quite definite dislike and anxiety in connection with triazol was also shown by two other patients in that series. It was never, in our experience, associated with the occurrence of a " failed " fit, but occurred quite independently of them.

The subsequent course followed by this case would appear to lend colour to the warning uttered by Walk and Mayer-Gross that " 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 ". At the same time it clearly bore out their quotation of Mader's observation that " the mental dullness and impairment of memory pass off in the course of a few months " (5).

This patient had 30 convulsions with cardiazol, followed by 24 with triazol. The immediate result was certainly very disappointing. Her mental condition generally did not appear to have been made *worse* by the therapy, but there did seem to be some degree of intellectual deterioration, mental dulness and impairment of memory superadded to it. This is clearly shown by the patient's occupation chart, on which the therapist recorded an inability to remember the number of stitches to be made in knitting and such-like lapses of memory, as well as some

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interesting examples of apraxia. These epileptoid manifestations gradually disappeared, however, and the patient is now stabilized in a reasonably good remission, and has become a useful and skilled member of the embroidery class in the occupation therapy department.

This case has been quoted at some length because, as well as affording a comparison between cardiazol and triazol, it appears to show that the full benefit from convulsion therapy may take some months to develop, and because it illustrates the following good results, apart from recovery, which may be expected from the therapy, even in chronic cases, and particularly, we think, in catatonics:

(1) Refusal of food may be favourably influenced by even a few injections of cardiazol or triazol, and, from our limited experience, we feel that these drugs are well worthy of trial in cases of tube-feeding, and that a subnormal physical condition need not be too absolute a contra-indication. For a debilitated patient the dose would naturally need to be reduced in proportion to the deviation of the patient's weight from the normal.

(2) Improvement in appetite and in physical appearance and increases in weight were constant features of the cases in our series, even those in whom the mental state was entirely unaffected. Gains in weight of 5–7 lb. in a week and 1–2 st. during the course of treatment were common.

(3) Convulsion therapy seems capable of making many resistive, catatonic and stuporose patients sufficiently accessible and extroverted to become occupiable. We had a striking case of a woman, aged 40, who had been four years in hospital without ever attempting to occupy herself. She had been patiently tried out in every department, and had had a course of pyrexial treatment with sulfosin without result. She was mute and entirely inaccessible when treatment was started, but, after eleven injections of cardiazol, she was talking freely and working in the occupation therapy department. Here, after 25 fits, she is now not alone actively employed at rug-making, but is teaching this craft to other patients.

Points in Technique.

(1) In the beginning we found the gradation of dosage of triazol rather difficult with ordinary syringes, on account of the relatively small dose required to produce a convulsion. Experience soon overcomes this difficulty, however, and the dosage can be very accurately adjusted by the use of a 2 c.c. tuberculin syringe, graduated to $\frac{1}{10}$ c.c. The convulsive "threshold" of the drug can be brought to a very fine point indeed. We are at present treating a patient who fails to have a fit with 1·2 c.c., but has a completely satisfactory seizure with 1·25 c.c.

(2) We have found that the procedure recommended by most workers with cardiazol of loosening the tourniquet only when most of the injection has been administered (6) tends to make the convulsive dose of triazol higher, and to delay the onset of the fit. We are unable to suggest any likely explanation of this unexpected finding, but, having encountered it accidentally, we have carefully "checked-up" on it, and are now convinced of its accuracy. We had adopted the recommended cardiazol procedure for all our earlier injections of triazol, but, having once found a more prompt fit to occur with ·5 c.c. less than the usual dose in a recalcitrant patient when the rubber tubing was released unintentionally before the injection had been started, we afterwards modified our injection technique accordingly, and recommend this modification as being entirely satisfactory.

(3) We are unable to endorse the observation of Walk and Mayer-Gross that, unlike cardiazol, the recommendation to give the injection of triazol as rapidly as possible is unnecessary. In our experience, rapidity of injection *can* decisively influence the promptitude with which a fit may be induced by triazol, and a very rapid injection can lead to a reduction of the "fit-provoking" dose. The essential difference, we believe, is that a very slow injection of a normally convulsive dose of triazol will not result in a "failed" fit, as may occur with cardiazol.

(4) The depth with which injections of triazol are introduced into the muscle

would appear to influence the duration of the induction phase of the fit when this drug is given intramuscularly. For instance we have repeatedly found, in the same patient, that the same dose will induce a seizure in five minutes when injected as deeply as possible into the deltoid muscle, as will take fifteen to twenty-five minutes to provoke convulsions when the needle is inserted only half as deeply. If this finding should be corroborated by other workers, and proved to have universal application, very deep intramuscular injections would have the decided advantage of appreciably lessening the tedious " waiting " periods incidental to intramuscular fit-induction.

(5) We have had three cases in a series of fourteen treated with triazol where it was necessary, as a routine, to press on the chest-wall to re-establish respiration at the end of the fit. This contrasts with Walk and Mayer-Gross's experience with a much larger series in whom they found hardly any apnœic period, and never any necessity to adopt this manœuvre.

Summary.

Fourteen patients have been treated with triazol and eleven with cardiazol over a concurrent period of eight months, this system enabling a close, " day-to-day " comparison of the action of the drugs to be drawn.

One patient has been given 30 fits with cardiazol, followed, after a short interval, by 24 fits with triazol, and a comparison is made between the action of the two drugs on the same patient.

In three cases in the triazol series cardiac complications were encountered. In one case these were not altogether unexpected, as the patient had been confined to bed for a long time, and had been tube-fed over a period of three years and eight months. The other two had apparently healthy myocardia prior to treatment (electrocardiograms were not taken). It is suggested that triazol imposes a greater and more prolonged strain on the heart-muscle than does cardiazol.

In spite of this we have come to prefer the use of azoman for most cases, and find ourselves in entire agreement with the claim of Walk and Mayer-Gross that it possesses several practical advantages over cardiazol as a convulsive agent.

Certain beneficial effects, short of complete recovery, which are likely to result from convulsion therapy generally are discussed.

Minor details of technique are referred to.

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