ON THE MECHANISM OF THE CARDIAZOL CONVULSION.

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The experiments described in this paper were performed in an attempt to elucidate the mechanism of the convulsion following the administration of cardiazol (pentamethylenetetrazol). The paper is divided into four sections—a description of experiments, a résumé of the relevant pharmacology of cardiazol, a discussion and a summary.

Experiments.

The question the authors asked themselves was, whether the convulsion following cardiazol might be due to a vascular spasm; alternatively, and in more practical terms, could vasodilatation be produced so that subsequent intravenous injection of cardiazol would fail to evoke a convulsion? Reitmann, in experiments on rabbits, has demonstrated that the convulsive phenomena due to insulin hypoglycæmia may be abolished by various vasodilators, among them amyl nitrite; the effect of sodium nitrite in inhibiting the convulsions was doubtful. Köst, using large doses of a 25% solution of amyl nitrite in ether by inhalation (4–8 grm. of the mixture) has shown in man that convulsions following cardiazol injection may also be prevented from occurring. Walk and Mayer-Gross have obtained similar results using triazol 156.

The question resolved itself into two parts: first, what was the appropriate amount of cardiazol required; second, which vasodepressant drugs should be used, and under what conditions? The appropriate dose of cardiazol, for the purpose of these experiments, is the least amount which will regularly produce a convulsion in any given individual. It is ascertained by lowering the dose from injection to injection until convulsion fails to ensue, and then subsequently increasing by 1 c.c. of the 10% solution used. The dose varies from individual to individual, but is moderately constant in the person over the period of a few weeks.

Of the available vasodepressant drugs three were chosen—amyl nitrite,

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sodium nitrite and histamine. These have in common the fact that their action is peripheral. Vasodepressant drugs which act centrally, such as the barbiturates, were avoided to prevent confusion of the issue. The conditions under which the three chosen drugs were used are described under the respective sub-titles.

The experiments were carried out as follows: The vaso-depressant drug was administered, and was followed after a suitable interval by the appropriate dose of cardiazol. Proof that convulsion had been prevented lay in the demonstration that, in the absence of the vasodepressant substance, convulsion ensued both at the previous and subsequent injections of the same dose of cardiazol. The interval between any two injections of cardiazol was either two or three days. In a few cases where there had been no previous cardiazol injections the proof lay in the results of subsequent injections only. The data are therefore tabulated in five columns—the initials of the patient, the appropriate dose of cardiazol, and the results of the two or three consecutive injections. It will be seen that the initials of six patients occur twice; this represents two separate demonstrations in each case. In the results "C" represents convulsion with unconsciousness, closely resembling a major epileptic fit, while "O" represents absence of convulsion and variable but incomplete loss of consciousness. When a convulsion is prevented from occurring by previously lowering the blood-pressure there is usually a general tremulousness and twitching of isolated groups of muscles. The patient may converse the whole time or remain silent. He may complain of unpleasant sensations which he is unable to describe, or of feelings of unreality which may last several hours. Occasionally there is considerable mental confusion and emotional instability. Some patients, on the other hand, experience nothing but the most fleeting sense of swimming of the head, and the majority feel well and are able to get up fifteen minutes after injection.

The experimental subjects were patients suffering from schizophrenia, undergoing or about to undergo a course of convulsion treatment. Thirty-two patients in all were used, 11 men and 21 women, of ages between 20 and 45, and in good physical health.

Amyl Nitrite.

When amyl nitrite is inhaled the blood-pressure quickly falls, the pulse becomes rapid, the skin, particularly of the head and neck, flushes, there is a feeling of faintness, and the respiration may quicken and deepen. The blood-pressure is lowest approximately one minute after beginning the inhalation. Three minims of the nitrite will lower the systolic pressure by 10–20 mm. Hg, 6 minims rather more. In these experiments two 3-minim capsules were broken under a lint mask and the patient was allowed to inhale for 50 seconds. The cardiazol was then injected. The results are tabulated below:

Initials of patient.	Appropriate dose of cardiazol (c.c.).	Result of injection of—		
		Cardiazol alone.	Cardiazol after amyl nitrite.	Cardiazol alone.
C. R—	3	C	O	C
L. P—	3	C	O	C
L. P—	3	C	O	C
E. B—	4	C	O	C
E. C—	6	C	O	C
A. S—	7	C	O	C
A. S—	6	C	O	C
I. G—	2·5	C	O	C
A. C—	4	C	O	C
W. J—	4·5	C	O	C
M. G—	3	C	O	C
M. L—	6	C	O	C
W. G—	4	C	O	C
J. M—	5	C	O	C
J. M—	5	C	O	C
A. B—	5	C	O	C
F. B—	5	C	O	C
F. B—	6	C	O	C

Sodium Nitrite.

Sodium nitrite may be administered by mouth or intravenously. Here it was used intravenously. After the injection of 1 gr. the blood-pressure falls, reaching its lowest after 20–30 minutes. It remains low for about half an hour, then slowly rises to its usual level. The fall of systolic pressure amounts to 20–25 mm. Hg. There is no appreciable quickening of the pulse, and there are no unpleasant subjective sensations. In the experiments tabulated below the appropriate dose of cardiazol was injected half an hour after the intravenous injection of 1 gr. sodium nitrite :

Initials of patient.	Appropriate dose of cardiazol (c.c.).	Result of injection of—		
		Cardiazol alone.	Cardiazol after sodium nitrite.	Cardiazol alone.
M. G—	6	C	O	C
E. W—	6	C	O	C
M. G—	6	C	O	C

Histamine.

Approximately 20 seconds after the intravenous injection of ·1–·2 mgrm. histamine the skin of the face and neck flushes, there is a metallic taste in the mouth, the blood-pressure falls, the pulse quickens, and there is a feeling of

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light-headedness. Almost immediately afterwards the blood-pressure rebounds to, or even above the normal level. Rather arbitrarily in these experiments the cardiazol was injected 10 seconds after the intravenous injection of ·25 mgrm. histamine. The results were as follows:

Initials of patient.	Appropriate dose of cardiazol (c.c.).	Result of injection of—		
		Cardiazol alone.	Cardiazol after histamine.	Cardiazol alone.
C. B—	6·5	C	O	C
C. B—	6·5	C	O	C
E. D—	4	C	O	C
D. R—	4	C	O	C
E. W—	6	C	O	C
W. F—	5	C	O	C
L. W—	6	C	O	C
N. H—	7	C	O	C
E. B—	6	C	O	C
M. G—	6	C	O	C
L. E—	5	C	O	C
F. B—	5	C	O	C

Above are recorded the successful attempts to prevent convulsion. In the course of the experiments with one or other of the vasodepressant drugs failure to prevent convulsion occurred in 29 instances. These failures are listed below. They are classified into (*a*) those due to the use of too large an amount of cardiazol, as it was shown on subsequent occasions that 1 c.c. less of the 10% solution used would suffice to evoke a convulsion; (*b*) those due either to insufficient vaso-depressant drug or to wrong time-interval between the administration of the latter and cardiazol, as it was later shown in these cases that by correcting these errors convulsion could be prevented; (*c*) those failures to which neither of the above explanations apply.

	Failure to prevent convulsion due to—		
	Too much cardiazol.	Wrong technique.	Unexplained.
Amyl nitrite	9	2	0
Sodium nitrite	7	1	0
Histamine	5	0	5

It will be seen that in the case of amyl nitrite and histamine, the failures to prevent convulsion are all due either to too much cardiazol having been used or to other errors in technique. The conclusion may be drawn that these drugs directly antagonize cardiazol in the production of a convulsion. In the case of sodium nitrite the evidence is doubtful. Out of 13 attempts to prevent convulsion there were 10 failures. Only 5 of these were due to the use of too

large a dose of cardiazol. Five failures remain unexplained. This equivocal effect of sodium nitrite corresponds with Reitmann's findings in the case of convulsions due to insulin.

Action of Cardiazol on the Cardiovascular and the Central Nervous Systems.

The known pharmacology of cardiazol is adequately presented by Hildebrandt in *Handbuch der Experimentellen Pharmakologie*, 1937, vol. v, where the action of cardiazol on the circulation is fully discussed. Most workers agree that in animals cardiazol affects the circulation via the vasomotor centre rather than peripherally. It stimulates the medulla, causing vasoconstriction and increased cardiac output. Vasoconstriction has been observed directly in the intestinal blood-vessels in rabbits (Leffkowitz), but has not been sought in other regions. Meduna, on the other hand, reports absence of spasm of the blood-vessels of the fundus during and after the injection of a fit-producing dose of cardiazol, and states that in the cat cardiazol causes a dilatation of meningeal arteries and veins. These observations need careful confirmation. The increased cardiac output produced by cardiazol is due to more forceful beating of the heart, the pulse-rate showing no rise. The effect of cardiazol on the blood-pressure is reported variously. It is generally agreed that when the blood-pressure is lowered in peripheral vascular failure, then injection of cardiazol causes a substantial rise. Thus a fall of blood-pressure due to the administration of chloroform, quinine, somnifaine, morphine, papaverine, acetylcholine, histamine, or due to splanchnic section, suprarenal extirpation or hæmorrhage is countered by injection of cardiazol. However, the effect of cardiazol on the normal blood-pressure in man is uncertain. When moderately large doses (·1–·2 grm.) are taken by mouth the blood-pressure sometimes rises, sometimes falls. When a large amount, just insufficient to provoke a convulsion, is injected intravenously a sudden but transient rise of blood-pressure occurs.

Much work has been done on the effect of cardiazol on the central nervous system. In the intact animal small doses increase reflex excitability, larger doses produce epileptiform convulsions, while massive doses cause paralysis. Many attempts have been made to locate a hypothetical point of attack of cardiazol in the central nervous system. The evidence is conflicting, but suggests that in animals at least the cerebral hemispheres play no part in the convulsion. Indeed Blume, experimenting on cats, reports typical epileptiform convulsions after decapitation. Camp showed that when the spinal cord is cut through in the thoracic region a convulsion is limited, as might be expected, to the head and fore limbs. Rather surprisingly, when the posterior roots of the brachial plexus of the cat are cut, the forelimbs then take no part in the convulsion (Blume).

Discussion.

It remains to correlate the experimental results reported in this paper with our knowledge of the pharmacology of cardiazol. It appears that the effects of cardiazol on the circulation occur solely through the vasomotor centre. The chief of these effects is vasoconstriction. The results of the experiments concerning amyl nitrite and histamine demonstrate that vasodilatation antagonizes the action of cardiazol, inasmuch as under appropriate conditions it prevents convulsion from occurring. The suggested conclusion is that the convulsion itself is due to a vascular spasm.

That the epileptic fit itself is due to a vascular spasm has for long been a favoured hypothesis, which as yet remains without proof or disproof, largely because the epileptic fit is not readily adaptable to experiment. The convulsions which occur in epilepsy on the one hand, and after cardiazol and triazol injections on the other, are closely similar, but it is not certain that they are identical phenomena. Nevertheless, investigations of the cardiazol and triazol convulsions offer a working approach to epilepsy, an approach which is eminently suited to experiment.

Summary.

1. Experiments on the effect of amyl nitrite, sodium nitrite and histamine on the cardiazol convulsion are reported, demonstrating that vasodilatation under appropriate conditions prevents the occurrence of the convulsion.

2. The relevant pharmacology of cardiazol is summarized.

3. The conclusion is drawn that the convulsion following cardiazol injection is due to sudden vasoconstriction.

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