BLOOD-PRESSURE IN CARDIAZOL EPILEPSY.

By E. GUTTMANN, M.D., and F. REITMANN, M.D.

(From the Research Unit, Maudsley Hospital, London.)

(Received April 29, 1939.)

No problem in neurology has been approached from so many different angles as has the pathogenesis of the epileptic fit; yet it is far from being solved. Histological examination of the brains of epileptics, electric stimulalation of the human brain during operation, chemical analysis of the body fluids both in general and of the arterial and venous blood of the cerebral vessels in particular, measurements of the intracranial blood-flow, investigations into metabolic changes before, during, and after fits, electro-encephalographic studies, have produced an enormous wealth of data, which it has not, however, been possible to weld into a single theory. The most recent monograph on epilepsy—Kinnier Wilson's article on the subject in Bumke's *Handbuch der Neurologie*—speaks only of various "determinants" of the fit: the vascular, the humoral, etc.

Since one of the difficulties of research into the pathogenesis of the epileptic fit in man is the irregularity of its occurrence, the opportunity of provoking a fit at a given time under experimental conditions should prove of great advantage to research. Foerster's method of hyperventilation gave a stimulus of this sort, resulting mainly in the recognition of physio-chemical factors in the production of the epileptic fit. The importance of the vascular factor could not, however, be overlooked, especially since histologists have demonstrated vascular lesions in the brain, on the interpretation of which much energy has been expended. Interest has recently been focused more on the vascular factor, since the convulsive treatment of schizophrenia has made available for study human fits produced by a drug, cardiazol, which in smaller doses is used as a powerful cardio-vascular excitant.

F. Georgi was the first to study this type of experimental convulsion in man in relation to the pathogenesis of epilepsy in general. Applying the methods he had previously used in studying hyperventilation tetany and hyperventilation epilepsy, he found "ionic changes only when the cardiazol injection was successful"—in other words, when a fit occurred; this led him to the conclusion

https://doi.org/10.1192/bjp.85.357.787 Published online by Cambridge University Press

" that the pathogenetic factor is not to be found in a primary vaso-spasm, but in the ionic changes at the cell membranes ".

The injection of a convulsant dose of cardiazol is followed by marked reactions in the cardio-vascular system. According to von Meduna, the systolic blood-pressure rises by 20–30 mm. Hg. in the course of the fit ; in some cases the rise was much greater, up to 70 mm. Hg. The diastolic pressure rises less than the systolic ; in other words, the pulse pressure increases. Von Meduna thinks that the fluctuations are due to the fit rather than to the drug ; the rise in blood-pressure in the same patient is twenty or thirty points greater if a fit is produced than if the injection fails to produce one. Other authors agree with this view, especially since in animal experiments the blood-pressure does not rise when the muscles are paralysed by curare (Coombs and Pike, Denny-Brown and Roberts, Maloney and Tatman).

A. Harris took blood-pressure readings before the injection, during the flaccid stage of the fit, and half an hour later. He found a paroxysmal rise in the majority of the cases, but the changes were irregular ; v. Meduna even found a fall of 5–10 mm. Hg. in the systolic pressure after cardiazol injections short of the convulsant dose. In every case the change in blood-pressure, v. Meduna says, was transient, and disappeared five minutes after the fit. Harris's measurements, taken half an hour after the fit, however, still show marked deviation from the pre-paroxysmal reading, and O. Briner was the first to describe a prolonged rise of blood-pressure after the convulsion treatment. Harris found in a few of his 21 cases a definite hyperpiesia with increased pulse-pressure, which in some cases persisted for several weeks after the end of the treatment, although no clinical signs of any damage to heart or kidneys could be discovered. Such a sustained rise in blood-pressure can obviously not be due to muscular activity during the convulsion, and therefore deserves attention if the role of the blood-pressure in the production of the fit is to be discussed.

In order to gain some personal knowledge of the blood-pressure curve, we took readings from a number of patients before the injection of cardiazol, in the latent period before the fit, immediately after the fit, and at short intervals thereafter. The latent period between the end of the injection and the onset of the convulsion is generally only about 30 seconds. It is, therefore, scarcely possible to get more than one reliable reading ; once the muscular action starts, the ordinary Riva-Rocci method fails to give reliable results, owing to the alteration of the elastic qualities of the bed against which the artery is compressed. Whenever it is possible to obtain readings between injection and fit (often it is impossible, owing to the patient's resistance or excitement), the values are higher than before. Considering the anxiety which generally follows the injection, the vasomotor reaction may be, and has been, regarded as an accompaniment of the emotion. It seems artificial, however, to separate the physical and psychological response in such an acute experiment. The

https://doi.org/10.1192/bjp.85.357.787 Published online by Cambridge University Press

curve reproduced below (Fig. 1) is an example. The original systolic blood-pressure (145) is somewhat higher than before the beginning of the convulsion treatment. Immediately after injection the blood-pressure rises. The highest reading obtained before the fit was 170. This experiment was not quite typical, in that the latent period was long enough to permit three blood-pressure readings to be obtained. Within a minute after the fit the maximum of 185 was reached, and in less than ten minutes the blood-pressure had gradually fallen to slightly above its original level.

The average blood-pressure curve, constructed from fifteen observations of this kind, had two gaps which could not be filled in for technical reasons. That the last reading before the fit really indicates the maximum rise cannot

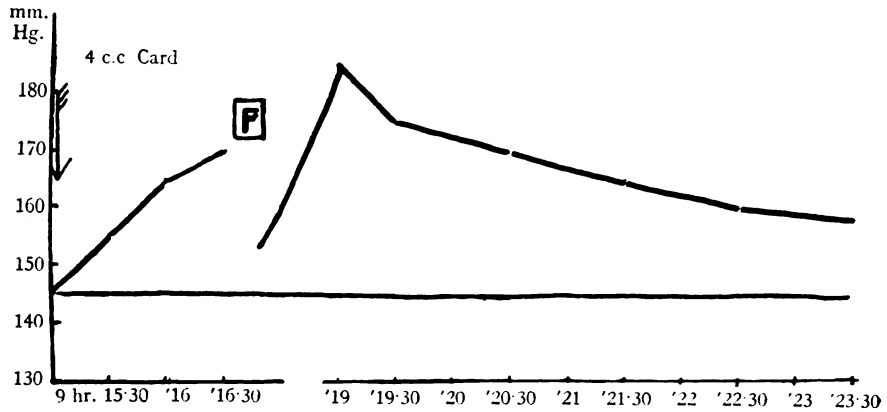


FIG. 1.—Blood-pressure after convulsant dose of cardiazol, 4·0 c.c. F = fit. Time in minutes.

be confirmed, because, as already mentioned, the usual readings with the Riva-Rocci technique are not reliable in the tonic stage. Furthermore, readings during the flaccid stage immediately after the fit, at a time when the patient is cyanotic and the respiration often ceases, give very low figures, and from many observations we are satisfied that the post-paroxysmal peak in our curve is preceded by a drop. The average of the first readings after the fit was well below the average of the initial values. When the first readings are obtainable, one can often hear the sounds at about 0 mm., and the systolic pressure rises more rapidly than the diastolic. The whole negative fluctuation, however, lasts less than a minute, and the maximum is reached within two minutes. This temporary fall of blood-pressure has either not been noticed by previous observers, or it has not been regarded as important. According to our observations, the fluctuation is quite definite, and may be responsible for some of the histological findings in the brain after convulsion. The sudden

https://doi.org/10.1192/bjp.85.357.787 Published online by Cambridge University Press

influx of blood into an anæmic organ is obviously a severe strain on the blood vessels.

For the study of the effect of cardiazol on the blood-pressure, the fit itself is an undesirable complication. We therefore recorded the blood-pressure curves after sub-convulsant doses of the drug. Three c.c. of a 10% solution is generally, and was in all our experiments, a dose suitable for this purpose. The average curve obtained in six experiments of this kind is given below

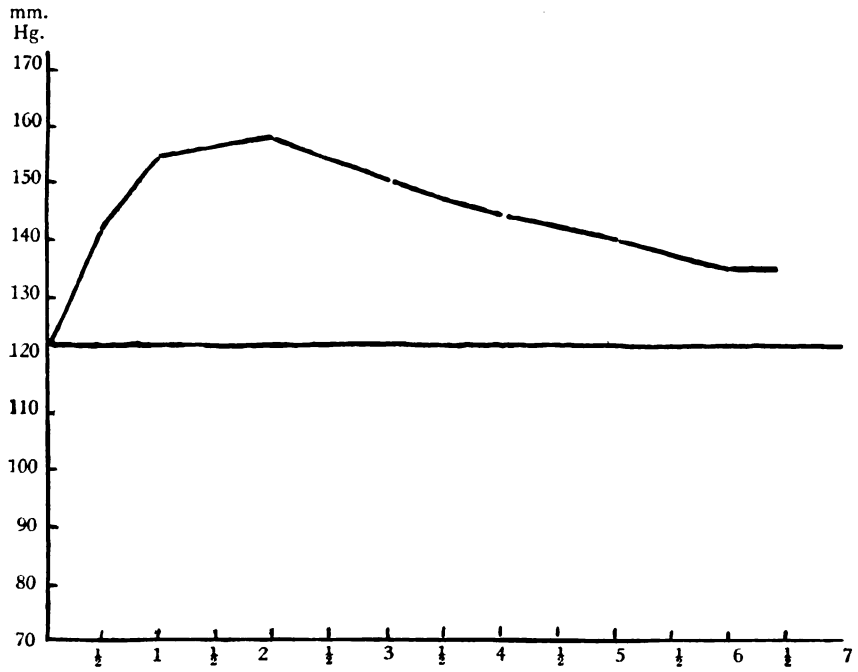


FIG. 2.—Average blood-pressure curve after a subconvulsant dose (3·0 c.c. cardiazol).

(Fig. 2). It reaches its maximum two minutes after injection. This appears to favour the assumption that the cardiazol fit (after larger doses) occurs before the maximum rise of blood-pressure. Considering, however, both the lack of precision in our clinical measurements and our lack of knowledge of the correlation between size of dose and rapidity of effect, no definite conclusions can be drawn from this curve.

Another approach was to study the comparative effect of variable doses of the drug on the same patient. In an experiment of this kind careful attention has to be paid to the rise of blood-pressure, which persists after the cardiazol fit. The following table gives the results in a schizophrenic patient at the

https://doi.org/10.1192/bjp.85.357.787 Published online by Cambridge University Press

beginning of his cardiazol treatment, while his convulsant dose was being tested:

Date.	Initial reading.	Dose.	Maximum reading.	Rise.
24.x	110	2·0 c.c.	110	0
25.x	110	2·5 ,,	122	12
26.x	122	3·0 ,,	155	33
27.x	140	3·5 ,,	145	5
29.x	122	4·0 ,,	Fit	Not used.
2.xi	132	4·0 ,,	160	28
3.xi	136	4·5 ,,	148	12
7.xi	128	5·0 ,,	165	37
8.xi	135	6·0 ,,	Fit	..

Three points can be made in interpreting this table. Each injection tends to increase the blood-pressure for a considerable period afterwards. The rise is transient, and a period of rest produces a fall—not necessarily to the original level. With increasing doses the maximum reached becomes higher, but the effect, both on the rise and on the maximum, depends on the initial level; if this is unusually high, the effects do not increase proportionally to the dose. The closer one gets to the convulsant dose the higher is the rise of blood-pressure.

This obviously seems to support those theories which regard the alteration in the systemic blood-pressure as important or even decisive in producing the epileptic fit.

Apart from blood-pressure studies, the main clinical arguments in favour of the vascular origin of convulsions are derived from observation of the effect of drugs of known circulatory effect on the prevention of fits.

After Reitmann had successfully used amyl nitrite—among other substances—to prevent insulin convulsions, Köst carried out similar experiments in cardiazol epilepsy with the same result. His experiments, however, are not conclusive, owing to his use of ether as a dissolvent for amyl nitrite.

Denyssen and Watterson, interested in the elucidation of the mechanism of cardiazol epilepsy, carried out similar experiments with amyl nitrite on a larger scale, and with better technique than Köst. They got the patient to inhale amyl nitrite from a lint mask for 50 seconds, and then injected a convulsant dose of cardiazol, as tested before. In this way they succeeded in preventing the convulsion in all their cases (18). Their results with histamine and sodium nitrite were similar. All three drugs used are peripheral vaso-depressants. "The experiments demonstrate that vaso-dilatation antagonizes the action of cardiazol, inasmuch as under appropriate conditions it prevents convulsions from occurring. The suggested conclusion is that the convulsion itself is due to a vascular spasm." This conclusion, however, might be

https://doi.org/10.1192/bjp.85.357.787 Published online by Cambridge University Press

questioned. The actual effect of cardiazol on the blood-pressure in the experiments of Denyssen and Watterson cannot be deduced from their publication. It does not appear justifiable simply to add the results of separate experiments with the two drugs; we know, for instance, that cardiazol is much more powerful in raising low blood-pressure, such as might result from infections or intoxications, than it is in influencing normal blood-pressure. To test this we

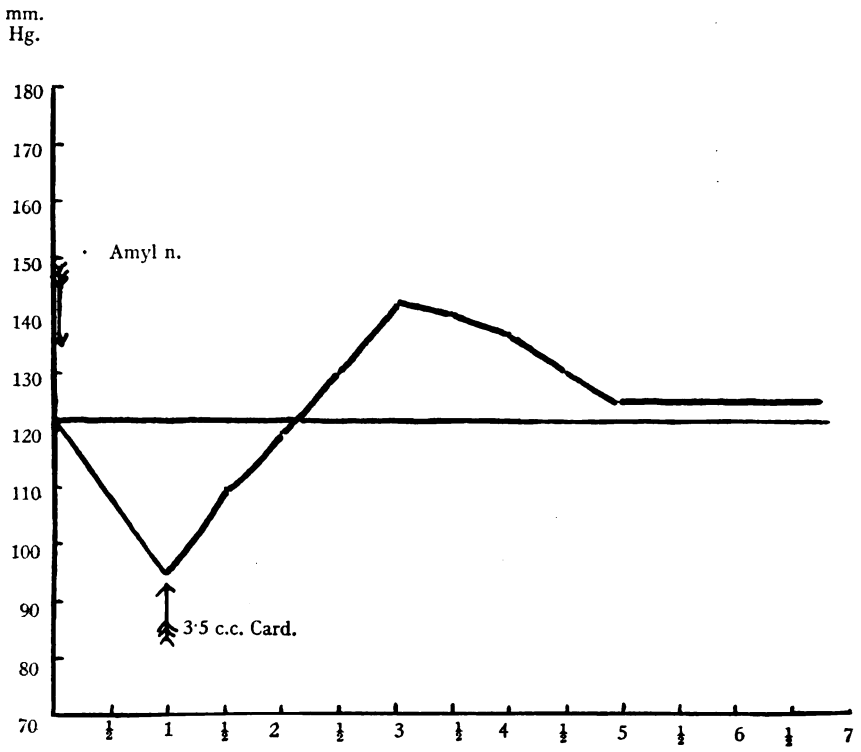


FIG. 3.—Blood-pressure curve after inhalation of 6 minims of amyl nitrite 50 seconds before injection of convulsant dose (3·5 c.c.).

took readings before the start of the whole experiment, again after amyl nitrite inhalation, and then after cardiazol injection; curves such as that reproduced in Fig. 3 show that the blood-pressure does not, in fact, reach the level at which the fit would otherwise occur. This confirms the results of Denyssen and Watterson's experiments.

Another point of theoretical importance has been observed by Denyssen and Watterson, but they drew no conclusions from it. Like these authors, we observed in the experiments with amyl nitrite and cardiazol that the patients were not indifferent to the combined effects of the two drugs—" there is usually

https://doi.org/10.1192/bjp.85.357.787 Published online by Cambridge University Press

a general tremulousness and twitching of isolated groups of muscles". These signs of motor excitation may be very marked, though the rise of blood-pressure is completely counteracted. Where there is an opportunity to observe the more gradual development of an epileptic fit, e.g., after triazol or insulin, it can often be seen that similar hyperkineses gradually blend into a generalized convulsion—in other words, after amyl nitrite plus cardiazol, there may occur symptoms which differ only in degree from the pure cardiazol symptoms. This may suggest an influence of amyl nitrite on the distribution of cardiazol rather than a direct antagonism (see below).

It seemed, further, that complementary evidence of the role played by the systemic blood-pressure could be obtained if the rise of blood-pressure could be effected otherwise than by cardiazol alone. The drug chosen for this purpose was benzedrine. As no data were available, the blood-pressure curve after intravenous injection had first to be determined.

The intravenous injection of 10 mg. of benzedrine was followed by the immediate increase of blood-pressure, which reached its maximum about two minutes after the end of the injection. The average increase was about 30 mm. Hg. For our purpose we selected patients who had shown a constant convulsant threshold during their treatment. We then gave them for these experiments 10 mg. of benzedrine intravenously, and one to two minutes later an injection of cardiazol. 2–3 c.c. below the convulsant dose. Blood-pressure readings by the usual method were taken almost continuously. The result is illustrated by curve No. 4. This curve shows that though the result of the combined injections on the blood-pressure was the same or even more marked than after cardiazol alone, no fit occurred. In subsequent control experiments it was ascertained that the convulsion threshold had not varied in the mean-time. Five experiments of this type were carried out on four patients, always with the same result. This result, of course, militates against the possibility of the systemic blood-pressure as such being the causative factor in producing the convulsion, and these experiments seem to indicate a direct toxic effect of cardiazol on the nerve-cell.

Before discussing whether it may play a more indirect role, another interpretation of these experiments with vaso-dilator and vaso-constrictor drugs may be considered. Assuming the fit to be the result of a direct action of the drug on the brain-cell, its occurrence or non-occurrence might depend on a time factor—in other words, on the amount of poison brought to the cell per time unit. Any increase of the blood-supply carrying the poison would favour the occurrence of the fit; any decrease would reduce the effect or prevent it. Experiments by Reitmann have demonstrated that amyl nitrite, given immediately after the cardiazol injection, does not prevent the cardiazol fit, but, on the contrary, intensifies the action of the drug. Taken in conjunction with the experiments already quoted at length, it could be explained that amyl nitrite prevents the cardiazol fit, if the convulsant is given when the blood-pressure

https://doi.org/10.1192/bjp.85.357.787 Published online by Cambridge University Press

is low, all vessels dilated, and the transport of the drug to the brain therefore slow and the poisoning gradual. When amyl nitrite is given after the cardiazol, the sudden dilatation of the vessels of the upper half of the body, and especially of the head, so characteristic of the initial amyl nitrite effect, increases the supply of poison to the brain and therefore reinforces the convulsant action.

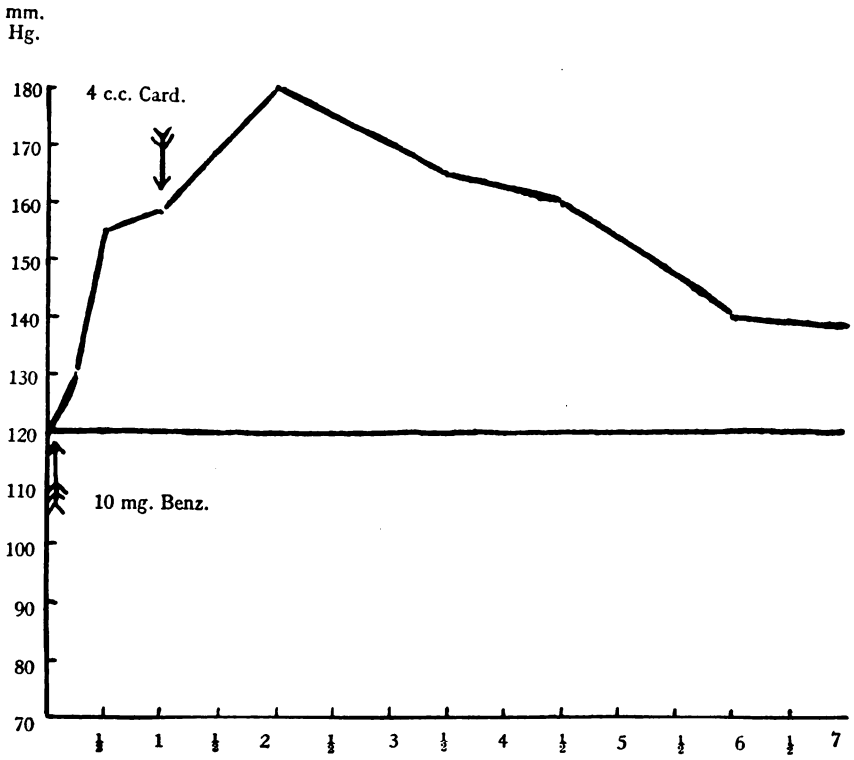


FIG. 4.—Blood-pressure curve after 10 mg. benzedrine intravenously, followed by subconvulsant dose of cardiazol.

There is no experimental foundation for a corresponding explanation of the experiments with benzedrine, the effect of which on the various vascular territories has not yet been studied.

Though arterial hypertension as such may have to be discarded as the ætiological factor of the epileptic fit, it may still be important. It is generally regarded as indicating a pathological functioning of the circulatory system, as v. Bergmann put it. It favours the occurrence of functional vasomotor disturbances, local or general, i.e., angiospasm followed by prestasis and stasis. Thus, the rise of blood-pressure may increase the predisposition to local vasomotor phenomena which are so commonly alleged to be the essential agents

https://doi.org/10.1192/bjp.85.357.787 Published online by Cambridge University Press

in producing the fit, and a fall may have the opposite effect. Alfred Meyer has recently pointed out how difficult it is to interpret correctly the histological findings on which the vascular theories are commonly based. We refer to his paper, as these pharmacological experiments do not furnish new facts for such a discussion.

Summary.

(1) The blood-pressure curve in cardiazol epilepsy was studied. There was, in the curve of blood-pressure between cardiazol injection and fit, an initial rise, followed by a fall which coincided with the fit, and finally a steep rise which did not later entirely subside to the initial line.

(2) Subconvulsant doses produced a rise of blood-pressure dependent in degree on the dose and the initial level. The nearer the dose to the convulsant threshold, the higher the rise of blood-pressure.

(3) Keeping the blood-pressure low by means of amyl nitrite prevented the fit. A sudden increase of blood-pressure by means of an intravenous benzedrine injection would not, however, produce a fit with a subliminal dose of cardiazol.

We wish to express our thanks to Prof. E. Mapother for allowing us to use the clinical material of the Maudsley Hospital, to Dr. A. J. Lewis for his criticisms and suggestions, and finally to Messrs. Menley and James, who kindly supplied the benzedrine used in these experiments.

References.

Briner, O.—*Schweiz. Arch. Neurol. Psychiat.*, 1937, xxxix, p. 118.
Coombs, H. C., and Pike, F. H.— *Amer. Journ. Physiol.*, 1931, xcvii, p. 92.
Denny-Brown, D., and Robertson, E. G.—*Journ. Neurol. Psychopath.*, 1934, xv, p. 97.
Denyssen, J. A. F., and Watterson, J.—*Journ. Ment. Sci.*, 1938, lxxxiv, p. 1002.
Georgi, F.—*Schweiz. med. Wochenschr.*, 1936, lxvi, p. 935.
Harris, A.—*Journ. Ment. Sci.*, 1938, lxxxiv, p. 735.
Kennedy, A.—*Ibid.*, 1937, lxxxiii, p. 609.
Köst, H.—*Psychiat.-neurol. Wochenschr.*, 1938, xiv, p. 156.
Maloney, A. H., and Tatman, A. L.—*Arch. intern. de Pharmacodyn. et de Thérapie*, 1932, xlii, p. 200.
Meduna, L. v.—*Die Konvulsicnstherapie der Schizophrenie*, Halle, 1937.
Meyer, Alfred.—*Journ. Ment. Sci.*, 1938, lxxxiv, p. .
Reitmann, F.—*Psychiat.-neurol. Wochenschr.*, 1938, xvi, p. 5.

https://doi.org/10.1192/bjp.85.357.787 Published online by Cambridge University Press