

Effect of Metrazol on Cerebral Vessels.

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At the beginning of a convulsive seizure in animals, caused by metrazol (pentamethylenetetrazol), pallor of the brain surface has been reported. Liebert and Weil attribute this to "vasospasm".¹ Watterson and Macdonald, on the other hand, find "no certain evidence that the convulsion is either caused or accompanied by cerebral vasoconstriction," but they do find that drugs causing vasodilation tend to inhibit metrazol seizures.²

To get more accurate data on the vascular response to metrazol 15 cats and one monkey have been studied as follows: The diameters of pial arterioles and venules over the parietal cerebral cortex were measured by microscope through a cranial window.³ Metrazol

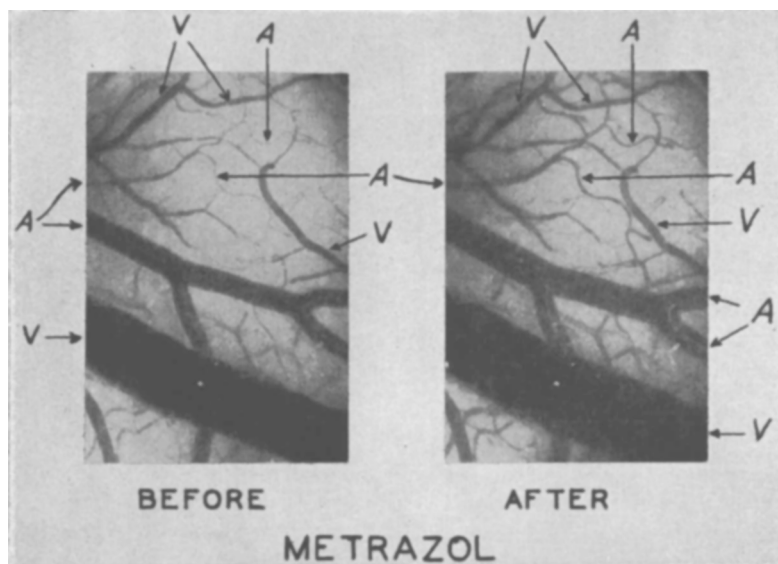


FIG. 1.

Photomicrographs of pial vessels before and after intravenous injection of 4% metrazol (40 mg per kilo). The arteries (A), veins (V) and their branches are all dilated in the second photo taken 65 seconds after the injection. Taken on 35 mm film—ocular $\times 10$, objective $\times 3$.

¹ Liebert, E., and Weil, A., *Arch. Neurol. and Psychiat.*, 1939, **42**, 690.

² Watterson, D. J., and Macdonald, R., *J. Ment. Sci.*, 1939, **85**, 392.

³ Forbes, H. S., *Arch. Neurol. and Psychiat.*, 1928, **19**, 751.

(8 to 80 mg per kilo, in 4% solution) was injected into the saphenous vein or carotid artery (46 trials), or it was applied locally to the surface of the brain (5 trials). Diallyl barbituric acid was used for anesthesia except in two instances, when intraperitoneal magnesium sulphate was used.* Cerebrospinal fluid pressure from the cisterna magna was recorded by photokymograph.⁴

The findings were these: The pial arteries (and veins) dilated (Fig. 1). The dilation usually started a few seconds before the first twitches were seen. Occasionally the seizure appeared first (Fig. 2). After a 5-second intravenous injection of metrazol the latent period before the first sign of dilation averaged 10 seconds (26 trials). The latent period before the seizure averaged 15 seconds.

Sometimes, however, the vasodilation had passed and the vessels were contracting when the convulsion started (Fig. 3) and some-

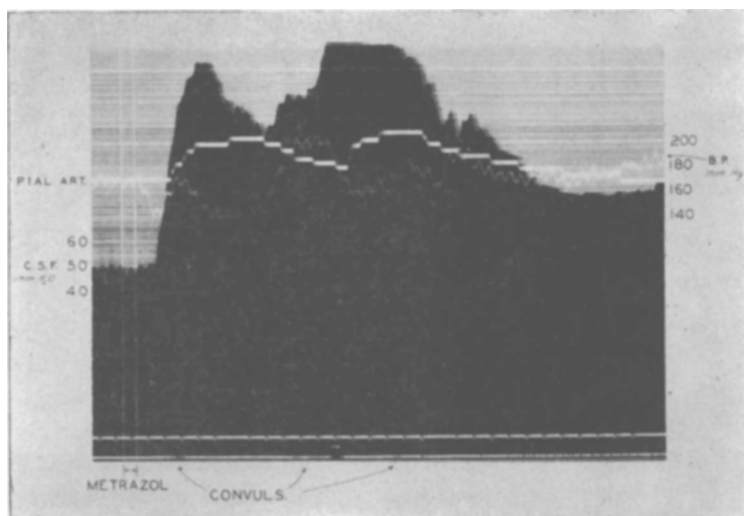


FIG. 2.

Dilation of pial artery. *Early convulsion.* Magnesium sulphate anesthesia. Artificial respiration. Metrazol—17 mg per kilo (1 cc 4% solution) was injected into a leg vein. Cerebrospinal fluid pressure (C.S.F.) is recorded by the top edge of the black area, which is the photographic tracing of the meniscus of fluid in a 1 mm bore manometer connected with the cisterna. Blood pressure was taken from the right common carotid. First convulsive twitches occurred one or 2 seconds before the pial artery started to dilate. No consistent relationship is apparent between C.S.F. pressure, blood pressure and arterial calibre.

* The magnesium sulphate animals did not react to metrazol differently from the others except by showing, often, a rise in blood pressure.

⁴ Forbes, H. S., Nason, G. I., and Wortman, R. C., *Arch. Neurol. and Psychiat.*, 1937, **37**, 334.

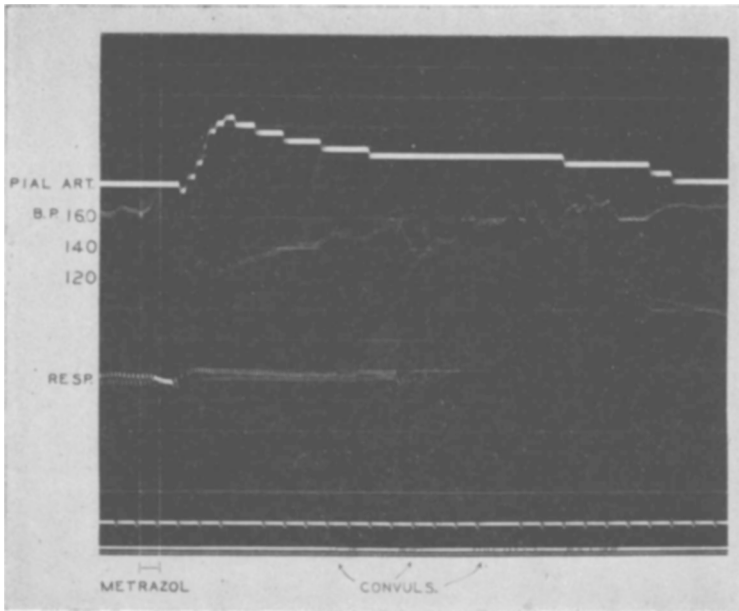


FIG. 3.

Dilation of pial artery. *Late convulsion.* Dial anesthesia. Metrazol—40 mg per kilo (2 cc 4% solution) injected into a leg vein caused sudden fall in blood pressure. Diameter of this pial artery was 254 microns. Blood pressure was taken from the right common carotid. Time marker records 5-second intervals. Breaks in signal line (at bottom) indicate the presence of clonic muscular contractions. The latent period before this seizure was 3 times longer than usual.

times the dilation occurred without any convulsion (Fig. 4). In other words, no constant relation was found between the seizure and the vascular change. Vasoconstriction was not observed.

The systemic arterial pressure, after a period of fluctuation, usually fell. Sometimes it remained almost unchanged. Respirations often stopped for 5 or 10 seconds and then became very rapid. In some experiments artificial respiration (with bilaterally opened thorax) was carried out. Neither the incidence of convulsions nor of vasodilations was affected by changes in respiration or in blood pressure.

Leibel and Hall found a decrease in cerebral blood flow (in rabbits) immediately following the injection of metrazol.⁵ They also noted a fall in blood pressure. Undoubtedly this fall was the cause of the decreased flow, which took place in spite of the local vasodilation. In those experiments of ours in which the blood pressure

⁵ Leibel, B. S., and Hall, G. E., *PROC. SOC. EXP. BIOL. AND MED.*, 1938, **38**, 894.

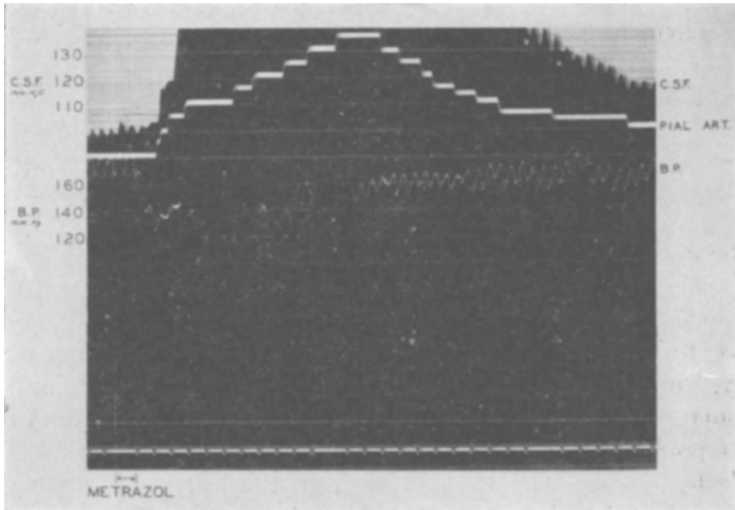


FIG. 4.

Dilation of pial artery. *No convulsion.* Dial anesthesia. Artificial respiration, open thorax. Metrazol—50 mg per kilo (3 cc 4% solution) injected into a leg vein caused a pronounced fall in blood pressure. The pial artery (104 microns in diameter) dilated promptly but no convulsion occurred. The rise in cerebrospinal fluid pressure—recorded by top of black area—happened in this instance to synchronize with the period of vasodilation. This relationship was not constant, however.

remained constant, or rose, it is fair to assume that the flow increased.

The rise in cerebrospinal fluid pressure, after each metrazol injection, showed no constant relation to any of the other variables which were measured (Fig. 2).

Summary. In animals metrazol caused cerebral vasodilation. This was unrelated to changes in blood pressure or in respiration, and showed no constant relation to convulsive seizures. No cerebral vasoconstriction was observed.