7. Althoff, H., and Rating, B.: Ueber lungenveranderungen beim morbus Bang. Klin. Wehnschr. **22**:597 (Sept. 18) 1943.
8. Elsom, K. A., and Ingelfinger, F. J.: *Eosinophilia and pneumonitis in chronic brucellosis*; report of two cases. Ann. Int. Med. **16**:995-1002 (May) 1942.
9. Huddleson, I. F.: Brucellosis in Man and Animals. (New York: The Commonwealth Fund, 1939).
10. Johnson, R. M.: Pneumonia in undulant fever; report of 3 cases. Am. J. M. Sc. **189**:483-486 (April) 1935.
11. Lafferty, R. H., and Phillips, C. C.: Pulmonary changes in patients suffering from Malta fever. South. M. J. **30**:595-600 (June) 1937.
12. Menefee, E. E., and Poston, M. A.: Chronic brucellosis of twenty-five months' duration. South. M. J. **31**:1061-1062 (Oct.) 1938.
13. Shipley, F. M.: Pulmonary manifestations of brucellosis. Bull. School Med. Univ. Maryland **30**:80-83 (Oct.) 1945.
14. Haden, R. L.: Treatment of undulant fever with sulphanilamide; report of a case. Cleveland Clin. Quart. **5**:241-242 (Oct.) 1938.

CLINICAL OBSERVATIONS ON THE MECHANISM OF HYPERTENSIVE HEADACHE AND THE RESULTS OF ITS TREATMENT WITH DIHYDROERGOTAMINE TARTRATE

ROBERT BIRCHALL, M.D., ROBERT D. TAYLOR, M.D., and IRVINE H. PAGE, M.D.
Research Division

Suggestive evidence indicates that hypertensive headaches are in some respects similar to migraine (Janeway[1]) and may be due to dilatation and distention of branches of the external carotid rather than intracranial arteries (Schumacher and Wolff[2]). As reported by Steiner,[3] migraine can often be relieved by vasoconstriction and the resultant decreased amplitude of arterial pulsation induced by ergotamine tartrate. However, this drug is not without unpleasant side effects such as nausea and vomiting. Although it has also been shown to elevate the blood pressure of human beings, the elevation is not of great magnitude, since Pool, von Storch, and Lennox[4] showed that subjects who were given injections of 0.5 mg. intravenously had an average rise of only 13 mm. Hg in both systolic and diastolic pressure.

Recently, dihydroergotamine tartrate has been made available for clinical trial and is believed to be less toxic than the parent drug. The

Cleveland Clinic Research Division tested its value in the control of headache associated with hypertension by giving doses of 1 mg. by subcutaneous injections to 13 patients who exhibited headache. A total of forty such injections was administered. To determine the effect of dihydroergotamine tartrate upon blood pressure 1 mg. was given by subcutaneous injection to 5 hypertensive persons. The blood pressure was measured every fifteen minutes for two hours.

In order to explore further the similarity of hypertensive headache to migraine headache, the effects of pressure on the external carotid artery and its palpable branches were tested in 6 patients with headache.

Results

Two patients had relief for one hour following the first dose. However, not only did they receive no relief from subsequent injections, but 1 complained of more severe headache after the second and nausea after the third; the other experienced diminishing relief with added nausea after the sixth injection. Two patients noted some improvement following the first treatment but later experienced nausea, and 1 vomited.

Seven of the 13 patients were nauseated by the drug, 6 vomited, and 1 complained of substernal oppression on two occasions. Five refused further injections.

None of the 5 hypertensive persons whose blood pressure was measured repeatedly following injection of dihydroergotamine showed any change in blood pressure during the two hours they were observed.

Of the 6 subjects in whom an effort was made to abolish pain by compression of the external carotid arteries or their palpable branches, none was relieved, regardless of the combinations of vessels temporarily occluded.

Discussion

Fay[5] demonstrated that stimulation of many extracranial and intracranial arteries and distention of venous sinuses produced headache. Sutherland and Wolff[6] and Ray and Wolff[7] corroborated this finding and, in addition, induced headache by traction on arteries at the base of the brain, traction on meningeal arteries, irritation of dura mater over the floor of the skull, and direct pressure on cranial nerves containing afferent pain fibers.[8] All of these procedures were capable of producing secondary contraction of the skeletal muscles of the neck and scalp, which was itself painful. The latter is a complaint common among hypertensives.

Sutherland and Wolff[6] and Schumacher and Wolff[2] showed that dilatation of cranial arteries and the accompanying increased amplitude of pulsation were responsible for headache associated with fever, injection of histamine, and migraine. Measures which decreased the amplitude of pulsation in extracranial arteries, such as injection of ergotamine tartrate[9,10] and pressure on the carotid artery, relieved the headache of migraine but not that of fever or histamine injection.

Headaches of hypertension are inconstant. Pain may be unilateral or bilateral, occipital, frontal, retro-orbital or parietal, may radiate downward to the neck and shoulders, or may be any combination of these.

Robey[11] found that only half of 448 hypertensives complained of headaches and that neither the arterial nor cerebrospinal fluid pressure bore any relation to their incidence or severity.

Janeway[1] in 1913 presented clinical evidence indicating similarity between hypertensive and migrainous headache. Sutherland and Wolff[6] have stated that in some patients with hypertensive headaches there is a cerebral vasodilatation comparable with that observed in migraine and have reported complete relief of pain for three months in 1 patient who underwent an operation for ligation of the temporal arteries. However, contrary to the results reported in migraine, none of our patients was relieved by pressure on extracranial arteries.

Although successful treatment of hypertensive headache with ergotamine tartrate has been reported by Steiner,[3] only 2 patients of our group had any relief from pain following injection of dihydroergotamine tartrate, a drug which can be expected to have the same activity as its parent. The other 11 obtained no improvement, and 8 experienced some nausea or vomiting. One patient twice complained of substernal oppression. Five refused further treatment with the drug.

Summary

The mechanism of migrainous headache, which is believed to include dilatation of extracranial vessels and increased amplitude of pulsation, appears to differ from that of the usual hypertensive headache. Compression of extracranial arteries or injection of dihydroergotamine tartrate, which relieve most migraine headaches, did not abolish the hypertensive headaches.

Dihydroergotamine tartrate administration is not useful in the treatment of hypertensive headache, as judged by the careful study of 13 hypertensive patients with severe headaches.

We are grateful to the Sandoz Chemical Company for the dihydroergotamine tartrate used in these experiments.

Results of Treatment of Hypertensive Headache with Dihydroergotamine Tartrate

Patient	Blood Pressure	Number of Injections	Results Obtained from Injections					
			Relief	Headache Exaggerated	Nausea	Vomiting	Substernal Pain	Refused Medication
1.	200/130	1 2	++++	√	√	√		
2.	190/130	1 2 3 4 5	+++ ++ 0 0 0					√
3.	140/100	1 2 3	0 0 0	√ √ √				
4.	250/150	1 2 3	0 0 0		√ √	√ √		√ √
5.	220/130	1 2	+ 0		√	√		
6.	172/112	1 2	0 0		√ √	√ √	√ √	√
7.	210/130	1 2	0 0		√	√		√
8.	210/130	1 2 3 4	0 0 0 0					
9.	150/100	1 2	0 0					
10.	210/100	1 2	0 0					

Results of Treatment of Hypertensive Headache with Dihydroergotamine Tartrate

Patient	Blood Pressure	Number of injections	Results Obtained from Injections					
			Relief	Headache Exaggerated	Nausea	Vomiting	Substernal Pain	Refused Medication
11.	170/95	1	++++					
		2	++		√			
		3	++					
		4	0					
		5	0					
12.	200/120	1	0					
		2	0		√	√		
13.	180/100	1	0					
		2	0					
		3	0					
		4	0					
		5	0					
		6	0					

References

1. Janeway, T. C.: *Nephritic hypertension; clinical and experimental studies.* N. York M. J. **97**:400-402. 1913.
2. Schumacher, G. A., and Wolff, H. G.: Experimental studies on headache; contrast of histamine headache with headache of migraine and that associated with hypertension; contrast of vascular mechanisms in preheadache and in headache phenomena of migraine. Arch. Neurol. & Psychiat. **45**:199-214 (Feb.) 1941.
3. Steiner, S. A.: The typical headache of essential hypertension. Med. Ann. District Columbia **14**:531-538 (Dec.) 1945.
4. Pool, J. L., von Storch, T. J. C., and Lennox, W. G.: Effect of ergotamine tartrate on pressure of cerebrospinal fluid and blood during migraine headache. Arch. Int. Med. **57**:32-45 (Jan.) 1936.
5. Fay, T.: Mechanism of headache. Tr. Am. Neurol. A. **62**:74-77. 1936.
6. Sutherland, A. M., and Wolff, H. G.: Experimental studies on headache; further analysis of mechanism of headache in migraine, hypertension and fever. Arch. Neurol. & Psychiat. **44**:929-949 (Nov.) 1940.
7. Ray, B. S., and Wolff, H. G.: Experimental studies on headache; pain-sensitive structures of head and their significance in headache. Arch. Surg. **41**:813-856 (Oct.) 1940.
8. Wolff, H. G.: Headache and cranial arteries. Tr. A. Am. Physicians **53**:193-198. 1938.
9. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics. (New York: Macmillan Co., 1941).
10. Lennox, W. G., von Storch, T. J. C., and Solomon, P.: Effect of ergotamine tartrate on non-migrainous headaches. Am. J. Sc. **192**:57-61 (July) 1936.
11. Robey, W. H.: Headache. (Philadelphia: J. B. Lippincott Co., 1931).