ANOMALOUS CARDIAC OCCURRENCES DURING CARDIAZOL TREATMENT OF THE PSYCHOSES AND PSYCHONEUROSES.

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IT is proposed, firstly, to summarize some anomalous cardiac occurrences observed and recorded by the writer in a series of seventy-five cases which underwent treatment with cardiazol for various types of mental illness in the mental observation wards of the Southern General Hospital during the period November 11, 1938, to April 30, 1939; secondly, to suggest an explanation for the occurrence of these anomalous cardiac occurrences, hereinafter referred to for the sake of brevity as abnormalities.

The writer's attention was first drawn to the occurrence of these abnormalities by a case which presented the clinical features of heart-block, with marked bradycardia, immediately after the occurrence of the convulsion. Routine auscultation was thereafter practised in all cases during and after the convulsion. It was then noticed that the occurrence of these bradycardias and other abnormalities was much more numerous than the literature on the subject might lead one to suppose.

The literature is that of Lubner (1), who describes a solitary case of auricular fibrillation, Dick and McAdam (2), who describe four cases of cardiac abnormality, and Kennedy (3). McAdam (4), in a separate paper, elaborates on three of these cases, and suggests as an explanation for the occurrence of the abnormalities a simple exhaustion of the heart muscle following upon the convulsion. Von Meduna (5) states categorically that he has found no evidence of cardiac abnormality clinically, electrocardiographically or by X-ray following cardiazol convulsion.

Following upon the very frequent discovery of these abnormalities during routine auscultation, the writer decided to investigate the series of cases treated with cardiazol between the above-mentioned dates.

The ages of the patients ranged from 17 to 65 years and their physical states from health to gross organic disease.

In connection with the latter, the writer found that von Meduna's dictum discountenancing the use of cardiazol in convulsive doses for patients suffering

from gross organic disease is, in general, untenable. In a recent paper (6), Meduna gives as absolute contra-indications to the employment of convulsive doses: (*a*) organic cardio-vascular disease, whether arterio-sclerotic, hypertensive or inflammatory; (*b*) acute febrile illness; (*c*) pregnancy; (*d*) active tuberculosis; and (*e*) abnormality of the blood or urinary constituents determined by complete laboratory examinations. Relative contra-indications are given as (*a*) exophthalmic goitre; (*b*) history of severe intracranial injury; (*c*) sero-positive syphilis; (*d*) latent tuberculosis; (*e*) confinement to bed for one year before treatment is undertaken.

The list of absolute and relative contra-indications seems to have been compiled on theoretical grounds alone, since von Meduna has had no fatalities and an absence of major catastrophes in connection with cardiazol treatment. The absence of theoretical justification for these contra-indications caused the writer to convulse, among others, patients who at the time of treatment were displaying such symptoms as albuminuria, severe glycosuria and acetonuria, and in addition an acute asthmatic attack, coryza and bronchitis with a temperature of 101° F., severe chronic myocarditis, in which group was one case whose transverse cardiac dullness was $4\frac{1}{2}$ in. from the mid-sternal line and who showed evidence of mitral regurgitation, one case who showed signs, clinically and serologically, of advanced syphilis with marked arterio-sclerosis. In none of these cases did any adverse results occur. The mental states of the patients of the series were varied, and included hysteria, anxiety states, dementia præcox, paraphrenia, paranoia, frank manic-depressive insanity, manias (including puerperal), melancholias, a case of post-encephalitis, dementia paralytica and senile dementia.

In the investigation, attention was directed chiefly to electrocardiographic records, of which over four hundred were taken. In a few cases the somatic tremor during the post-convulsion confusion made the electrocardiograms unreadable. At all times, however, it was found possible to detect abnormalities in the cardiac rhythm (such as irregularities, tachy-and bradycardias) by simple auscultation; with but little practice it was found possible to determine the rhythm by simple auscultation, the sounds being easily determined from the coarse muscular susurrous of the muscles in the clonic phase and from the rhonchi and râles which make their sudden appearance in the chest after the convulsion.

Scope of the Investigations.

There being no doubt as to the existence of the abnormalities, the question which immediately presented itself was: Were the abnormalities met with due to the administration of cardiazol? The cases were accordingly divided into two groups: (1) those who were treated with sub-convulsive doses, and (2) those who were treated with convulsive doses of cardiazol, and

the E.-Cs. of the two groups compared.* This constituted the main line of investigation, from which several minor ones devolved; e.g., investigations to determine whether or not cardiazol had any action, direct or indirect, upon the heart; whether or not the convulsion consequent upon the administration of cardiazol could be ascribed to the cardiazol itself or to the sudden intravenous administration† of the volume of the 10% cardiazol solution into the circulation, etc. The scope of and the reason for these subsidiary investigations will become apparent from what follows below.

Description.

All the abnormalities met with, with one exception, occurred within five minutes of the termination of the convulsion, particularly in the brief "limp phase" (which immediately follows the termination of the convulsion) and, less so, in the period of stertorous breathing with return to consciousness which follows the limp phase, or, in the case of sub-convulsive doses, within five minutes of the administration.

For convenience of description, the abnormalities are divided into four groups:

(1) Fixed disturbances of rate—
  (*a*) Tachycardias.
  (*b*) Bradycardias.
(2) Irregularities.
(3) Mixed types.
(4) Others, a heterogeneous group.

No one of these types of abnormality was peculiar to any type of patient or to any one patient after any one convulsion, e.g., frequently the same E.-C. would show tachycardia, bradycardia and irregularity, i.e., an example of a mixed type, and it is in this sense that the term "mixed type" is used above.

The occurrence of examples of groups (2) and (3) preponderated over those of groups (1) and (4). The following figures are, for the most part, representative examples of the various groups.

(1) Fixed Disturbances of Rate.

(a) *Tachycardia.*

Tachycardia (used herein to denote a rate of 150 per minute or over) may appear immediately after the convulsion, it may follow gradually from a

* In obtaining these E.-Cs. a record was taken immediately before and, the plates of the leads having been left in position, records taken immediately after the convulsion (Group 2) or after the cardiazol administration (Group 1).

† Unless otherwise stated, "administered" in this article should be taken as applying to the intravenous administration of *x* c.c. of 10% solution of cardiazol in the shortest possible time, the solution being adjusted with di-sodium hydrogen phosphate to a H_2-ion concentration of pH = 7·5–8·0.

normal rate or its onset may be sudden from a normal rate. The reversion to normal is usually abrupt. When, apart from any other abnormality, the tachycardia was invariably found to be at the rate of 150 per minute save on two occasions (both in the same patient) where the rate was over 150 per minute, one of the two examples being given.

FIG. 1.—Case VI, female, aged 17, unmarried: hysteria. 6th injection: dose 4·0 c.c., productive of a convulsion. Lead IV (Groedel)*: note the

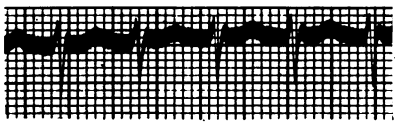


FIG. 1.

tachycardia of approximately 170 per min. Lead I showed tachycardia of exactly 150 per min. Rate before convulsion 105 per min.

(b) *Bradycardia.*

The rate of the bradycardias was found to vary within wide limits, e.g., 25–50 per min. The onset of the bradycardia was usually gradual and its return to normal equally so. It was usually of the sinus type, i.e., the stimulus to contraction arose at the sino-auricular node.

FIG. 2.—Case VIII, female, aged 42, married: manic-depressive psychosis, depressed phase. 7th injection: dose 5·6 c.c., productive of a convulsion. Lead II: bradycardia at the rate of 26 per min., of the sinus type, the Q.R.S.

FIG. 2.

complex being preceded by a P wave; note the varying amplitude of the R deflections and the very high T waves. This bradycardia was of gradual onset. Rate before the convulsion 75 per min.

FIG. 3.—Case IX, female, aged 28, married: manic-depressive psychosis, hypo-maniacal phase. 1st injection: dose 3 c.c., not productive of a

* Lead IV in this article should be taken as applying to Groedel's right ventricular partial electro-cardiogram. Lead V should be taken as applying to Groedel's left ventricular partial electrocardiogram (see Franz M. Groedel, *Das Electrokardiogramm*, Dresden and Leipzig, 1934 edition).

convulsion. Lead IV (Groedel): intense bradycardia, falling at one period to 25 per min. A diphasic P wave was present in one record, with the inversion

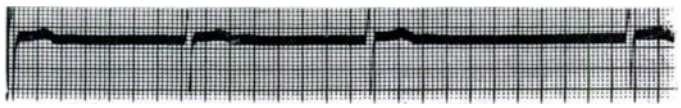


FIG. 3.

of the P wave in the middle and bottom records, not showing well on the print. This bradycardia was of gradual onset and the deflections shown on the E.-C. before administration were normal. Rate before administration 75 per min.

(2) IRREGULARITIES.

FIG. 4.—Case V, male, aged 27, unmarried: dementia præcox. 11th injection: dose 8·2 c.c., productive of a convulsion. Lead I: typical sinus

FIG. 4.

irregularity of a slow rate, also shown in Leads II and III. Rate before the convulsion 95 per min.

FIG. 5.—Case XI, female, aged 30, married: mental defective with a superimposed dementia præcox. 9th injection: dose 5·6 c.c. Lead III: fast irregularity of a sinus type: note the variations in amplitude of the R deflections and the occurrence of waves toward the end of the record similar to

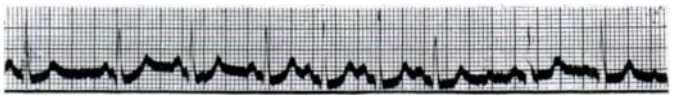


FIG. 5.

those obtained in cases of auricular fibrillation, but also possibly due to somatic tremor. Records of cases of this type are very numerous; clinically, the fast irregularly irregular rate and the deficit between the pulse and cardiac rates that is found make them indistinguishable from cases of auricular fibrillation. Lead I showed a slow sinus irregularity of about 50 per min., and Lead II a slightly faster irregularity intermediate between the rates of Leads I and III. Rate before the convulsion 95 per min.

FIG. 6.—Case I, female, aged 32, married: dementia præcox. 26th injection: dose 9·0 c.c., productive of a convulsion. Lead II: coupling of beats, the second of each of the coupled beats being a ventricular extra-systole. Lead I showed a slow sinus irregularity, and Lead III an irregularity

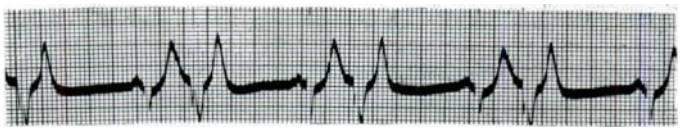


FIG. 6.

which passes clinically for auricular fibrillation. Rate before injection 85 per min. (This patient had shown cardiac abnormality after each of her preceding twenty-five convulsions and, after three of these previous convulsions, there had been coupling of beats.)

FIG. 7.—Case V, male, aged 27, unmarried: dementia præcox. 11 previous injections with abnormality after every convulsion. 50·0 c.c. (5·0 grm.) orally (vide infra), followed in forty minutes by the intravenous administration

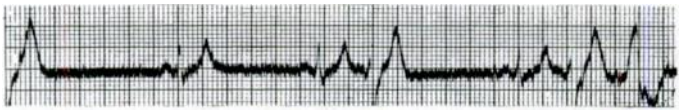


FIG. 7.

of 9·2 c.c. with the production of a convulsion. Lead II: note the occurrence of three left ventricular extra-systoles, the last of which is immediately followed by a left ventricular extra-systole. Lead I showed bradycardia of 40 per min. Rate before injection 83 per min.

FIG. 8.—Case I. See legend to Fig. 6 above. 27th injection: dose 10·0 c.c., productive of a convulsion. Lead I: suggestive of nodal rhythm with absent

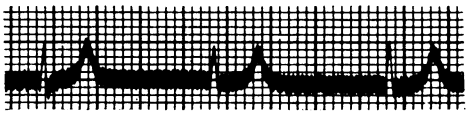


FIG. 8.

P wave contrasting with the nodal rhythm of Fig. 3, where the P wave was present but inverted. (In all cases treated, nodal rhythm was very commonly met with.) Rate before injection 85 per min.

(3) Mixed Types.

Fig. 9.—Case IX. See legend to Fig. 3. 3rd injection: dose 4·0 c.c. of unneutralized 10% cardiazol solution, productive of a convulsion. Lead II:

Fig. 9.

note the sudden conversion of a moderate degree of bradycardia of approximately 50 per min. (also present in Lead I) into a moderate tachycardia, which in Lead III attained a rate of 115 per min. Rate before injection 77 per min.

(4) Others.

This heterogeneous group comprised such phenomena as changes in the shapes and dispositions of the deflections, delay in the conduction of the T wave, splintering of the R wave (both upstroke and downstroke), change of preponderance, e.g., from a left ventricular to a right ventricular and *vice versa*, etc.

Fig. 10.—Case XLI, control, male, aged 37, married: advanced disseminated sclerosis. 1st injection: dose 5·0 c.c., repeated once (10·0 c.c. in all),

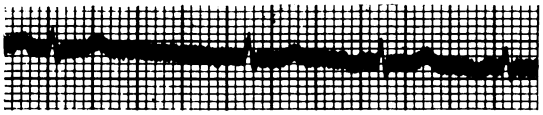


Fig. 10.

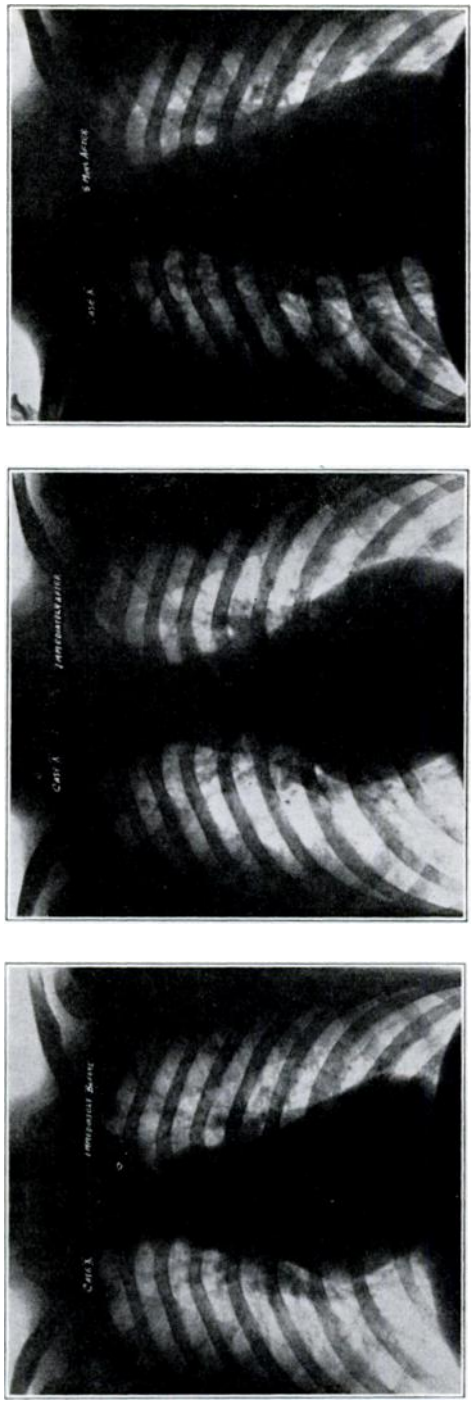
productive of a convulsion. Lead III: note irregularity of rate (also present in Leads I and II) and also the inverted P wave, not present in E.-C. before. Rate before injection 60 per min.

Fig. 11.—Case X. See legend to Fig. 7. 13th injection: dose 8·0 c.c., productive of a convulsion (*a*) immediately before convulsion, (*b*) immediately after, (*c*) five minutes after. Note the acute cardiac dilatation shown in (*b*) and recovered from five minutes later in (*c*).

Discussion.

It may be stated generally that, both in cases with normal and abnormal hearts,* ordinary "analeptic" doses of cardiazol (e.g., 2 c.c. administered

* Two of the cases had severe chronic myocarditis.



a *b* *c*

FIG. 11.

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intravenously and slowly through a fine-bored needle) produce no effect on the E.-C.

With regard to 2 c.c. doses given quickly (e.g., in a half to one second or less) and to still larger subconvulsive doses, such as 3 or 4 c.c., it was found from the study of the E.-Cs. of twelve cases that these doses were productive of no change or a slight acceleration or slowing of the cardiac rate, but that (with one exception) there was no irregularity or other abnormality to be noted in the shape or disposition of the P, Q, R, S or T deflections unless the dose (intended to be a sub-convulsive one) convulses (which is common: indeed, as little as 1·5 c.c. may convulse), when the convulsion thus produced may or may not be followed by a cardiac abnormality in the sense previously defined.

The exception referred to is that of Fig. 3, where not only is there an intense bradycardia, but also an irregularity of rate and an alteration in the shape and disposition of the deflections.

It is necessary at this point to discuss the method of action of cardiazol in so far as it bears a relation to mental disorders. From a study of (now) over 100 cases and the administration of over 1,500 doses, the writer is of the opinion that any effect resulting from the administration of cardiazol is due not to any primary action on the heart or lungs or to any direct action on their respective centres on the medulla oblongata, but to direct excitation of the higher centres of the brain. Preceding a convulsion there is invariably an aura, thus indicating that the cardiazol has reached the central nervous system. It is not until some time after the occurrence of the aura (never less than three seconds) that the convulsion occurs or, with sub-convulsive doses, any increase or decrease in the cardiac rate or a diminution or deepening of the respiratory excursion. The writer believes this to indicate that the convulsion is not the effect of the cardiazol on the lower motor neurones, but that it follows the stimulation of the upper centres with a secondary effect on the lower neurones.

It is now proposed to take the three phenomena, the aura, the cardiac rate and the respiratory excursion, for separate discussion and then, secondly, to demonstrate how they are or may be correlated.

To take the aura: the administration of cardiazol is invariably accompanied, even in small doses given quickly, by an aura. This aura for any given patient is practically constant provided the same dose is given in the same time, and the disturbing nature (*vide infra*) of the aura is directly proportional to the dose administered. Thus a patient with a skin condition used as a control* could be depended upon to experience the smell and taste (stimulation of the olfactory and gustatory centres) of toffeed almonds after the administration of 1 c.c. and, after the administration of 2 c.c., he invariably felt that he was being "mildly electrocuted".

* It was found as an incidental fact that in patients who had skin diseases and who were treated with convulsive doses of cardiazol the skin diseases could be depended upon either to improve or cure.

When the dose of cardiazol administered reaches higher amounts, such as 3–4–5 c.c. or more, such as is ordinarily given to mental patients, the aura becomes terrifying in the extreme. Depending upon the intelligence and gift of verbal expression possessed by the patients, the auras are variously described, of which the following are a few examples: "Like murder", the mind standing still, but the head hurtling away from the mind at a speed of 30 m.p.h., "hovering like a disembodied spirit on the brink of eternity", hurtling downwards through an illimitable inky nothingness, being roasted alive in a white-hot furnace, going suddenly blind, "like being in a 'bus smash and wakening up in hospital", and occasionally when asked about the aura the patient is quite inarticulate and can only shudder.

It will be observed that common to all these cardiazol auras is the experiencing of fear, and the writer has never dealt with one case or even one injection where the absence of fear could be conclusively demonstrated. Even in the case where the patient experienced the smell and taste of toffeed almonds, the aura was accompanied by a vague foreboding—a variety of fear.*

From a psychosomatic viewpoint, it is a commonplace that fear may be reacted to chiefly in two ways, even by the same patient at different times and under differing circumstances. In the first place, there is the well-known "flight" reaction, in which the sympathetic nervous system has predominant control. In the second place, there is the fear which "paralyses", in which the parasympathetic nervous system has predominant control, with the production of such phenomena as bradycardia (the heart temporarily "standing still"), diminished depth of respiratory excursion, a desire to defæcate or an involuntary motion of the bowels. That there is or may be a slowing of the pulse and cardiac rate† in people who have been frightened and that people do actually die of fright (7) is well known.

As the rapid administration of cardiazol causes fear, it would be not unreasonable to expect in these cases the phenomena associated with the two types of reaction (flight and paralysis) just mentioned. Such signs are found and, as in normal life, the flight reaction numerically preponderates over the paralysis reaction.

* For a rough pharmacological measure of this fear, Case X may be cited. Ordinarily, ʒij paraldehyde was an excellent night sedative for this patient, but ʒviij paraldehyde per rectum was quite ineffective in producing sleep or even a dulling of the faculties—he was kept awake by the fear of the injection which he knew was coming. The same occurs using other sedatives, e.g., morph. sulph. gr. ¼ and hyoscine hydrobrom., gr. $\frac{1}{100}$.

It is, in the writer's opinion, due to the fear that the efficacy of cardiazol in the treatment of mental disorder results, and not to the convulsion or to any postulated and hitherto undemonstrated metabolic happening as is suggested by von Meduna. A separate paper on the psycho-dynamics of cardiazol treatment is in preparation.

† This subject is mentioned very briefly in Sir T. Lewis's *Diseases of the Heart*, 2nd edition, 1939, p. 98. The writer has noticed the same phenomena occur in himself when he has been both the agent and witness of unexpected seeming catastrophes in connection with the administration of cardiazol. He has questioned several medical colleagues upon the same subject, and is quite satisfied that a bradycardia of varying severity is among the signs of the paralytic type of reacting to a fright.

It is difficult, however, to obtain E.-C. records, for, to produce intense fear, large doses of cardiazol are required and such usually convulse within a period too brief (generally under ten seconds) to obtain a record, or, when it is obtainable, the somatic tremor arising from the patient's agitation makes the record unreadable; besides, handling of the patients to prevent them from injuring themselves also produces blurred records.

In such cases, therefore, one is forced to rely on clinical observation, e.g., in the flight reaction there is apparent an increase in the respiratory rate and depth of respiratory excursion, explicable, in the writer's opinion, by the fear rather than by a direct action on the medulla—the hyperpnœa of emotional states is well known. In the other and much less common paralytic type of reaction the respiratory rate and excursion are markedly diminished. In one such case an E.-C. *was* obtained; the patient had the feeling of being coffined prior to being killed with the injection; this feeling passed into one wherein she believed herself to be dead. Her resemblance to a corpse was a very close one; she was extremely pale, lay motionless, stared fixedly and signs of respiration were not detected—an extreme case of the paralytic reaction, and the E.-C. showed an intense bradycardia of gradual onset—Fig. 3. In another case the heart-rate fell from 75 to 60 per minute after the administration of 2 c.c.

The patient whose E.-C. is shown in Fig. 3 was given a further 3 c.c. two minutes after the bradycardia was at its greatest and another 4 c.c. was administered half a minute later (10 c.c. in all), after which latter dose the patient convulsed.* The E.-C. after the convulsion showed no abnormality beyond a slight fluctuation in the cardiac rate ranging from between 50 and 100 per minute. The complexes showed no alteration. These fluctuations in rate are very common and comprise the majority of abnormalities. The intravenous dose was again administered in the same time two days later. The cardiac rate before injection was 65 per minute, and the rate after injection did not drop below 50 per minute and showed no alteration in the shape of the complexes. The aura of this second day was different (the exception to the general rule that the aura is constant for the same dose) as the patient said that she "was ready for it"; in other words, the element of the unexpected had gone and she was thus able to brace herself against a coming ordeal.†

In respect to other causes of bradycardia, in the case of Fig. 3 heart-block can be excluded. The existence of a high vagal tone in the patient (a gradual

* Paradoxically, when a patient fails to convulse after a large dose of cardiazol has been administered, it is often desirable for humanitarian as well as for nursing reasons to terminate the patient's mental distress resulting from the aura by giving a convulsive dose forthwith, and it was for this reason alone that, although the author is convinced of the efficacy of sub-convulsive doses in cases of mental disorder, convulsive doses were given in the majority of cases.

† There is evidence in all cases that all patients endeavour (after the first injection) to brace themselves against the ordeal of the aura. The slight degree of tolerance to cardiazol in practically all cases may be an indication of this.

slowing of the cardiac rate from 75 to 60 per minute on pressure of the eyeball) does not vitiate the hypothesis, as the stimulus acting on the autonomic nervous system causes the predominant part (the parasympathetic) to manifest itself.

It should be noticed that in two cases, one of which had severe chronic myocarditis, the rapid intravenous injection of 20·0 c.c. of distilled water produced a slowing of the heart-rate from 93 to 70 and from 65 to 60 per minute; in a third case, with severe chronic myocarditis, the rate was unaltered. The slowing of the cardiac rate in these two cases was so infrequent as to be negligible in considering the E.-Cs. of the whole series. These findings dispose of sensitization due to "speed shock" (8). The administration of 20·0 c.c. distilled water intravenously was followed in all three cases within two minutes by 2 c.c. cardiazol intravenously given in under one second. No convulsion followed in any of the three cases or any signs of a "nitritoid crisis"—or indeed signs of any description other than the above-noted.

These abnormalities still occur if cardiazol be administered alone in solution (see Fig. 9) without the addition of di-sodium hydrogen phosphate.

The absence of abnormality save in Case IX, Fig. 3, resulting from sub-convulsive doses of cardiazol points to the occurrence of the convulsion as the necessary factor in their production,* and it is difficult to escape the hypothesis advocated by McAdam that these abnormalities are due to a simple exhaustion of the heart muscle, to which the writer would add the proviso of an anoxæmic heart muscle unaccustomed to the strain of an epileptic attack.

No E.-Cs. immediately before and after a single attack of idiopathic epilepsy were able to be taken, but such E.-Cs. were obtained during *status epilepticus* in a case of idiopathic epilepsy before and after the 42nd (major) convulsion following his admission to hospital, and no difference between the two E.-C.s is to be noted save a very slight difference in rate; possibly this patient's numerous previous attacks extending over a period of twenty years had "accommodated" his heart to any adverse effects of the convulsions.† An E.-C. of this patient was taken two months after his dismissal from hospital and it showed no difference from those taken during his period of *status epilepticus*.

There is abundant evidence of exhaustion after the convulsion therapeutically induced with cardiazol; the cessation of respiration with increasing anoxæmia and cyanosis, the increased cardiac rate during the convulsion (also present in cases of idiopathic epilepsy), the extreme violence of the

* The writer has an E.-C. record of such abnormality occurring after a convulsion produced by triazol. Other cases are recorded—see Molony and Conlon, *Journ. Ment. Sci.*, September, 1939.

† Support for this accommodation theory (for want of a better term) of the writer's is to be found in his inability to find references on the subject of cardiac abnormalities occurring after attacks of idiopathic epilepsy, despite the great antiquity of the disease, although the writer obtained an irregularity in one such other case (a *status epilepticus* of idiopathic epilepsy) and McAdam (personal communication) has had two, one after a convulsion of a *status* and the other after a single attack of idiopathic epilepsy. Unfortunately, E.-Cs. of these cases were not obtainable.

muscular movements, which may cause fractures (9), are sufficient reasons for exhaustion in themselves. Of this exhaustion there is abundant clinical evidence—tricuspid bruits were heard in three cases after the convulsion, mitral bruits in three, reduplicated first sounds at the tricuspid area in five cases; sometimes the first sound would disappear altogether at the mitral and tricuspid areas (although a pulse was felt at the wrist): the sudden appearance in the chest of rhonchi and râles after a convulsion is an indication of an exhausted heart as it is, say, in decompensated heart disease; the enlargement of the area of cardiac dullness to the left, which is comparatively often found to percussion (sometimes in the writer's experience to the extent of half to three-quarters of an inch); the delayed T waves often found (delay in conduction); the high T waves such as are found in other relative anoxæmic states, such as after normal exercise—all these facts point unmistakably to an (acute) exhaustion and anoxæmia of the heart muscle.

The cardiac enlargements met with clinically were verified by X-ray examination. The eight cases were unselected, with one exception in which a frank cardiac dilatation was found clinically. A straight X-ray was taken immediately before the convulsion, after which the patient was convulsed lying on top of the unexposed second X-ray plate, which was exposed immediately after the last of the clonic movements of the convulsion, the necessary adjustments to the unconscious patient having been made; the third plate was exposed 4–5 minutes after the termination of the convulsion as there were clinical (e.g., disappearance of cardiac abnormalities and the rhonchi and rales) and E.-C. evidence that the hearts of those convulsed with cardiazol had recovered from their acute dilatation in that period, which point was confirmed by X-ray (Fig. 11, *a*, *b*, *c*). Five of the cases showed enlargement which taken individually might not have been regarded as significant, but taken together with the frank enlargement found in the remaining three of the cases, may be regarded as evidence of acute dilatation in every case.

Case XXI died during a convulsion "*in statu epileptico*". The post-mortem examination demonstrated that the right side of the heart was much dilated and the organs of the trunk, especially the lungs, were acutely congested. A sub-arachnoid hæmorrhage of considerable size had occurred into the posterior cranial fossa; a porencephalic cyst, 1 cm. in diameter, was situated in the lateral portion of the left cerebellar hemisphere. Although the sub-dural hæmorrhage was undoubtedly a contributory factor in causing death, from a general consideration of the case the opinion was formed that the main factor was a gradual myocardial insufficiency associated with acute dilatation of the right side of the heart.

The duration of the cardiac abnormalities above described was not found to exceed five minutes (the time taken for the acutely dilated heart to return to normal) save in one case very similar to the one who died. This second case is illustrative of many points.

CASE V.—Cardiazol treatment had been discontinued by a previous house-physician owing to the onset of auricular fibrillation during a convulsion, and the patient's mental and physical condition had progressively deteriorated over the intervening six months' interval. Cardiazol treatment was re-instituted by the writer and produced both mental and physical amelioration. The patient showed cardiac abnormality after each of his convulsions, particularly of the "auricular fibrillation" type referred to on p. 264. On April 28, 1939, the day he would normally have received his 12th convulsive dose, as part of a subsidiary investigation into the effects of cardiazol when administered orally, he was given 50 c.c. (5·0 grm.) of cardiazol by mouth at 3 p.m.

The B.P. (150/90 mm. Hg.) and E.-C. did not alter, and clinically no change was noted in the depth or rate of the respiratory excursions.

As he did not seem likely to convulse, he was given 9·2 c.c. intravenously at 3.40 p.m. (see Fig 7).

At 4.45 p.m. he took the first of a series of six major convulsions without intervening lucid periods which lasted until 10.40 p.m.

He was next seen by the writer at 1 a.m. of the following morning, being comatose, incontinent and of a peculiar bluish-grey pallor. He was in a state of profound collapse with a B.P. of 90/70 mm. Hg. He had had two hæmatemeses (each of 5 oz., coming presumably from the congested stomach, such as was found in Case XXI, who had died in *status epilepticus*), and later, when the writer was still present, a third of one ounce.

The heart-rate was then regular, though the cardiac sounds themselves were soft in tone.* The cardiac rate was 122 per min., and the area of cardiac dullness enlarged from $3\frac{1}{2}$ to $4\frac{1}{2}$ in. to the left of the mid-sternal line in the fifth interspace. The temperature was 102° F. Owing to the ceaseless fibrillary and myoclonic movements which the patient exhibited, together with spasmodic twitchings of the whole limbs and trunk, it was found impossible to take an E.-C.

The persistence of these movements and the time taken for active treatment prevented an E.-C. being taken until 5.30 a.m., when no abnormality was revealed save a solitary extrasystole occurring very late (at the end of the R wave) in Lead III.

During the course to complete recovery from the "*status*" (a broncho-pneumonia and a slight hæmoptysis intervening) no further abnormality was noted.

The persistence of cardiac abnormality for seven hours ten minutes after the last convulsion of the "*status*" is easily understood—the extreme exhaustion of the patient and the dilatation of the heart, which was still present at 5.30 a.m., but returned to normal at the end of thirteen hours ten minutes

* This contrasts markedly with the cardiac sounds that are to be heard after a solitary cardiazol convulsion when they are of a clear and more determined tone such as is found in a patient excited from any cause, e.g., lying on an operation table awaiting an operation for which no sedative premedication has been given.

at 11.30 a.m., when normal E.-Cs. were obtained. The physical condition of the patient did not permit of an X-ray being taken.

With regard to the ultimate effect of cardiazol upon the heart, the writer is unable to say anything beyond the fact that those patients who were able to be followed up demonstrated no abnormality at any time, either clinically or electrocardiographically, even after several months' dismissal from hospital, and during which time they had been leading normal, active and healthy lives.

Summary.

The total number of cases (excluding controls) herein reviewed was 75. Of this number, 65 were given convulsive doses, 42 of these cases showing abnormalities, i.e., 65%. Ten cases were treated with subconvulsive doses, and of these ten only one showed abnormality.

In view of the fact that circumstances precluded the taking of an E.-C. of every patient after every convulsion (at one period seventeen males and twelve females were treated in one afternoon), and that frequently an E.-C. showed abnormality where simple clinical methods showed none, it is very probable that the figure given above for the occurrence of cardiac abnormality following cardiazol convulsions would have been much higher (probably in the region of 100%) had a more rigorous investigation been possible.

No relation was determined between the occurrence of these abnormalities and, say, age, sex, stature, state of nutrition, physical health, duration of the convulsion, the dose of cardiazol administered or its rate of administration, the depth of cyanosis, etc.

Conclusions.

A series of cases which underwent treatment with cardiazol is reviewed and the following conclusions drawn :

(1) Cardiazol administered intravenously in ordinary "analeptic" doses (e.g., 2 c.c. given slowly) has no effect either directly or indirectly upon the heart ; it is equally without effect when given by mouth.

(2) Administered quickly (e.g., within half a second) ordinary "analeptic" doses (e.g., 2 c.c.) and larger sub-convulsive doses may produce no change, an increase or decrease of the cardiac rate, the increase or decrease being a consequence of a primary stimulation of the higher centres of the brain and the production of an aura.

(3) Administered in still larger doses, cardiazol produces convulsions (not due to the sudden entrance of fluid into the circulation) which are epileptiform in nature, but differ from the convulsions of idiopathic epilepsy in the occurrence of such phenomena as cardiac abnormalities (anomalous cardiac occurrences) which result from an exhaustion and anoxæmia of the heart muscle as a consequence of the convulsion—a heart muscle unaccustomed to the strain of a

convulsion and which undergoes a varying degree of acute dilatation. This exhaustion and anoxæmia are soon recovered from and leave no permanent damage to the heart.

(4) Paradoxically, the occurrence of these abnormalities should be regarded as normal after a convulsion and is thus no indication for cessation of treatment.

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