THE ACTION OF CERTAIN DRUGS ON BRAIN CIRCULATION IN MAN*

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The pharmacologic response of the brain vessels in man is a question presenting more than ordinary difficulty to experimental study, particularly under normal, nonoperative conditions. The only work of any significance in the latter connection is that of Shepard,¹ and even here the matter of specific drug effect is but incidentally dealt with—only one group, that of the nitrites, having been definitely reported. It was deemed distinctly fortunate, therefore, when the presentation of a suitable subject rendered further investigation possible.

REPORT OF CASE

The subject R. K., aged 40, a male patient at the State Psychopathic Hospital, had undergone double subtemporal decompression for the relief of increased intracranial pressure, presumably of tumor origin. The first decompression had been performed nine months, and the second, eight months prior to the initiation of this study, the patient, having by that time, fully recovered from all operative reaction. There developed residually, however, at the decompression sites, two large, pulsating cerebral hernias, each about the size and shape of a lemon. Mentally, the patient, though showing a certain deterioration, was fully capable of satisfactory cooperation.

METHOD OF PROCEDURE

Specifically, the procedure was as follows: The subject was required to lie at full length on his left side, with his face flat to the pillow, thus furnishing a level and stable support for the presenting right hernial mass, and extreme care was taken to maintain this position throughout each observation period. The site of the presenting mass was shaved and encircled by a bed of putty into which was set, so as to enclose the mass completely, an ordinary glass funnel of suitable size. To the tip of this was affixed a length of rubber

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1. Shepard: *The Circulation and Sleep*, New York, Macmillan Co., 1914, p. 80 et seq.

tubing, provided with a regulating T-arm, and terminating in a delicate recording-tambour of the Meister type, which was so placed as to record on a moving drum. It was found easily possible in this manner to secure a perfectly satisfactory pulse tracing. As a preliminary precaution, in order to rule out possible skin and muscle effects, duplicate appliances were affixed over the forehead, jaw, and thorax; these, however, yielded no demonstrable pulsation or other change.

RESULTS

The first drug investigated was amyl nitrite, administered by inhalation. The response was immediate and frank. There was noted

Fig. 1.—Pulse tracing showing effect of amyl nitrite.

(Fig. 1) a distinct upward movement of the lever indicative of increased volume in the part under observation, i. e., vasodilation. This was attended by a distinct increase in the pulse rate, the beat showing characteristic dicrotism. These findings were distinctly in corroboration of Shepard's.¹ They were also in agreement with Hirschfelder's² results, as determined through observation on the retinal and pial vessels of cats and rabbits.

The second drug studied was epinephrin, administered intravenously, very slowly and in minute, diluted dosage until effects were observed. The response to this drug, also, at every trial, seemed

2. Hirschfelder: *J. Pharmacol. & Exper. Therap.* **6**:597, 1914-1915.

quite definite. There was noted first (Fig. 2) a slight but distinct constriction, soon followed by a marked dilation, the reaction being characterized throughout by an increased pulse rate and amplitude. There was no demonstrable "leukoreaction" or blanching of the face, as reported by Milian.³ It is conceivable that these results may be explained on the basis of a primary specific brain vessel constriction which is soon overcome, mechanically, by the massive reflux of blood from other more powerfully contracting centers, such as the splanchnic and limb areas. These observations seem of particular interest in view

Fig. 2.—Pulse tracing showing effect of epinephrin.

of the prevailing differences of opinion in regard to the exact response of the brain circulation to epinephrin. The only available findings approaching those of the present study have been reported by Kahn⁴ based on observation of the retinal vessels of cats and rabbits.

The drug next investigated was caffeine—administered, intravenously, as caffeine—sodium benzoate, each dose containing 3.75

Fig. 3.—Pulse tracing showing effect of pituitary extract.

grains of the alkaloid. The findings in this connection were negative—no change in rate or volume being demonstrable. Such a response is readily conceivable in the normal animal when one considers the opposite tendencies excited by caffeine, to wit: bulbar vasomotor stimulation as against local vasodilation and vagus excitation as opposed to direct stimulation of the heart muscle. Still it is possible that, with greater dosage, a more definite reaction might have been secured. The

3. Milian, G.: Administration of Epinephrin, *Paris méd.* **8**:81 (Feb. 2) 1918.

4. Kahn: *Centralbl. f. Physiol.* **18**:153, 1904.

results seem to be at variance with findings by Berezin⁵ and Hirschfelder.² Both these investigators, the former working with the perfused brain in pikes and rabbits, and the latter on the pia and retina of cats and rabbits, have reported a dilation. Roy and Sherrington,⁶ however, in their volumetric studies on trephined dogs, claim an initial increase in volume followed by a decrease which, in turn, is succeeded by another rise.

The last drug exhibited was pituitary extract (pituin, Parke, Davis & Co.). This also was administered intravenously very slowly and in minute diluted dosage until effects were noted. In this connection there was found (Fig. 3), characteristically, a distinct though slight rise in volume, unaccompanied by any definite change in pulse rate or amplitude. It is probable that the dilation here may have the same basis as indicated in the case of epinephrin, i. e., representing a passive distention in accommodation to the generalized systemic constriction induced by the drug. It seems worthy of note that, after pituitary extract, there was observable what might be regarded as a marked "leukoreaction"—the subject evidencing a distinct greenish pallor accompanied by a moderately profuse perspiration, though complaining of no actual bodily discomfort.

SUMMARY

On the basis of plethysmographic observation on the brain circulation in man under normal, in vivo, condition, it seems that:

1. Amyl nitrite causes a marked dilation of the brain vessels.
2. Epinephrin induces a primary constriction of the brain vessels, which is followed by a marked dilation.
3. Caffein produces no demonstrable change in the dosage employed.
4. Pituitary extract is followed by a dilation of the brain vessels, accompanied by a distinct "leukoreaction."

5. Berezin: *Russk. Vrach* **15**:513, 1916.

6. Roy and Sherrington: *J. Physiol.* **11**:85, 1890.