ON THE MECHANISMS OF CONVULSIVE PHENOMENA, WITH REFERENCE TO THE EFFECTS OF VASODILATOR DRUGS.*

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IT is not known to what extent convulsions induced experimentally by various agencies are related pathogenetically to epileptic fits. There are, however, facts which suggest that the induced convulsions have, in their several mechanisms, points in common with one another and with epilepsy. Thus, caffeine and absinthe both cause convulsions in cats; when sub-convulsant doses of both are administered together convulsion ensues, suggesting that the two drugs operate on the same mechanism (Notkin and Pike, 1931). Insulin hypoglycæmia occasionally causes convulsions; it has been shown that during hypoglycæmia in man there is a lower fit-threshold to cardiazol (Georgi and Strauss, 1938), and in cats to thujone (Keith, 1935). The elicitation of convulsions by electrical stimulation of the cortex is facilitated by camphor monobromide, absinthe (Muskens, 1928), and cardiazol (Santha, 1939) on the one hand, and in epileptics as opposed to non-epileptics, on the other (Penfield, 1936). Hydration has been shown to play a part in the precipitation of convulsions due to hypoglycæmia (Drabkin and Ravdin, 1937), thujone (Keith, 1935), and epilepsy (Fay, 1929; MacQuarrie, 1929).

Vascular and circulatory happenings have often been thought to play a part in causing or precipitating epileptic convulsions. Accordingly, much attention has been paid to events in the cardio-vascular system in induced convulsions. Among recent observations in this connection is one which might be thought to support the contention that cerebral anoxæmia, produced by circulatory disturbance, is an important causal factor in convulsive states—namely, the observation that certain induced convulsions may be inhibited by the administration of vaso-dilator drugs.

The evidence concerning the effects of vaso-dilator drugs relates to convulsions produced by thujone, hypoglycæmia and cardiazol. Keith and Stravaky (1935), impressed by the variety of signs of autonomic stimulation in convulsive states, performed careful experiments to determine the effects of sympathetic and parasympathetic stimulant and paralysant drugs on the convulsion following intravenous thujone injection in rabbits. They showed

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that epinephrine, pitressin, nicotine and histamine enhanced the convulsion, while acetyl choline and acetyl-β-methyl choline caused inhibition. Atropine, pilocarpine and physostygmine had no marked effect. The general conclusion was that substances which belong to the group of sympathetic hormones and drugs increased the susceptibility of rabbits to thujone convulsions, whereas drugs causing predominant stimulation of the parasympathetic system had the reverse effect. The effect of acetyl choline and acetyl-β-methyl choline in inhibiting the convulsion was not attributed to their property of causing vasodilatation, possibly because histamine had the opposite effect. It should, however, be pointed out that histamine does not cause vasodilatation in the rabbit (Schmidt and Hendrix, 1938).

In later experiments, Reitmann gave large doses of insulin to dogs, so that between two and three hours after injection the animals showed signs of convulsion, either clonic only, or tonic followed by clonic. A few minutes later amyl nitrite was administered by inhalation. Out of 30 animals so treated further convulsions did not occur in 21, the conclusion being drawn that the inhibition was due to vasodilatation. The experiments do not appear to have been controlled.

It has also been shown that the triazol convulsion may be inhibited by amyl nitrite (Walk and Mayer-Gross, 1938) and that the convulsion induced in patients by the intravenous injection of cardiazol may be inhibited by the previous administration of amyl nitrite, histamine, carbaminoyl choline, and acetyl-β-methyl choline (Denyssen and Watterson, 1938; Watterson and Macdonald, 1939); and the remainder of the paper will be devoted to this topic.

Experiments on the Effects of Vasodilator Drugs on the Cardiazol Convulsion in Guinea-Pigs.

In the experiments described below cardiazol was administered intramuscularly to guinea-pigs and an attempt was made to determine the effects on the convulsion of certain vasodilator drugs.

Experimental details.—Male, adult guinea-pigs were used. The cardiazol was injected as a 4% solution into the muscles of the thigh, and the animals were weighed before each injection. After injection the animals were placed, for observation, in a cage made of sheet rubber mounted on a metal frame and covered with wire netting. The interval between successive injections in the same animal was usually 7, occasionally 6, days; and the injections were performed in the morning before the animals were fed. Apart from this, diet was not controlled except to see that the animals had sufficient to eat. The temperature at which the animals were kept between and during the experiments was also not controlled. In all 52 guinea-pigs were used. The largest number of injections of cardiazol any given animal received was 12.

The animals were picked at random for the various experiments; when an animal was due to be injected it was used in whatever experiment was at that time in hand. During the course of the experiments there was no indication that the guinea-pigs became increasingly tolerant or sensitive to the convulsant action of cardiazol.

Description of the convulsion.—Two or three minutes after the intramuscular injection of a convulsive dose of cardiazol jerking movements of the body appear. These begin characteristically by the animal lowering its head, as if sniffing, then suddenly jerking it back. This jerking movement gradually becomes more violent. After a few seconds or a few minutes the whole body is involved. The animal crouches stiffly, its legs abducted; with each jerk it is jolted backwards, so that a regular "backward progression" may develop. At the same time there is champing of the jaws. Usually the jerking movements increase to a certain pitch of violence, then die away, to reappear a minute or so later. During the jerking movements the animal may develop a torsion of any part of the body. The head and neck may become twisted in the axis of the body; the body itself may take up the same spiral twist. Alternatively, the guinea-pig may become arched until its fore limbs are lifted off the ground, which movement may cause it to topple over backwards. During the early jerking movements any slight stimulus, either auditory or tactile, causes a jerk; later on the animal holds itself rigidly and this irritability is lost. The twisting and circling movements give place, usually after a short interval of quietude, to the next stage, namely, racing movements. The racing starts suddenly and is best described as frenzied. The animal races straight forward, making no attempt to avoid obstacles in its path. Usually it squeaks at the same time. The racing lasts only a few seconds; at the end the animal throws itself on its side, gives a few clonic jerks of the whole body, then immediately goes into tonic convulsion. At this moment protrusion of the penis and ejaculation occur. The position during tonus is typically opisthotonous with extension of the limbs, occasionally flexion of both trunk and limbs; in both positions the jaw is held open. The tonic stage is always brief, never more than a few seconds. It is succeeded by clonic convulsions, which come in surges, like the earlier jerking movements. After a few minutes the clonic convulsions usually cease, and the animal gets up and walks about. It presents a bedraggled appearance, some of its fur lying smoothly, the rest standing up. The convulsive dose is near the lethal dose, and the animal may die during the exhausting clonic convulsions. If such an animal is anæsthetized lightly with ether the spasms cease, and do not return subsequently.

For purposes of notation the convulsion is divided into three stages namely, jerking, racing and tonus. Occasionally the first stage of the convulsion is very brief, so that an apparently normal animal, walking about quietly, suddenly shoots forward in violent convulsion.

Effect on the heart-rate and rhythm.—During the course of various experiments

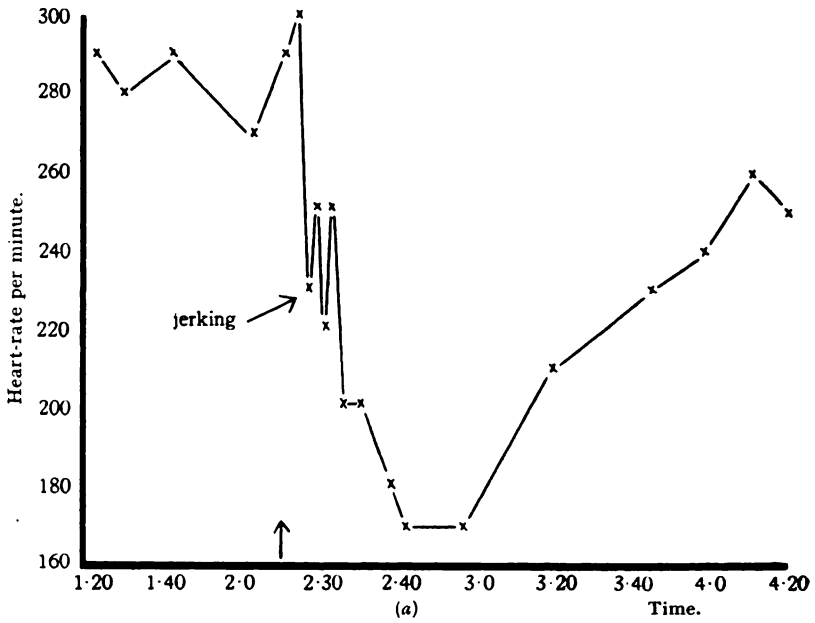
the heart-rate was measured by recording the E.C.G. for periods of 6 seconds at intervals. Metal collar-studs, held against the shaved skin of the chest and back by adhesive tape, were used as the electrodes. The records were made by a writing oscillograph on a large Palmer kymograph.

When cardiazol is injected intramuscularly in guinea-pigs the heart slows. The dose needed to produce this effect is a little less than that needed to cause convulsion. The slowing begins two or three minutes after injection, is greatest after 30 to 40 minutes, and disappears after 2 hours. Convulsion always occurs after and during the slowing of the heart, although slowing is not always accompanied by convulsion. As the heart slows the P–R interval lengthens. Changes of rhythm often occur in the slowed heart, either before or after, or in absence of convulsion. The most frequent causes of irregularity are extrasystoles and dropped beats (Fig. 1). In one instance irregularity was associated with the impulse arising from an aberrant focus (Fig. 2). On four occasions the E.C.G. was recorded continuously during the convulsion, including the tonic and clonic stages. The convulsive movements occasionally obscured the records over brief periods, but in no case did the heart cease to beat.

The slowing of the heart produced by cardiazol is abolished by atropine, whether a convulsion has occurred or not (Fig. 3*a* and 3*b*). If atropine is administered before the cardiazol the heart does not slow, but the convulsion appears to be unaltered (Fig. 3*c*). Slowing of the heart due to cardiazol is not seen in the decapitate preparation (Fig. 4). Thus, the action of cardiazol on the heart-rate is central, and the bradycardia is not associated causally with the convulsion.

The effects of vasodilator drugs: (i) *Experimental details.*—Three doses of cardiazol were employed: 60, 65 and 70 mgrm./kg. The results of the injections of these doses in control animals are tabulated (Tables I, II, III). It will be seen that the probability of convulsion after an injection of 60 mgrm./kg. is low, after an injection of 70 mgrm./kg. high, and after 65 mgrm./kg. intermediate. These doses are, therefore, suitable for determining whether vasodilator drugs inhibit or enhance the convulsion. A tendency to inhibition should reduce the percentage of animals showing convulsion after a given dose of cardiazol, while a tendency to enhancement should increase the percentage.

Carbaminoyl choline.—After subcutaneous injection of carbaminoyl choline the guinea-pig lacrymates profusely; it empties its bladder and passes loose stools; it lies down, presumably weakened by fall of blood-pressure. These outward effects last about 15 minutes if the dose is less than ·025 mgrm. If much more than this is injected the animal dies almost immediately. The effect on the heart-rate is shown in Fig. 5. In these experiments carbaminoyl choline was injected subcutaneously into the opposite leg at the same time as the cardiazol. The doses of carbaminoyl choline, and the results of the injections using the three chosen doses of cardiazol are listed in Tables IV, V and VI.



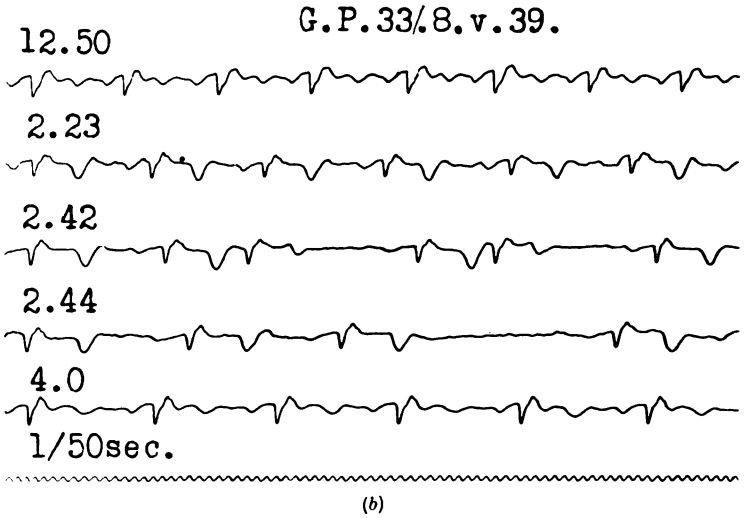


FIG. 1.—G.P. 33, 8.v.39. ·95 c.c. 4% cardiazol (63 mgrm./kg.) intramuscularly at arrow (2·14). Jerking at 2·17; no other signs of convulsion. (*a*) Effect on heart-rate. (*b*) Electrocardiagram. Note extrasystoles at 2·42, and dropped beat at 2·44.

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Acetyl-β-methyl choline.—When injected subcutaneously acetyl-β-methyl choline causes immediate lacrymation and weakness. Respiration becomes laboured or gasping. Micturition and defæcation do not occur. The effect on the heart-rate is shown in Fig. 6. In the experiments tabulated below

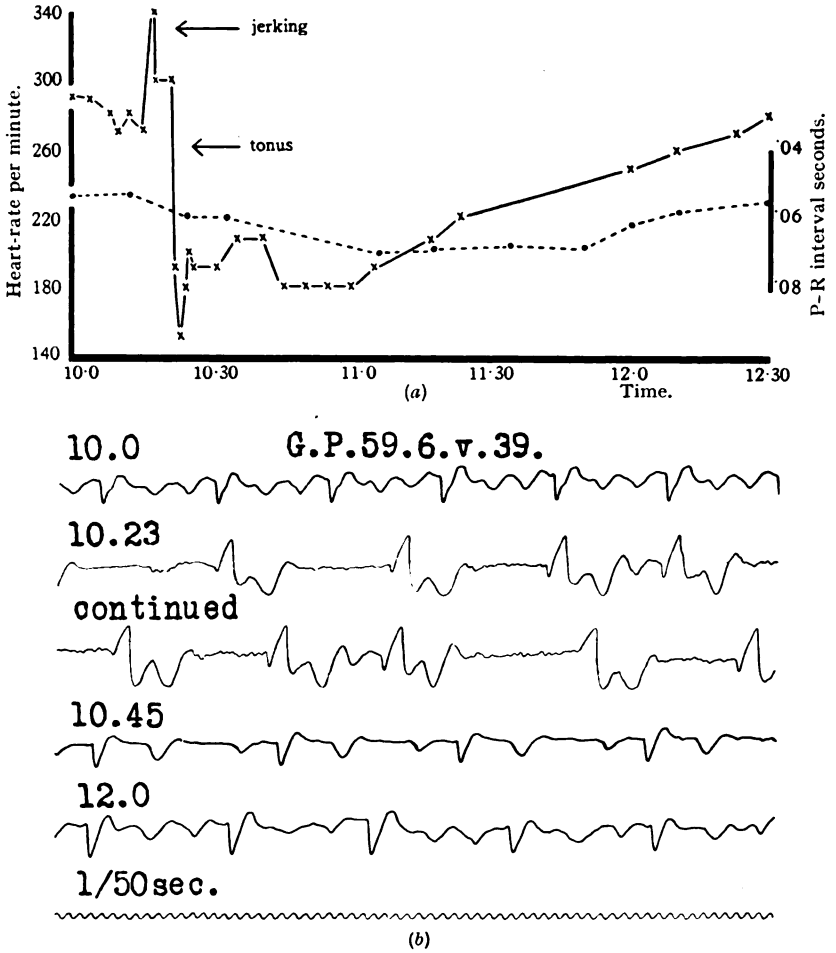

FIG. 2.—G.P. 59, 6.v.39. 1·2 c.c. 4% cardiazol (65 mgrm./kg.) intramuscularly at 10.17. Tonic convulsion at 10.22. (*a*) Effect on heart-rate and P–R interval. (*b*) Electrocardiagram, leads chest and back. At 10.23 note irregularity of rhythm, absent P wave, and impulse arising from unusual focus. The "fibrillation" comes from the skeletal muscles.

(Tables VII, VIII, IX) acetyl-β-methyl choline was injected subcutaneously into the opposite leg at the same time as the cardiazol.

Amyl nitrite.—When a guinea-pig is placed in an atmosphere of amyl nitrite no change is visible for a minute or two. Then the animal becomes obviously weak, either lying down or staggering about. Its breathing becomes

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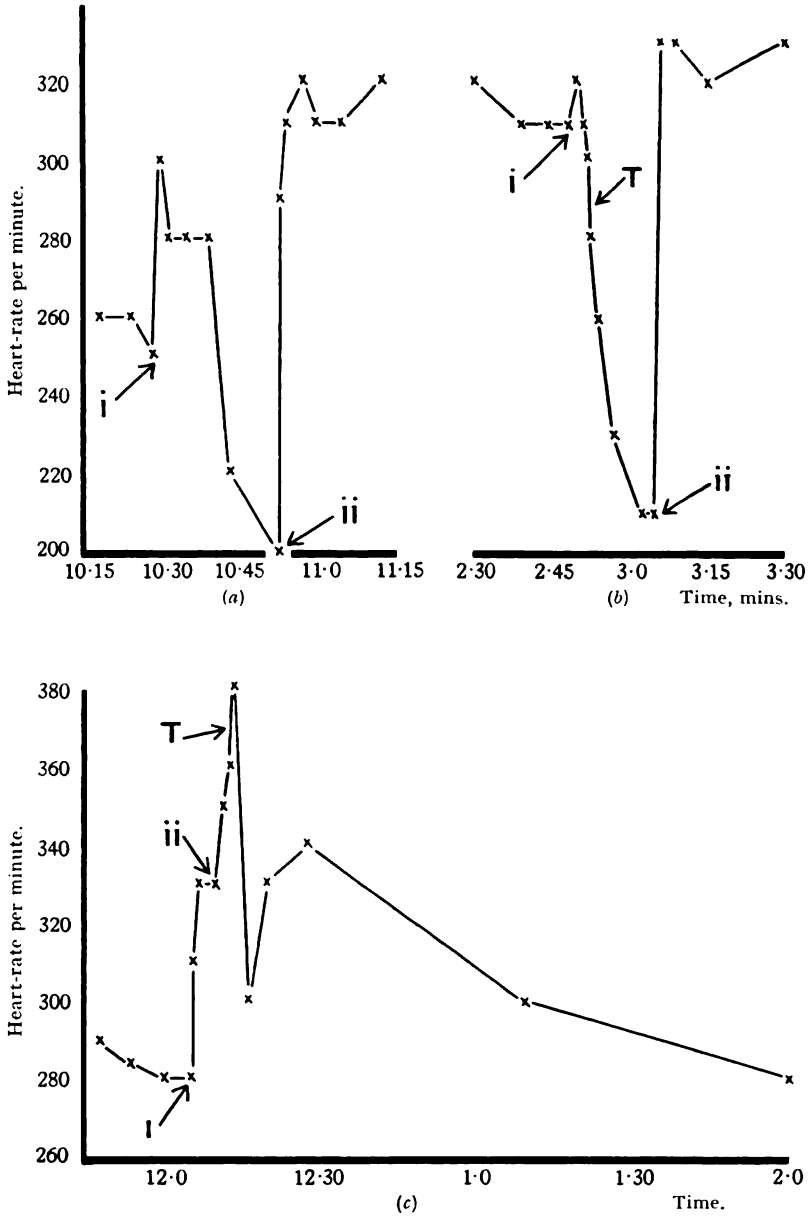

FIG. 3.—(*a*) G.P. 34, 12.v.39. Cardiazol (60 mgrm./kg.) at i, 0·02 mgrm. atropine sulphate at ii. No convulsion. (*b*) G.P. 34, 15.v.39. Cardiazol (64 mgrm./kg.) at i, 0·02 mgrm. atropine sulphate at ii. Tonus at T. (*c*) G.P. 34, 24.v.39. 0·02 mgrm. atropine sulphate at i, cardiazol (68 mgrm./kg.) at ii. Tonus at T.

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gasping. While lying down it shows running or pawing movements of the fore limbs. When removed to the air it revives in a few minutes and appears normal. In the experiments recorded in Table X, each guinea-pig was given an injection of cardiazol (60 mgrm./kg.) and immediately placed in a closed glass vessel of about 14 litres capacity. Two 3-minim capsules of amyl nitrite were broken inside the chamber at once, and a further two capsules after 3 minutes. Eight minutes after injection the animal was lifted out into the air.

(ii) *Description of experimental results.*—The description, made at the time, of the experiments to determine the combined effect of amyl nitrite and

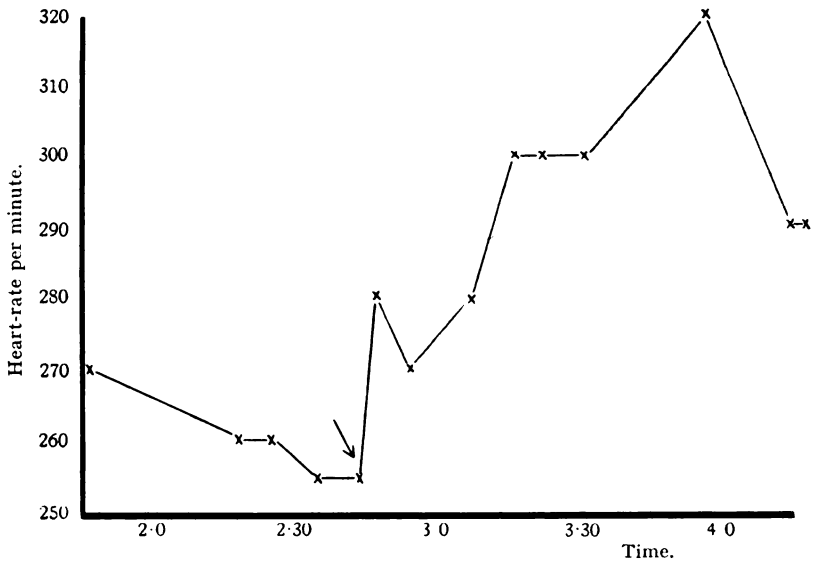

FIG. 4.—Effect of cardiazol on the heart-rate of the decapitate preparation. G.P. 64, 17.v.39. Decapitation complete at 12.30. Cardiazol (78 mgrm./kg.) injected intramuscularly at arrow.

cardiazol is as follows: "4–5 minutes after the animal is placed in the atmosphere of amyl nitrite it shows weakness. When it attempts to walk it reels and falls over. The jerking movements are not sharp and precise, but limp. Running movements occur, but they cannot be distinguished from the movements caused by amyl nitrite alone. When lifted out into the air the animal shows occasional jerks of the whole body. Placed in a cage it lies on its side or staggers about. There is weakness of the limbs, especially of the adductors and flexors of the hind limbs, so that the latter are dragged. About 3 minutes after removal the animal shows a series of convulsive jerks of the whole body, culminating in a strong tonic spasm. During tonus the trunk, limbs and neck are flexed, the jaw held open. Tonus lasts between 2 and 10 seconds and is followed by clonus, usually lasting 1 hour. This contrasts markedly with the

fit following the same dose of cardiazol alone, which is succeeded by a short clonus (a minute or two). Eight of the 20 animals died at the end of clonus. This dose of cardiazol alone has killed no guinea-pigs ; nor has amyl nitrite alone administered under the same conditions (5 experiments)." From the tables of results it will be seen that the amyl nitrite increased the percentage

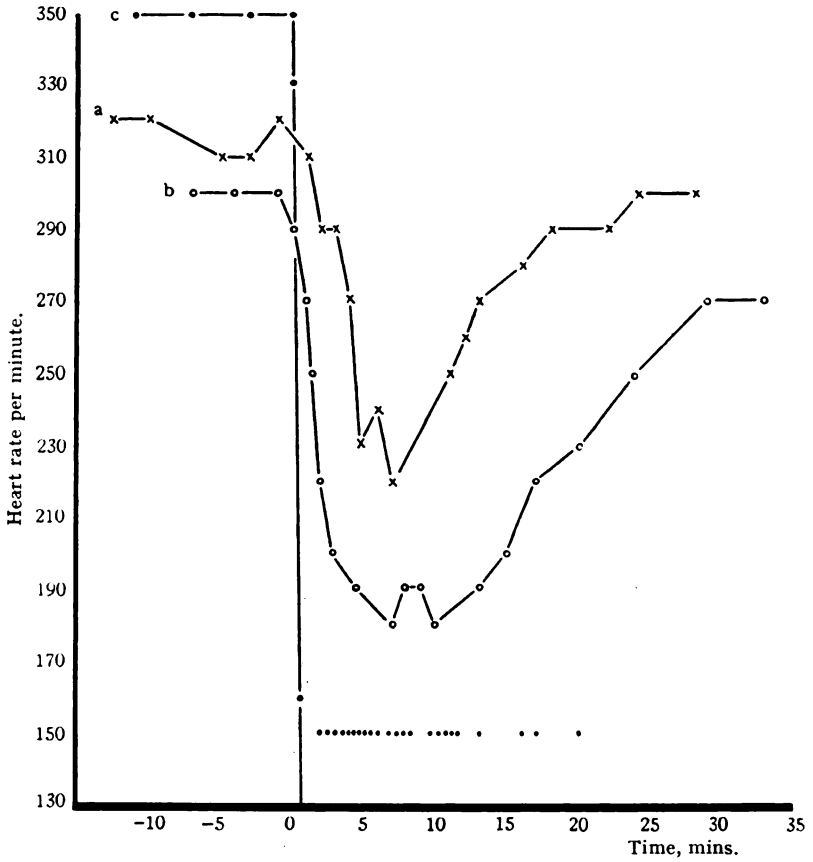

FIG. 5.—Effect of subcutaneous injection of carbaminoyl choline on heart-rate of guinea-pig. Injections at 0. (*a*) 0·008 mgrm., (*b*) 0·0125 mgrm., (*c*) 0·0375 mgrm., causing death within a few minutes. Dots indicate the times at which tonic convulsion occurred in the experiments using carbaminoyl choline.

of animals showing tonic convulsion from 13 to 85. The experiment of leaving the animal after injection with cardiazol for a longer time in the amyl nitrite has not been tried ; nor has the effect of amyl nitrite after larger doses of cardiazol been determined.

In the experiments using carbaminoyl and acetyl-β-methyl choline it was apparent that cardiazol protected the animals from the debilitating effects of these drugs alone. Moreover, considerably more than the lethal dose of

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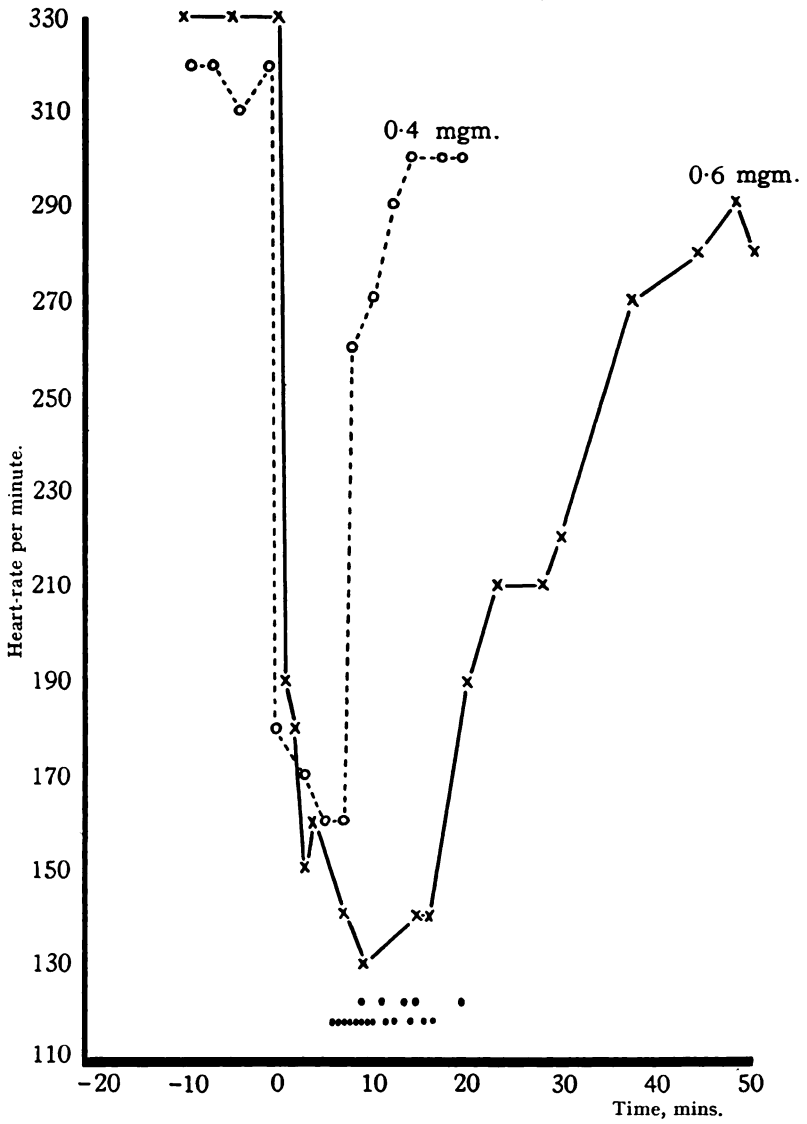

FIG. 6.—Effect of acetyl-β-methyl choline, injected subcutaneously at 0, on heart-rate of guinea-pig. Dots indicate the times at which tonic convulsion occurred in the experiments using acetyl-β-methyl choline; upper row after 0·4 mgrm. or less, lower row after 0·5 mgrm. or more.

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either carbaminoyl or acetyl-β-methyl choline could be injected along with cardiazol without fatal result. The convulsions following the simultaneous injection of cardiazol and either carbaminoyl choline or acetyl--βmethyl choline did not differ visibly from the convulsions following cardiazol injection alone.

Weight for weight the doses of carbaminoyl choline and acetyl-β-methyl choline used were more than five times the doses which have been shown to produce marked effects on the cardiovascular system in other animals (Comroe and Starr, 1933 ; Dautrebande and Maréchal, 1933), and between two and ten times the doses used in the corresponding experiments in man. All the convulsions following carbaminoyl choline injection occurred while that drug was present in sufficient quantity to slow the pulse (Tables IV, V and VI ; Fig. 5). Similarly, when the dose of cardiazol was 65 or 70 mgrm./kg. the convulsions following acetyl-β-methyl choline occurred while the effects of the latter were marked (Tables VIII and IX ; and Fig. 6). Five tonic convulsions followed the simultaneous injection of acetyl-β-methyl choline and 60 mgrm./kg. cardiazol ;

TABLE I.—*Results of Injections of* 60 *mgrm./kg. Cardiazol alone.*

G.P. number.	Date.	Weight (grm.).	Dose. (c.c. 4%).	Dose. (mgrm./kg.)	Interval (mins.) before— Jerking.	Racing.	Tonus.
23	15.iii.39	640	0·95	60	..	..	..
15	16.iii.39	430	0·65	60	8	..	..
30	21.iii.39	440	0·65	59	..	..	..
2	21.iii.39	570	0·85	56	6	6	..
23	22.iii.39	650	1·0	61	6	6	..
28	22.iii.39	660	1·0	60	6	6	..
19	22.iii.39	640	0·95	60	6	..	..
34	25.iii.39	595	0·90	60	8	..	..
35	25.iii.39	635	0·95	60	4	6	..
36	25.iii.39	615	0·9	59	2	10	..
21	27.iii.39	740	1·1	60	..	..	..
24	27.iii.39	640	0·95	60	..	..	..
29	27.iii.39	680	1·0	60	..	..	..
14	30.iii.39	680	1·0	60	8	..	..
13	30.iii.39	810	1·2	58	..	..	..
30	30.iii.39	430	0·65	60	4	4	4
40	5.iv.39	700	1·05	60	10	..	..
42	5.iv.39	690	1·05	61	2	3	..
13	25.iv.39	910	1·35	60	2	6	..
19	25.iv.39	700	1·05	60	..	..	..
20	25.iv.39	610	0·9	59	3	4	..
28	26.iv.39	760	1·15	60	13	19	19
33	26.iv.39	565	0·85	60	..	..	..
40	27.iv.39	755	1·15	60	14	15	15
51	27.iv.39	620	0·95	60	2	..	..
30	28.iv.39	590	0·9	61	2	6	6
6	1.v.39	720	1·1	60	4	6	..
22	1.v.39	580	0·85	60	9	12	..
20	2.v.39	620	0·95	60	3	3	..
28	2.v.39	770	1·15	60	..	..	..

TABLE II.—*Results of Injections of 65 mgrm./kg. Cardiazol alone.*

G.P. number.	Date.	Weight (grm.).	Dose. (c.c. 4%).	Dose. (mgrm./kg.).	Interval (mins.) before— Jerking.	Racing.	Tonus.
19	18.v.39	700	1·15	66	2	4	4
36	18.v.39	605	1·0	66	3	..	..
61	18.v.39	630	1·0	63	3	..	..
58	18.v.39	605	1·0	66	3	4	4
4	23.v.39	540	0·9	66	3	3	3
10	23.v.39	640	1·05	66	8	9	..
52	23.v.39	660	1·1	66	2	4	..
60	23.v.39	780	1·25	64	3	9	9
14	23.v.39	815	1·3	64	4	10	10
62	23.v.39	770	1·25	65	5	10	..
35	23.v.39	600	0·95	64	8	8	8
51	23.v.39	670	1·1	66	4	..	..
37	24.v.39	560	0·9	64	7	..	..
38	24.v.39	650	1·05	65	2	3	..
40	1.vi.39	765	1·25	65	..	..	..
67	1.vi.39	820	1·35	66	2	..	..
66	1.vi.39	600	1·0	66	3	..	..
52	7.vi.39	710	1·15	65	4	..	..
60	7.vi.39	855	1·4	65	1	2	..
66	7.vi.39	560	0·9	65	3	..	..

TABLE III.—*Results of Injections of 70 mgrm./kg. Cardiazol alone.*

G.P. number.	Date.	Weight (grm.).	Dose. (c.c. 4%).	Dose. (mgrm./kg.).	Interval (mins.) before— Jerking.	Racing.	Tonus.
6	16.v.39	745	1·3	70	2	5	5
10	16.v.39	595	1·05	70	2	4	..
14	16.v.39	840	1·45	70	1	3	3
42	16.v.39	800	1·4	70	3	3	3
36	17.vi.39	740	1·3	70	3	..	..
38	20.vi.39	710	1·25	70	2	3	3
34	20.vi.39	675	1·2	71	2	3	3
66	30.vi.39	560	1·0	70	1	4	..
61	30.vi.39	720	1·25	70	1	2	2
67	30.vi.39	770	1·35	70	4	5	5
62	3.vii.39	720	1·25	70	1	2	2
71	3.vii.39	590	1·05	70	9	..	..
66	5.vii.39	580	1·05	72	1	..	..
51	5.vii.39	795	1·4	70	2	3	3
61	5.vii.39	750	1·3	70	3	13	..
35	5.vii.39	695	1·2	69	4	7	7
67	5.vii.39	775	1·35	70	1	2	2
35	11.vii.39	600	1·05	69	4	5	5
67	11.vii.39	780	1·35	69	6	..	..
66	11.vii.39	615	1·1	71	2	..	..

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TABLE IV.—*Results of Injections of* 60 *mgrm./kg. Cardiazol plus Carbaminoyl Choline.*

G.P. number.	Date.	Weight (grm.).	Dose cardiazol. (c.c. 4%).	Dose cardiazol. (mgrm./kg.).	Dose carb. chol. (mgrm.).	Interval (mins.) before— Jerking.	Racing.	Tonus.
10	1.v.39	515	0·75	58	0·003	3	..	..
14	1.v.39	815	1·2	59	0·005	13	..	..
19	2.v.39	690	1·05	60	0·007	12	17	17
13	2.v.39	920	1·4	60	0·01	..	..	..
35	3.v.39	530	0·8	60	0·015	4	5	5
34	3.v.39	630	0·95	60	0·02	3	4	..
37	3.v.39	590	0·9	60	0·025	7	..	..
38	3.v.39	600	0·9	60	0·03	3	3	3
52	4.v.39	610	0·9	59	0·035	4	10	..
58	4.v.39	640	0·95	60	0·04	..	..	..
60	5.v.39	800	1·2	60	0·045	5	..	..
61	5.v.39	650	0·95	58	0·05	..	..	..
4	5.v.39	585	0·9	60	0·055	10	11	..
10	8.v.39	590	0·9	60	0·0625	18	..	..
22	8.v.39	630	0·95	60	0·075	15	..	..
6	8·v.39	780	1·15	60	0·0875	6	11	11
14	8.v.39	850	1·25	59	0·1	6	..	..
19	8.v.39	755	1·15	61	0·1125	16	21	..
28	8.v.39	780	1·15	60	0·125	20	22	..
20	8.v.39	670	1·0	60	0·1375	13	16	16

TABLE V.—*Results of Injections of* 65 *mgrm./kg. Cardiazol plus* 0·025 *mgrm. Carbaminoyl Choline.*

G.P. number.	Date.	Weight (grm.).	Dose. (c.c. 4%).	Dose. mgrm./kg.).	Interval (mins.) before— Jerking.	Racing.	Tonus.
36	24.v.39	650	1·05	65	3	8	8
61	24.v.39	600	1·0	66	1	3	..
40	24.v.39	745	1·2	64	1	7	7
52	1.vi.39	720	1·15	64	3	6	..
60	1.vi.39	845	1·35	64	29	..	..
65	1.vi.39	705	1·15	65	15	..	..
14	1.vi.39	810	1·3	64	9	11	11
34	1.vi.39	670	1·1	66	14	41	..
35	1.vi.39	610	1·0	65	..	..	..
10	1·vi·39	650	1·05	65	..	..	..
61	1.vi.39	650	1·05	65	..	..	..
51	1.vi.39	670	1·1	65	..	..	..
37	1.vi.39	640	1·05	65	4	..	..
36	1.vi.39	680	1·1	65	6	8	..
67	7.vi.39	790	1·3	66	1	11	11
40	7.vi.39	780	1·25	64	9	9	10
35	7.vi.39	580	0·95	65	5	6	8
10	8.vi.39	650	1·05	65	6	..	..
34	8.vi.39	645	1·05	65	9	19	20
38	8.vi.39	750	1·2	64	3	4	4

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TABLE VI.—*Results of Injections of 70 mgrm./kg. Cardiazol plus 0·025 mgrm. Carbaminoyl Choline.*

G.P. number.	Date.	Weight (grm.).	Dose. (c.c. 4%).	Dose. (mgrm./kg.).	Interval (mins.) before— Jerking.	Racing.	Tonus.
10	20.vi.39	670	1·15	70	1	2	2
14	20.vi.39	800	1·4	70	2	3	..
62	20.vi.39	710	1·25	70	1	3	3
71	20.vi.39	575	1·0	70	1	6	..
61	24.vi.39	710	1·25	70	2	4	..
52	30.vi.39	760	1·35	71	4	6	6
60	30.vi.39	875	1·55	71	2	5	5
52	5.vii.39	760	1·35	71	3	8	10
60	5.vii.39	890	1·55	70	9	12	13
36	5.vii.39	795	1·4	70	4	..	..
37	5.vii.39	630	1·1	70	7	..	..
62	11.vii.39	690	1·2	70	3	7	7
71	11.vii.39	600	1·05	70	3	..	..
34	11.vii.39	640	1·1	70	2	4	4
52	11.vii.39	760	1·35	71	5	..	..
14	11.vii.39	760	1·35	71	4	5	5
38	11.vii.39	730	1·3	71	3	4	4
51	11.vii.39	745	1·3	69	4	..	..
61	11.vii.39	730	1·3	71	3	6	..
37	11.vii.39	680	1·2	70	4	..	..

TABLE VII.—*Results of Injections of 60 mgrm./kg. Cardiazol plus Acetyl-β-Methyl Choline.*

G.P. number.	Date	Weight (grm.).	Dose cardiazol. (c.c. 4%).	Dose cardiazol. (mgrm./kg.).	Dose acetyl-β-methyl choline (mgrm.).	Interval (mins.) before— Jerking.	Racing.	Tonus.
18	10.iii.39	380	0·6	63	0·3	..	..	..
25	14.iii.39	515	0·8	60	0·4	6	10	14
30	14.iii.39	470	0·7	60	0·4	5	13	14
21	15.iii.39	740	1·1	59	0·5	..	..	..
24	15.iii.39	670	1·0	60	0·5	11	..	..
28	15.iii.39	670	1·0	60	0·5	..	..	..
29	15.iii.39	730	1·1	60	0·5	..	..	..
6	21.iii.39	550	0·8	58	0·4	4	4	..
20	22.iii.39	570	0·85	60	0·5	19	..	..
29	22.iii.39	730	1·1	60	0·6	20	..	..
31	25.iii.39	725	1·1	60	0·3	7	8	..
32	25.iii.39	600	0·9	60	0·3	6	10	..
33	25.iii.39	615	0·9	59	0·3	37	37	..
41	25.iii.39	630	0·95	60	0·4	9	11	11
42	25.iii.39	710	1·05	59	0·5	6	7	9
37	25.iii.39	540	0·8	60	0·4	7	..	..
40	25.iii.39	730	1·1	60	0·5	10	19	19
19	27.iii.39	655	1·0	61	0·4	8	..	..
20	27.iii.39	590	0·9	60	0·4	7	13	..
23	27.iii.39	630	0·95	60	0·4	..	..	..

TABLE VIII.—*Results of Injections of 65 mgrm./kg. Cardiazol plus 1·0 mgrm. Acetyl-β-Methyl Choline.*

G.P. number.	Date.	Weight (grm.).	Dose. (c.c. 4%).	Dose. (mgrm./kg.).	Interval (mins.) before— Jerking.	Racing.	Tonus.
66	13.vi.39	585	0·95	65	3	..	..
60	13.vi.39	840	1·35	64	7	..	..
35	13.vi.39	615	1·0	65	11	11	12
67	13.vi.39	780	1·25	64	15	17	..
10	15.vi.39	675	1·1	65	..	..	..
14	15.vi.39	800	1·3	65	5	14	14
62	15.vi.39	760	1·25	66	7	7	8
34	15.vi.39	675	1·1	65	6	8	8
38	15.vi.39	730	1·2	66	7	8	8
71	15.vi.39	640	1·05	66	11	12	..
38	27.vi.39	700	1·15	66	11	12	12
34	27.vi.39	620	1·0	64	6	9	9
10	27.vi.39	660	1·05	64	3	10	..
14	27.vi.39	780	1·25	64	5	9	..
62	27.vi.39	690	1·1	65	7	16	16
71	27.vi.39	555	0·9	65	8	18	..
34	3.vii.39	650	1·05	65	4	7	7
38	3.vii.39	720	1·15	64	13	20	..
10	3.vii.39	570	0·95	66	..	..	..
14	3.vii.39	780	1·25	64	9	..	..

TABLE IX.—*Results of Injections of 70 mgrm./kg. Cardiazol plus Acetyl-β-Methyl Choline.*

G.P. number.	Date.	Weight (grm.).	Dose. (c.c. 4%).	Dose. (mgrm./kg.).	Dose acetyl-β-methyl choline (mgrm.).	Interval (mins.) before— Jerking.	Racing.	Tonus.
51	17.vi.39	725	1·25	70	1·0	5	9	10
61	17.vi.39	705	1·25	71	1·0	3	8	..
35	18.vi.39	650	1·15	71	1·0	8	12	..
37	18·vi.39	690	1·2	70	1·0	4	9	..
66	18·vi.39	590	1·05	71	1·0	3	..	..
52	18.vi.39	735	1·3	71	1·0	10	..	..
10	18.vi.39	915	1·6	70	1·0	9	20	..
67	18.vi.39	775	1·35	70	1·0	16	16	16
36	30.vi.39	750	1·3	70	1·0	6	..	..
51	30.vi.39	735	1·3	70	1·0	2	3	..
35	24.vi.39	645	1·15	71	0·5	5	6	7
37	24.vi.39	650	1·15	70	0·5	4	7	..
66	24.vi.39	550	0·95	70	0·5	3	8	..
52	24.vi.39	720	1·25	70	0·5	3	..	..
60	24.vi.39	855	1·5	70	0·5	5	9	..
67	24.vi.39	750	1·3	70	0·5	..	..	..
36	24.vi.39	710	1·35	71	0·5	4	6	..
51	24.vi.39	775	1·25	70	0·5	5	6	..
35	30.vi.39	630	1·1	70	0·5	3	6	6
37	30.vi.39	700	1·2	69	0·5	3	..	..

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TABLE X.—*Results of Injections of 60 mgrm./kg. Cardiazol plus Administration of Amyl Nitrite.*

G.P. number.	Date.	Weight (grm.).	Dose. (c.c. 4%).	Dose. (mgrm./kg.).	Interval (mins.) before— Jerking.	Racing.	Tonus.
40	21.iv.39	750	1·1	59	10	11	12
*39	21.iv.39	600	0·9	60	7	7	10
*42	21.iv.39	700	1·05	60	7	9	10
51	21.iv.39	660	1·0	60	9	10	..
52	22.iv.39	580	0·85	60	10	18	..
53	22.iv.39	545	0·8	58	8	8	16
* 2	24.iv.39	620	0·9	58	3	9	..
6	24.iv.39	710	1·05	60	7	7	10
10	24.iv.39	530	0·8	60	8	9	9
14	24.iv.39	790	1·2	60	8	15	15
*21	25.iv.39	825	1·25	60	8	12	12
*24	25.iv.39	730	1·1	60	6	10	10
*31	25.iv.39	710	1·05	59	6	6	10
*23	26.iv.39	720	1·1	60	7	7	11
35	26.iv.39	570	0·85	60	6	6	8
34	27.iv.39	640	0·95	60	7	15	15
37	27.iv.39	610	0·9	59	7	13	13
38	27.iv.39	665	1·0	60	6	11	11
52	28.iv.39	630	0·95	60	7	6	10
*53	28.iv.39	575	0·85	59	5	10	10

* Died immediately afterwards.

TABLE XI.—*Percentage of Animals Showing Convulsion after the Various Treatments.*

	Number of experiments.	Percentage of animals showing— Jerking.	Racing.	Tonus.
Cardiazol 60 mgrm./kg. alone	30	70	50	13
Cardiazol 60 mgrm./kg. plus carbaminoyl choline	20	85	50	25
Cardiazol 60 mgrm./kg. plus acetyl-β-methyl choline	20	75	50	25
Cardiazol 60 mgrm./kg. plus amyl nitrite	20	*	*	85
Cardiazol 65 mgrm./kg. alone	20	95	55	30
Cardiazol 65 mgrm./kg. plus carbaminoyl choline	20	80	60	40
Cardiazol 65 mgrm./kg. plus acetyl-β-methyl choline	20	90	75	45
Cardiazol 70 mgrm./kg. alone	20	100	75	60
Cardiazol 70 mgrm./kg. plus carbaminoyl choline	20	100	70	50
Cardiazol 70 mgrm./kg. plus acetyl-β-methyl choline	20	95	70	20

* See text.

by the time they occurred the effects of the acetyl-β-methyl choline (on the pulse-rate) had disappeared. Table VII, therefore, yields no information concerning a possible inhibition or enhancement of the cardiazol convulsion by acetyl-β-methyl choline. It demonstrates that when the latter drug is administered during the "incubation" period of the convulsion the probability of convulsion occurring is not altered. This contrasts with the experiments using amyl nitrite.

From Table XI it will be seen that carbaminoyl choline neither inhibited nor markedly enhanced the convulsive action of doses of 60 and 65 mgrm./kg. cardiazol. The percentage of tonic convulsions following 70 mgrm./kg. was reduced, but not significantly. Acetyl-β-choline increased the percentage of tonic convulsions following 65 mgrm./kg. cardiazol, but markedly decreased the percentage following 70 mgrm./kg.; in fact, fewer tonic convulsions followed the injection of 70 mgrm./kg. than 65 mgrm./kg. cardiazol. Neither carbaminoyl choline nor acetyl-β-methyl choline appreciably altered the percentages of animals showing the earlier stages of convulsion, noted as "jerking" and "racing".

Discussion.

Slowing and irregularity of the heart produced by cardiazol has been reported by other workers. Eichler and Hildebrandt (1926) observed that such slowing was abolished by vagal section. Kennedy (1937) reported bradycardia immediately after the cardiazol convulsion in patients, while Dick and McAdam (1938) noticed marked irregularity of rhythm in four patients. Meduna found no changes in the E.C.G. either during or after the cardiazol convulsion. When cardiazol was injected during insulin hypoglycæmia nodal rhythm and inversion of the P wave were seen (Schmitt, 1939).

The minimal convulsive dose of cardiazol, when injected subcutaneously in the guinea-pig, was found by Hildebrandt and Mugge (1937) to be 35 mgrm./kg., i.e., about half the dose which the experiments reported in this paper would indicate. The discrepancy may be due in part to different nomenclature of the various stages of convulsion. When cardiazol is injected intravenously the convulsion may be divided, fairly objectively, into three stages. The first stage consists of a series of jerks, involving the whole body, increasing in tempo and violence during the space of a few moments, and culminating in the second or tonic stage of the convulsion. The tonic stage is followed by the third or clonic stage. When a sub-convulsive dose is injected, either no convulsive movements ensue or the first stage of convulsion only is seen; the same occurs when the tonic stage is inhibited by vasodilator drugs. It is apparent that in the convulsion following the intramuscular injection of cardiazol in the guinea-pig the tonic and clonic stages are almost identical with the corresponding stages following intravenous injection (with the exception

that tonus sometimes occurs in the position of flexion). The impression is also gained that the pre-tonic convulsive movements after intramuscular injection are qualitatively the same as the corresponding movements after intravenous injection, but that they are seen *in extenso*. The first and last stages of the cardiazol convulsion are sometimes named the first and second clonic stages. This is misleading ; in both stages there are jerking movements, but in the first the body is held stiffly, and there is overactivity and marked excitability, while in the last there is no response to stimulation, and, between the jerks, the musculature is quite flaccid. The dose of cardiazol required to produce the early convulsive movements only is considerably less than that needed to elicit the total pattern of convulsion outlined above.

Induced convulsions are often poorly described in the literature. Phrases such as " true convulsion ", " real convulsion " and others, equally ambiguous, are used. For this reason it is difficult to compare one induced convulsion with another. However, the cardiazol convulsion as seen in man and the guinea-pig appears to resemble qualitatively the convulsions following administration of camphor (Muskens, 1928), thujone (Macdonald and Cobb, 1923 ; Keith, 1935), and picrotoxin (Uyematsu and Cobb, 1922 ; Low *et al.*, 1939). The various convulsive movements seen in the pre-tonic stage in the guinea-pig are also similar to those described in patients after the intramuscular injection of triazol (Walk and Mayer-Gross, 1938).

The effect of vasodilator drugs in inhibiting the convulsions following the intravenous injection of thujone and cardiazol has not yet been satisfactorily explained. The hypotheses outlined below are, therefore, quite speculative. It may be suggested, for example, that the convulsions are caused or precipitated by cerebral vasoconstriction, and that the administration of vasodilator drugs prevents this from happening. There are many reasons for regarding this suggestion sceptically, quite apart from the lack of evidence from other sources that the convulsions are preceded by cerebral vasoconstriction. One such reason is the limited inhibitory ability which the vasodilator drugs possess.

The effect of these drugs on the rate of cerebral blood-flow rather than on blood-vessel diameter must be considered as a possible factor. There is experimental evidence that amyl nitrite, histamine, acetyl choline and acetyl-β-methyl choline may increase the rate of cerebral blood-flow ; but such increase does not occur consistently. Moreover, epinephrine and pitressin also increase the rate of cerebral blood-flow (Schmidt and Hendrix, 1938), yet they enhance the convulsion following the intravenous injection of thujone.

Explanation of the inhibition of the cardiazol and thujone convulsions may lie in the experimental findings of Schmidt and Hendrix (1938) concerning the effects of histamine, acetyl choline and acetyl-β-methyl choline on the relative rates of intracranial and extracranial blood-flow in the cat. In these experiments the blood-pressure was kept constant by the device

of injecting the drugs into the carotid artery, so that the results may be interpreted directly as changes in blood-vessel diameter. All three drugs caused a greater increase of blood-flow in the tongue or mylohyoid muscle than in the parietal cortex. Assuming that, from the point of view of changes in vascular diameter, the parietal cortex is representative of central-nervous-system tissue, and the tongue of extracranial tissue, it may be deduced that the amount of blood passing to the central nervous system relative to the amount passing elsewhere per unit of time is diminished by the administration of histamine, acetyl choline, and acetyl-β-methyl choline.* In other words, the partition of a convulsant drug, injected into the blood-stream, between the central nervous system and elsewhere may be altered by the administration of certain vasodilator drugs so that less of the covulsant drug reaches the central nervous system than otherwise, the result being "inhibition" of the convulsion. In the same experiments Schmidt and Hendrix found that epinephrine and pitressin caused a greater increase in intracranial blood-flow than in extracranial. Thus, administration of these drugs might be expected to alter the partition of an intravenously injected convulsant so that more of the convulsant reached the central nervous system than otherwise, causing enhancement of the convulsion. As mentioned previously, Keith and Stravaky found that epinephrine and pitressin enhanced the thujone convulsion in rabbits.

The effects of carbaminoyl choline and acetyl-β-methyl choline on the cardiazol convulsion are apparently not the same under all circumstances. When a minimal convulsive dose of cardiazol is injected intravenously, administration of either carbaminoyl choline or acetyl-β-methyl choline inhibits the convulsion; when a minimal convulsive dose is injected intramuscularly there is no such inhibition, though inhibition becomes apparent if more than the minimal convulsive dose is used. There is, at present, no experimental evidence bearing on the different modes of distribution of intravenously and intramuscularly injected drugs; nor is there information concerning the effects of vasodilatation on the rates of absorption into, and excretion from, the blood-stream of a drug injected intramuscularly. Moreover, the two series of experiments were performed in different species, and in neither of the species have the effects of the various vasodilator drugs on the cerebral vasculature been determined. For these reasons fruitful speculation cannot be pursued.

Enhancement of the cardiazol convulsion in guinea-pigs is produced by the administration of huge doses of amyl nitrite during the "incubation" period of the convulsion. It is known that massive doses of amyl nitrite may

* It is known that all regions of the central nervous system do not respond either quantitatively or qualitatively in the same way to the same vasodilator drug. The above assumption that the central nervous system responds on average in the same way as the parietal cortex is, therefore, purely speculative. There appears to have been no direct investigation into the partition of blood leaving the heart between the central nervous system and the rest of the body.

cause asphyctic convulsions. In the control experiments, in which the same dose of amyl nitrite was administered for the same time, convulsions, in the usual sense, did not occur, but the animals showed gasping respiration and pawing or running movements. It is possible that the enhancement of the cardiazol convulsion was caused by the asphyxia. There appears to be no experimental evidence concerning the effects of asphyxia on other induced convulsions. Another possible explanation is that the cerebral blood-flow was greatly increased either during or after the administration of amyl nitrite, thus carrying a greater amount of cardiazol to the central nervous system.

It is not known whether blood-pressure *per se* plays a part in the precipitation of induced convulsions. In the experiments using amyl nitrite it is probable that the blood-pressure was lowered during the administration of the drug, and raised when the animal was taken out into the air. The tonic convulsion occurred about three minutes after removal from the atmosphere of amyl nitrite. Similarly, Coombes and Pike (1931) found that when the blood-pressure (of cats) was low it was difficult to elicit absinthe convulsions, but when it was increased, either by adrenalin injection or by compression of the abdominal aorta, the convulsive action of absinthe was enhanced. Adrenaline increases the rate of cerebral blood-flow in the intact animal; compression of the abdominal aorta may be expected to have the same effect; either manœuvre would, therefore, increase the quantity of injected convulsant reaching the central nervous system. The enhancement of the absinthe convulsion noted by Coombes and Pike might have been caused in this way. Blood-pressure as a specific factor cannot, however, be entirely ruled out.

Summary.

1. The convulsion following the intramuscular injection of cardiazol in the guinea-pig is described.

2. When amyl nitrite was administered during the "incubation" period of the convulsion, the convulsive action of 60 mgrm./kg. cardiazol was enhanced.

3. Carbaminoyl choline neither enhanced nor markedly inhibited the convulsive action of 60, 65 and 70 mgrm./kg. cardiazol.

4. Acetyl-β-methyl choline caused neither enhancement nor inhibition of the convulsive action of 65 mgrm./kg. cardiazol, but inhibition of 70 mgrm./kg.

5. The effects of drugs, which act on the cardiovascular system, on induced convulsions are discussed. Systemic blood-pressure, cerebral blood-vessel diameter, rate of cerebral blood-flow, and altered partition of an injectant between the central nervous system and elsewhere are considered as possible factors in the inhibition or enhancement of induced convulsions.

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Laboratory of the London County Mental Services ; and to Dr. A. A. W. Petrie, Medical Superintendent, Banstead Hospital, for granting the necessary leave of absence.

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Discussion.

Dr. J. M. WOLFSOHN (Professor of Neuropsychiatry, Stanford University, San Francisco), in response to an invitation from the President to join in the discussion, said he would be very glad to do so were he qualified, but he had been working entirely on the clinical side of this question. They had been using cardiazol, and he wanted to make one comment. In giving patients suffering from schizophrenia the cardiazol convulsion treatment they had found that preceding the giving of these convulsions a great many patients showed the curious phenomenon of a panic state, and in order to prevent this panic state occurring they had given about 3 to 6 gr. of sodium amytal about one hour before giving the cardiazol (or metrazol as it was called in America). In the cases in which 6 gr. of sodium amytal was given they had to increase the dose of cardiazol up to 14 c.c. in order to produce the convulsion. In other words, this was a way of preventing the convulsions produced by drugs, and it was possibly brought about by an effect upon the vessels which controlled the convulsive action.

Dr. HAROLD PALMER (Woodside Hospital, London) said that in the United States, recently, they had discovered that anything up to 50% of patients given cardiazol got fractures of the vertebræ, and this factor was bound to modify this therapy. There were various suggestions being put forward to get rid of this complication, and one of these was to give intravenous injections of curare. It would be very interesting to have animal experiments to find what the effect of these injections would be, and as an ancillary, of course, to note exactly what it was that caused the convulsion.

Another point he wished to raise was an observation originally made by a general practitioner some years ago in a letter, that prontosil suppressed epileptic fits. That was communicated in a letter to the Editor of the *British Medical Journal*, but the suggestion had not been followed up in this country. In Boston (Massachusetts), however, it was claimed that prontosil did stop these epileptic fits. The speaker had got into communication with the general practitioner, who told him that for about three months the patient was free of fits with prontosil and then relapsed. There must be something in that work, and it seemed to him that Dr. Watterson was in a peculiarly happy position to work it out.

Dr. A. A. W. PETRIE (Banstead) said that perhaps Dr. Watterson might enlighten some of them as to how far his animal experiments had confirmed his previous work with these drugs on the effect of the cardiazol convulsion in the human being. The speaker was sure that with his scientific caution Dr. Watterson would be very careful in what he said, but he did develop certain theories, and he thought he was correct in stating that this work on the animals was done with a view to enlarging his experiences with regard to the effect of the cardiazol convulsion on the human being. Dr. Watterson had covered an immense amount of ground, and a word or two on the human applications of the animal experiments might interest the meeting.

Dr. WATTERSON replied that he did set out to do experiments in animals to confirm findings in patients that one could inhibit epileptic fits if a clinical dose was injected. The findings did not correspond in the least, unfortunately. With guinea-pigs the position was that choline or acetylcholine did not inhibit the convulsion, when a minimal dose of acetyl-β-methylcholine did appear to inhibit convulsion. He purposely refrained from speculating on this fact that these vasodilator drugs seemed to inhibit the fit when the cardiazol was given intravenously, but not when given intramuscularly. One could make fairly plausible speculaions to account for the difference, but he did not think they were worth putting forward.

Prof. GOLLA referred to Dr. Walk's observations with triazol.

Dr. WATTERSON asked if Dr. Walk would give his experience with triazol.

Dr. A. WALK (Horton) said he thought Dr. Watterson had really covered all the points he wanted to raise. Dr. Mayer-Gross and he had done similar experiments with triazol last year and felt they could certainly confirm that amyl nitrite inhibited fits produced by triazol and by cardiazol as well. They tried with both intravenous and intramuscular injections. It was much more difficult to produce any such effect with intramuscular injections. They were not surprised, because the correct timing of the injections was so much more difficult. In giving the intravenous injections they had the advantage of knowing Dr. Watterson's technique, and they found the time relations different with triazol, because it was a slower-acting drug. When triazol was used intramuscularly it became difficult to decide when to give the inhibiting drug, whether towards the end of the induction or earlier. In one or two cases, in the kind of patients who had a good deal of primary twitching, it was found possible to stop the twitching by administering amyl nitrite, but twitching began again and one could not produce more lasting results except by using doses which were dangerous.

Acetyl-β-methylcholine had been used in a number of cases, and their impression was that it tended to inhibit the fits, but they could not produce anything like 100% results. He noticed that Dr. Watterson had based his results on a statistical method and he would re-examine his own material in the light of this.

They had also done some work on the effect on induced convulsions of prostigmin, a drug which had no special effect on the vasomotor system, but had a marked effect on the peripheral innervation of muscles. It might throw some light on the action of drugs, like the choline derivatives, which acted on both mechanisms, but they had not yet obtained definite results.

The PRESIDENT said that the papers showed what valuable research was being done. She thanked the contributors very heartily for an interesting session.

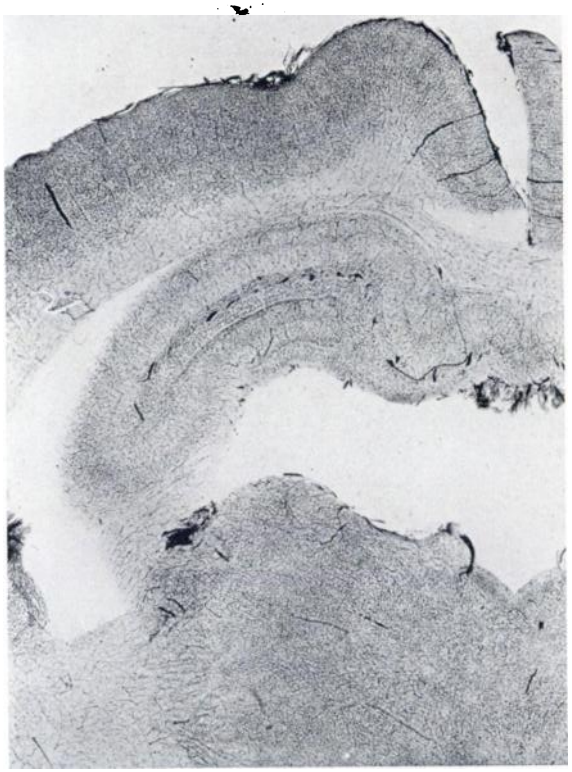

FIG. 5.—(*a*) Normal rabbit (Pickworth stain).

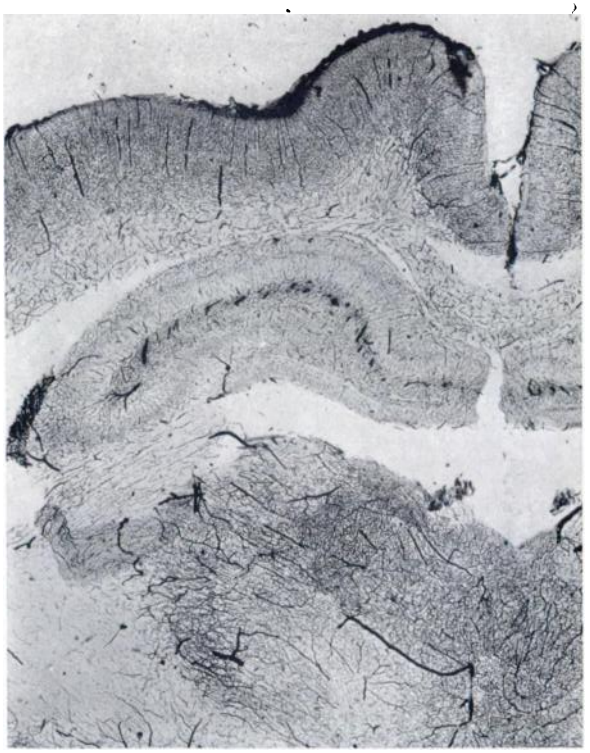

FIG. 5.—(*b*) Rabbit showing marked vasodilatation and irregularity, particularly in the thalamus (Pickworth stain).

These sequelæ are, as a rule, slight, without grossly altering the shape of the brain and the convolutional pattern. More substantial lesions may, however, occur, such as heavy diffuse glial sclerosis, disseminated cortical softenings and scarring, diffuse granular or lobar atrophy. Gross lesions of this type are particularly frequent in infantile epilepsy and the suggestion has been made (Scholz, 1936) that the epilepsy accompanying conditions of mental defect and cerebral diplegia may often be the cause rather than a mere symptom of the condition. Though this is certainly not the rule, it may be correct in certain otherwise obscure cases of infantile progressive mental and neurological deterioration with a long initial history of epilepsy and with post mortem findings of the type described above.

In pursuance of Scholz's viewpoint an interesting attempt has been made recently (Tebelis, 1939) to ascertain how far certain atypical features in congenital general paralysis may be due to the accompanying epileptic convulsions. The pathology of many more conditions may be considerably advanced from a systematic approach in this direction.

All mental deterioration in epileptics cannot be expressed, however, in terms of destroyed brain tissue, as is sometimes stated even in modern textbooks. For the characteristic epileptic dementia or, better, personality change no histological substrate is so far known (Wertham, 1934, personal experiences).

The post-epileptic lesions have been taken to indicate that vasomotor disturbances form an important part of the chain of pathological events in the epileptic seizure (Spielmeyer). They have even been widely used as evidence for cerebral vasoconstriction to be the cause of the fit. An angiospastic theory was the more willingly accepted, since it not only tallied with traditional ideas but was also in agreement with biopsy observations of blanching and shrinking of the brain immediately before the onset of the fit (Foerster, 1926, and others). These earlier observations have been contradicted, however, by Penfield (1936), who never saw any vasomotor changes before the fit, though very definite ones in the later stages. Nor was the fact that vasodilator drugs suppress a fit such a convincing evidence for vasoconstriction as it first appeared to be (Reitmann, 1938). Measurements of cerebral blood-flow did not show decrease before and at the beginning of the fit (Gibbs, Lennox and Gibbs, 1934; Lennox, 1935; von Santha, 1939), but this does not exclude the possibility of local anæmia. Recently Dreszer and Scholz (1938/39) have made a histological attempt to restore the vasoconstrictor theory. They claimed to be able to show in cats, in which cardiazol fits were induced, that there is anæmia in the cortex and other regions before the fit begins. Their method was to kill the animals in various stages before and during the fit and demonstrate the hæmoglobin in sections treated with a benzidine stain. Dr. Watterson, Mrs. Meyer and the present writer are at present doing experimental work on various problems of a histo-pharmacological nature by means of the valuable method elaborated and recommended by Pickworth (1934).

In the course of this work the problem of the cardiazol fit has also attracted our attention. The following table shows the general layout of the experiments.

Cardiazol experiments (total number 42)

	Guinea pigs	Rabbits
Normal controls	11	8
Pretonic phase		
a: jerking	3	4 (1)
b: racing	3	
Tonic phase	4 (2)	4
Clonic phase	2 (2)	3 (1)

The figures in brackets indicate the number of experiments in which the identification of the stage of the fit was difficult. Normal and experimental animals were killed in the same way by crushing the neck between two strong, blunt steel blades, thus ensuring instantaneous death and the minimum of bleeding. It would lead too far if all possible fallacies and the precautions taken against them were to be discussed here. There will be a full report later when the material is larger. Numerous controls are necessary because, to mention only one difficulty, there exist already in the normal group individual variations of blood-content in the brain. So far we have not yet seen the general or circumscribed anæmia such as is described by Dreszer and Scholz. On the other hand, marked vasodilatation and irregularity of the vascular pattern in the later clonic stage of the fit has been a very constant phenomenon (Fig. 4, *b*). It could be seen throughout the brain, but was occasionally more marked in the basal ganglia than in the cortex (Fig. 5, *b*). For comparison and also as evidence for the usefulness of the method, vasodilatation after inhalation of amyl nitrite is shown in Fig. 4, *c*. Cats have not yet been investigated, but will be included in our further work.

Although vasoconstriction as an integral causative factor of epileptic convulsions becomes more and more doubtful, it should be kept in mind that disturbances of the circulation in the widest sense may under circumstances be of importance. This is instanced by the frequency of seizures in asphyxia and anoxia, in hyperpiesis, in syncope due to a hyperirritable carotid sinus and so forth. There is also Penfield's unique and puzzling case in which, after

unilateral cervical sympathectomy, symmetrical epileptic manifestations became unilateral.

It is, of course, open to criticism if conclusions drawn from observations on cardiazol convulsions in animals are applied to the problem of human epilepsy. Penfield never saw in symptomatic cases vasomotor changes of the intensity that he noticed in idiopathic epilepsy. To him an increased cerebral vasolability is a stigma chiefly of the idiopathic group. Observations on the pathology of cardiazol convulsions are scanty and somewhat contradictory. Severe ischæmic changes and subarachnoid or parenchymatous hæmorrhages have been described (Reitmann, 1938; Opper, 1939; Strecker and collaborators, 1939), but others saw changes of an unusual nature or failed to observe any. As regards human material Dreszer and Scholz mention briefly early ischæmic nerve-cell changes in a case which died during treatment. Dr. Drewry is at present investigating at the Central Laboratory two similar cases. The first was a patient with melancholia who, after a treatment with 23 injections of cardiazol, died in a state of sudden maniacal excitement. Exhaustion in conjunction with myocardial degeneration was regarded as the cause of death. The second case (schizophrenic) died without having shown a lasting improvement a year after insulin treatment and consecutive cardiazol treatment with 25 injections. The terminal disease was acute ulcerative enteritis. Both cases showed a diffuse, slight but distinct glial fibrosis of the subpial layer and of the white matter. No necrosis of the cornu ammonis, cerebellum or elsewhere was seen. A full report of these cases will be given later; here it may suffice to say that though an interpretation is difficult in view of the complex situation, the mild glial changes are what might be expected in cases of epilepsy.

It has been suggested that the post-epileptic lesions are non-specific, since they occur in a great many other conditions, such as whooping-cough, toxæmia of pregnancy, eclamptic uræmia, poisoning with carbon monoxide, cyanide, ether, hyperinsulinism and so forth. The choice of site has been considered to be due to a general susceptibility of the affected regions to ischæmic necrosis. So far no entirely satisfactory explanation for this selective vulnerability has been offered. Moreover, it should not be overlooked that the evidence in favour of non-specificity is considerably weakened by the fact that during most of the conditions mentioned above epileptic convulsions regularly occur. There is a growing belief that the affection of the cornu ammonis at least is more specifically associated with the mechanism of the epileptic convulsion and that we may have to seek additional factors in order to explain this connection. So far the discussion on this problem has been inconclusive (Stauder, 1934; von Braunmühl). Exposure to damage in tonsillar pressure cone during increased intracranial pressure frequently accompanying the epileptic seizure has been considered by Pfeiffer (1938) to be of importance in the pathogenesis of the cerebellar lesions. This idea might well be of wider

significance for our problem, since recent studies on the tentorial pressure cone (Hasenjager and Spatz, 1937/38; Jefferson, 1938) suggest that the uncus and the posterior cerebral artery as well as the cerebellar tonsils bear the brunt of increased intracranial pressure. It is perhaps more than a coincidence that one of the most characteristic photographs of uncinate pressure in the paper of Hasenjager and Spatz concerned a case of epilepsy. At present, in the absence of relevant facts, it would be idle to enter into further discussion. Research in this direction may well yield helpful results.

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