CONVULSION THERAPY BY AMMONIUM CHLORIDE.

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IT is generally agreed that there are many objections to the use of cardiazol and azoman (triazol) as convulsants. The treatment is generally disliked and the injections are attended by much apprehension. There is frequently amnesia, though usually of a temporary nature. There may be some actual damage to the brain, fractures are not infrequent, and other complications sometimes occur. Old tuberculous lesions have been reactivated and deaths have occurred in *status epilepticus* from the use of azoman.

For these reasons much interest is attached to the description by Bertolani (1938) of the production of epileptiform convulsions by the intravenous injection of a solution of ammonium chloride. He believes that the irritant effect of the solution on the walls of the blood vessels causes an acute vaso-motor action. Good clinical results are stated to have been obtained in cases of schizophrenia by the use of this drug.

Mazza (1938) treated 27 acute cases of schizophrenia in this way. 22 per cent. showed a complete remission, 15 per cent. a marked improvement, and 63 per cent. were unaffected. The number of convulsions given varied from 4 to 19.

It was hoped that in ammonium chloride a drug had been found which would avoid some of the ill-effects associated with the other convulsants and give comparable clinical results. Although the drug fulfils neither of these wishes completely, it appears that it may still be considered as a useful accessory in this form of treatment.

The following investigations were nearly all made on female patients. No sedatives are given in the previous twelve hours, the bowels are opened on the morning of treatment and breakfast is withheld.

The same procedure for avoiding fractures and dislocations is used as in other convulsions, except that the jaw need not be held and no gag is necessary. The patient wears nothing but knickers. The bedclothes are completely removed in the period of hyperpnoea and only replaced after the convulsions cease. A hard pillow is used and the patient lies flat on her back before the

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injection is given. No one touches her during the convulsions, and if there is any likelihood of her falling from the bed, all that is done is to raise the edge of the sheet. The writer is in agreement with Good (1940) in believing that certain of the recorded dislocations and fractures of the limbs are due to restraint of the patient and not to the convulsions.

Ten c.c. of a 5 per cent. solution of pure ammonium chloride are given through a large needle as rapidly as possible. A No. 10 needle has been used on the easier and a No. 12 on the more difficult veins, with little difference in the results. If a vein in the ante-cubital fossa be used, the forearm must be rapidly flexed and extended a number of times directly following the injection to avoid thrombosis. If the vein is lost there is pain of a smarting or burning character. Occasionally the patient complains of cramp or a feeling of uselessness in the arm, which disappears on further movement. The blood does not coagulate and may be aspirated into the syringe.

The Fit.

There are four stages to the fit, which may be termed (1) preliminary, (2) hyperpnoeic, (3) convulsive, (4) recovery.

(1) In about five seconds after the injection the patient sometimes complains that she is "going off," and may become rather red about the face. She is in a state of apprehension, often screws her eyes up or clutches at the bedclothes. There is no cough. One patient complained of a bitter taste before she lost consciousness.

(2) Ten to 20 seconds after the injection there is hyperpnoea and a simultaneous dilatation of the pupils with a deviation of the head and eyes. The pupils do not react to light and they are often oval and eccentric. The corneal reflex is lost. There may be a lace-like blotching about the neck and upper chest, as is seen with cardiazol. The face may be slightly congested, sometimes with circum-oral pallor. The rather objectionable odour noticed with the other convulsive drugs is absent. This stage lasts from 10 to 20 seconds.

(3) The hyperpnoea and head deviation are suddenly replaced by convulsive movements, varying largely in degree, but never approaching the severity of those seen with cardiazol or azoman. In the mildest form there has been a twitching of the muscles about the lower jaw, but there may be choreiform movements of the hands and forearms. Usually there is abduction of the arms, movement of the forearms and hands, and an accompanying flexion and extension or twitching of the legs. In the severest form the body has been thrown into the position of stretching with extension of the legs and spine, and abduction of the arms with flexion of the forearms. In some cases this has been followed by relaxation and repetition of the contractions, ending with a localized clonus of the legs. The pupils return to normal at the beginning

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of this stage, and the eyes are no longer deviated. There is no cyanosis, but sometimes pallor. Incontinence of the urine or faeces has not occurred. In the male there is no seminal emission. This stage lasts 10 to 20 seconds, then consciousness is regained before the muscular movements have ceased.

(4) The position in which the convulsion ends is maintained for two or three seconds; the conduct is then variable. In many cases there is an attempt to sit up or to get out of bed, and usually there is bewilderment. The patient asks such questions as "Where am I?" "What are you doing?" or "What is the matter?" Two used to regain consciousness with a beatific smile, and in several an erotic phase followed the convulsions. Mild confusion is not infrequent, but some patients become quite rational for perhaps half a minute before gradually fading into their abnormal mental state. Sometimes there is uncontrolled weeping, which is often amenable to suggestion. Increased suggestibility is one of the characteristics of this stage and many patients may even be persuaded to agree that they have never felt better.

The patients' descriptions of the fits are interesting. Many describe something going up their arms and a sensation of blackness or emptiness. The following are typical accounts: "It went along my arm to my head and down my legs"; "It goes to my chest and up to my throat"; "When I said 'Where am I?' I was seeing stars as if atoms were splitting." After a mild convulsion another said, "I didn't go off; it made my legs shiver, but it felt like peace on earth." Two or three have had the sensation of seeing colours as they lost consciousness.

In five or ten minutes they are well enough to sit up and have lunch and many can get up soon afterwards. Nausea is rare, there has been no vomiting and headaches are infrequent. The patients who had previously had cardiazol or azoman without exception preferred the ammonium chloride.

Observations.

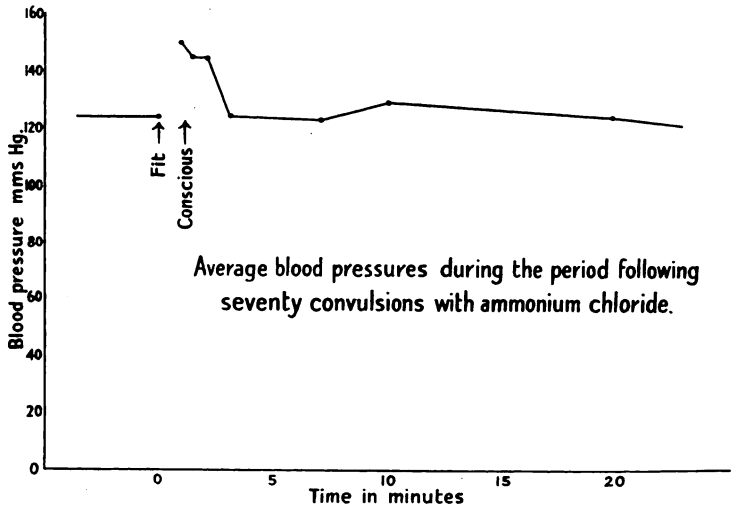
Blood pressure.—The blood pressure is raised following the convulsions, but usually falls again within three minutes. An hour later it is often less than it was 20 to 30 minutes before the injection, but the state of expectation may make this latter reading higher than normal. The curve shows the compounded readings for a series of 70 observations on the systolic blood pressure. The diastolic pressure rarely rises by more than 10–15 mm. Hg and is sometimes unchanged.

The rise in systolic blood pressure is not more than half that usually observed with azoman or cardiazol, but since a corresponding number of readings have not been made on the same patients no curves are drawn for comparison. The temporary fall which often occurs immediately after the clonic contractions of the cardiazol (Guttmann and Reitmann, 1939) and azoman fits was never observed with ammonium chloride. With cardiazol the pressure an hour

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after the convulsion was sometimes observed to be higher than the initial reading, but with azoman it fell as with ammonium chloride. In electrically induced convulsions there is a rise of systolic blood pressure immediately after the fit by 50–60 mm. Hg, and a fall to normal within 30 minutes; in this case also, the diastolic pressure does not rise by more than 10–15 mm. Hg (Kalinowsky, 1940).

Pulse rate.—The pulse rate may increase to as much as 180 during the fit, but it usually settles within three minutes after the convulsions have ended. Irregularity has not been observed.



Pupillary reactions.—The pupillary dilatation is often oval and eccentric, which is the type of reaction obtained in a positive Loewi's eye sign. For this reason adrenaline was dropped into one eye before, during or after the fit on a number of occasions. The pupil on this side was sometimes observed to be more sluggish in its reaction to light, or to remain dilated longer than the other; on several occasions its oval dilatation and eccentricity has been maintained for more than an hour.

Reflexes.—The reflexes are brisk directly after the fit. There is usually a flexor plantar response; once or twice there has been a dubious extensor reaction.

The urine.—Several 30-gr. doses of ammonium chloride are usually given by the mouth to acidify the urine. The single intravenous dose is only about $7\frac{3}{4}$ gr., and thus little change in urinary reaction would be expected. The muscular exercise and hyperpnoea are probably the main factors in influencing the reaction of the urine passed after the fit.

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The average pH values before and after 102 fits were 6·86 and 6·83; for 16 azoman convulsions the values were 7·2 and 6·25 respectively.

The average total acidity values in the urine excreted before and after 40 fits were 16·5 and 15·4 c.c. $\frac{N}{10}$ NaOH/100 c.c., and the average amount of ammonia excreted was ·061 and ·058 gm./100 c.c. respectively.

Thus the ammonium chloride injections make a negligible difference to the acidity of the urine and the ammonia nitrogen excreted.

No albumen or sugar has been found in the urine following the fits.

Modified convulsions.—(1) If the convulsant dose of cardiazol is known and an equal volume of the ammonium chloride is mixed with it and injected, the effect is that of the ammonium chloride alone with perhaps slight prolongation of the twitching and confusion.

(2) If a convulsant dose of azoman is mixed with about 8 c.c. of the ammonium chloride solution and injected intravenously, the usual effects of the ammonium chloride are observed. The fourth stage of the fit is, however, replaced by one corresponding to the pre-convulsive period after azoman has been given intramuscularly. The usual azoman convulsion occurs after perhaps ten minutes instead of within a few seconds of the injection.

(3) If three or four c.c. of sodium amytal solution are given intravenously and followed by a convulsant dose of cardiazol or azoman no fit results, though there may be twitching and restlessness. If this is followed by ammonium chloride the first and second stages occur as usual, but the twitching is very slight.

(4) An intravenous injection of 10 c.c. of 5 per cent. sodium chloride has no comparable effect to that of ammonium chloride, but ammonium bromide has an identical effect.

Ammonium chloride thus appears to inhibit the action of cardiazol or azoman when mixed with them, without losing its own effect.

Perhaps the inhibitory action of sodium amytal on the convulsions due to azoman is not well enough known. When 5 c.c. are given intramuscularly the fits stop so promptly that it seems doubtful if deaths in *status epilepticus* will occur if it is used. It appears from the third of the observations that the ammonium chloride convulsions may have a similar cerebral mechanism to those due to cardiazol or azoman, but that the second stage of the ammonium chloride fit is peculiar to this drug.

From the fourth observation it appears that the effect of the drug is due to the ammonium radical.

The stages of the fit are very definite and the above observations appear to assist in their interpretation.

The pain caused by leakage into the surrounding tissues is probably due to an irritant action. The thrombosis which can occur and the sensations apparently accompanying the passage of the drug through the vessels suggest

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that they, too, are irritated, thus accounting for the unpleasant preliminary stage.

The time taken for the hyperpnoea to develop and the sensations described suggest that there is a direct action of the drug on the lower brain centres. The results of the injection of sodium chloride and ammonium bromide indicate that the effect is due to the ammonia present.

Further support to this theory is given by the simultaneous deviation of the head and eyes and the rise in the pulse rate and blood pressure.

The muscular movements of the third stage may be compared, it seems, with those produced by the other convulsants.

Results.

The injections were given twice weekly to 24 patients. (*a*) 16 had received no previous treatment. (*b*) Four had completed a course with cardiazol or azoman without success. (*c*) Four received injections during a course which had been commenced with cardiazol or azoman.

(*a*) Ten of these 16 were patients with schizophrenia, of which one was acute, one had had a remission for two years and the present illness for six months, three had a history of from one to two years, and five had been ill from two to ten years.

Of the other six patients, one was an involutional melancholic, two were cases of mania who showed no signs of recovery, one was confused and not improving, and the other two were depressed.

The acute case of schizophrenia had 13 injections of ammonium chloride with some improvement, though she remained impulsive in her actions, hallucinated for hearing and uncertain in conduct. After nine injections of cardiazol she recovered and has been discharged. The girl with the previous remission recovered and was discharged after nine ammonium chloride convulsions. Of the remaining eight patients with schizophrenia four showed improvement, one had heart failure after five convulsions though making good progress, three were no better and were given other convulsants.

The involutional melancholic had 20 fits with improvement and now appears to be recovering. The confused patient had ten injections with little change, but is now awaiting discharge after having three cardiazol convulsions. One of the cases of melancholia had 20 ammonium chloride fits with only moderate improvement. One injection of cardiazol was given, but she complained of pain following the fit and a small crack was found in one of her dorsal vertebrae. The other melancholic had 13 fits with ammonium chloride, resulting in only a slight improvement, but after four injections of cardiazol she recovered. One case of mania showed little improvement with ammonium chloride, but has not cleared up with the other convulsants. The other maniacal patient had ten ammonium chloride convulsions and became a little less restless;

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these were followed by one injection of cardiazol, another of azoman and three more of ammonium chloride; she then recovered.

(*b*) The four cases who had previously been treated by convulsion therapy were all schizophrenics. Two had fifteen ammonium chloride convulsions without effect. The others have both shown considerable improvement and have not had injections for the past two months. They have been home for week-ends, and application is being made for discharge in each case. Neither is quite well, but they can live in the convalescent villa without upsetting the other patients. Both have been ill for more than three years. The one had previously received 17 injections of cardiazol and 5 of azoman with a little improvement. She has had 28 ammonium chloride fits. The other had been given 14 cardiazol injections in the past and improved a little. She has had 16 ammonium chloride convulsions.

(*c*) The only case of note in this group is one of schizophrenia. She had been in one of the hospital wards for restless patients for a year. She improved considerably after eleven cardiazol injections, and was discharged as a recovery when a further ten convulsions with ammonium chloride had been given.

Discussion.

Although patients much prefer ammonium chloride injections to those of azoman and cardiazol they do not like them, and there is a good deal of apprehension beforehand. This preliminary fear is naturally attendant on all such treatment.

The muscular movements are so slight, in comparison with the convulsions produced in other ways, that the risks of fracture or dislocation appear to be negligible providing the staff do not interfere during the fit.

There appears to be a danger of heart failure. In the case where this occurred the lesion was unnoticed, although it appears that there was probably mitral disease and possibly some decompensation. The patient has since had dyspnoea on exercise, tachycardia, palpitations and precordial pain. She is improving slowly, but has been in bed for two months.

Although the patients look well during the treatment, they often lose several pounds in weight. It is regained after the injections are stopped.

From these few investigations it does not appear that the results given by ammonium chloride convulsions are nearly so good as when cardiazol or azoman are used. It is, however, less unpleasant in use, the risk of fractures is negligible, and the elevation of blood pressure after the fit is comparatively small. It is believed that it may be found to fulfil a useful purpose in completing courses of treatment after an improvement has been obtained with the other drugs. It seems to be well worth trying on chosen cases where cardiazol or azoman have failed, and it may prove to be of use in the older, more feeble or bedridden cases.

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Summary.

Ammonium chloride has been used as a convulsant on 24 psychotics, 16 of whom were cases of schizophrenia.

The fits are described and the action of the drug is discussed.

The results do not appear to be so satisfactory as those given by cardiazol or azoman. The risk of fractures or dislocations appears to be negligible, but there was one case of heart failure.

It appears, nevertheless, that ammonium chloride may be usefully employed in the treatment of certain cases of mental illness.

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