

extract of the adrenal cortex. The fall in blood pressure of the fourth animal was attributed to the spontaneous remission of the experimental hypertension.

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Influence of Ergotamine Tartrate Upon Peripheral Blood-Flow in Subjects with Liver Disease.

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It has been established in animals¹⁻⁵ and in man⁶ that ergotamine tartrate in therapeutic doses generally constricts peripheral arteries with a consequent decrease in blood flow. The recent reports of the occurrence of peripheral gangrene following the use of this drug^{7, 8} for the relief of pruritus associated with jaundice^{9, 10} raises the question as to whether the presence of liver insufficiency might not influence quantitatively this response of the blood vessels. Accordingly, the effect of a single subcutaneous injection of ergotamine tartrate (0.5 mg.) upon the rate of blood-flow was determined in a series of patients with liver disease and compared with that in a control group.

The principles and details of the method of determining blood-flow outlined by Brodie,¹¹ and Hewlett and Van Zweluwburg¹² were

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¹ Dale, H. H., *J. Physiol.*, 1906, **34**, 163.

² Lewis, T., and Gelfand, B., *Clin. Sc.*, 1935, **2**, 43.

³ Herrick, J. F., *Proc. Soc. Exp. Biol. and Med.*, 1933, **30**, 271.

⁴ Pool, J. L., and Nason, G. I., *Arch. Neurol. and Psychiat.*, 1935, **35**, 276.

⁵ Rubin, M. I., and Rapoport, M., *Arch. Int. Med.*, 1937, **59**, 714.

⁶ Graham, J. R., and Wolff, H. G., Reported before The Am. Soc. for Clin. Invest., Atlantic City, May 3, 1937.

⁷ Yater, W. M., and Cahill, J. A., *J. A. M. A.*, 1936, **106**, 1625.

⁸ Gould, S. E., Price, A. E., and Ginsberg, H. I., *J. A. M. A.*, 1936, **106**, 1631.

⁹ Lichtman, S. S., *J. A. M. A.*, 1931, **97**, 1463.

¹⁰ Snell, A. M., and Keyes, H. C., *M. Clin. N. Am.*, 1933, **16**, 1455.

¹¹ Brodie, J. G., Seventh International Physiological Congress, Aug., 1907.

¹² Hewlett, A. W., and Van Zweluwburg, J. G., *Arch. Int. Med.*, 1909, **3**, 254; *Heart*, 1909, **1**, 87.

adhered to. The subjects were allowed a light repast at least 2 hours before the test. They rested comfortably in the supine position, covered with a light blanket in a room at a constant temperature, usually about 24°C. The hand was placed in a plethysmograph possessing the improved modifications of Freeman¹³ and the machine was filled with water which was maintained at a temperature of 32°C. All air was excluded. A rubber cuff about 1.5 inches in width encircled the wrist approximately 2 inches above the rubber diaphragm of the plethysmograph. In order to obtain blood-flows, the cuff was suddenly inflated at a pressure of 70 mm. of mercury from a pressure bottle so as to obstruct the venous outflow from the hand; the increase in hand volume at the end of the first second after the application of the pressure was accepted as a measurement of unimpeded arterial flow into the limb. This increase in volume was recorded on a kymograph by means of a Brodie's bellows and a lever pen. After a control period of 30 minutes, during which time determinations of blood-flows were obtained every 3 minutes, 0.5 mg. of ergotamine tartrate (Sandoz) was injected subcutaneously. For 40 to 60 minutes thereafter, readings were made at intervals of 3 to 5 minutes. In no instance did the drug cause emesis or nausea.

The system was calibrated by injecting air in one cubic centimeter amounts with the aid of a syringe and the results were expressed as cubic centimeters of blood-flow per minute per 100 cc. of hand volume. The latter was determined by subtracting the figure representing the amount of water added to the plethysmograph with the hand *in situ* from that representing the actual capacity of the machine. Various details of the procedure and apparatus are being standardized by one of us (D.I.A.)¹⁴ to assure reliable absolute blood-flow values. However, the method used here was considered adequate for the purpose of comparing relative changes in blood-flow in the same subject before and after a stated procedure.

The blood-flow in the hands of 3 normals and 3 patients without established liver abnormality was compared with that in 6 patients with liver disease or jaundice. Five of the 6 patients in the control group showed a decreased blood flow after the injection of ergotamine, 13 to 61% lower than their initial flows. In most instances this decrease was evident in the first 10 minutes after the drug was given, becoming more pronounced later in the experiment. Observations were not continued for longer than 50 minutes after the injection as the subjects at that time usually exhibited fatigue and became restless. In one instance, Case No. 6, there was a slight rise

¹³ Freeman, N. E., *Am. J. Physiol.*, 1935, **113**, 384.

¹⁴ Abramson, D. I., unpublished observations.

TABLE I.
Hand Blood-Flow in Normals and in Subjects without Liver Disease Following the Subcutaneous Injection of 0.5 mg. of Ergotamine Tartrate.

Case No.	Age	Sex	Diagnosis	Av. Flow Before cc./min./100 cc. Hand Vol.	Av. Flow After Injection 10 minute periods					Maximal Change* in Rate of Flow, %	Blood Pressure		Heart Rate	
					10	20	30	40	50		Before	After	Before	After
1. P.D.	22	Male	Normal	6.7	7.2	4.4	3.8	2.6	—	-61	94 60	90 70	88-112	88-96
2. I.S.	46	"	"	12.5	9.4	7.0	5.8	5.8	5.8	-54	135 90	135 110	80	72-80
3. J.M.	31	"	Conversion Hysteria	7.3	6.0	4.6	4.6	4.5	—	-39	130 70	140 92	80	70-80
4. K.B.	24	Female	Migraine	13.5	11.3	11.8	10.0	9.3	—	-14	105 58	118 90	72-84	64-80
5. D.H.	47	Male	Peptic Ulcer	7.0	7.7	7.0	7.0	6.1	—	-13	130 80	120 80	80-96	60-84
6. L.S.	36	"	"	6.9	8.3	8.1	8.0	7.4	—	+7	105	112	80	64-84

*The maximum increase or decrease following the injection of ergotamine was calculated by comparing the resting blood-flow with the figure obtained at the end of the period of observation which in all cases manifested the maximum change.

TABLE II.
Hand Blood-Flow in Patients with Liver Disease.

Case No.	Age	Sex	Diagnosis	Av. Flow Before cc./min./100 cc. Hand Vol.	Av. Flow After Injection 10 minute periods						Maximal Change in Rate of Flow, %	Blood Pressure		Heart Rate	
					10	20	30	40	50	Before		After	Before	After	
7. J.Ba.	32	Male	Subacute Liver Atrophy	15.7	15.4	13.1	13.2	12.6	—	—20	100/70	115/80	72	64-72	
8. J.Br.	29	"	Salvarsan Hepatitis	16.0	19.1	11.8	15.5	8.0	—	—50	110/65	120/90	72	48-68	
9. H.B.	44	"	Cirrhosis Hematemesis	35.8	38.5	33.0	34.8	34.8	35.8	0	110/65	130/70	84	60-76	
10. M.R.	40	"	Carcinoma Pancreas Jaundice	12.7	8.9	11.7	10.2	9.3	8.0	—37	120/90	130/90	78	60-74	
11. A.B.	60	"	Carcinoma Pancreas Jaundice	23.4	22.5	20.7	19.9	18.4	—	—22	135/75	140/90	76	74-80	
12. E.A.	53	Female	Cholangitic Cirrhosis	4.0	4.6	5.7	6.0	7.2	8.6	+215	129/80	130/80	72	64-72	

in blood-flow of 7% above the initial value. The initial blood-flows of the group averaged 6.7 to 13.5 cc. per minute per 100 cc. of hand volume.

In the 6 patients with liver disease, 4 gave evidence of decreased blood-flow. In the latter, after the injection of ergotamine, the original values fell 20 to 50%. In one instance, case No. 9, no change in blood-flow was recorded while in another, case No. 12, the blood-flow increased over 200%. This was still evident 50 minutes after injection. The initial blood-flows in this group ranged between 4 and 35.8 cc. per minute per 100 cc. of hand volume.

In 2 of the control and in 3 of the liver cases there was a definite rise in blood pressure of 10 to 20 mm. of mercury, while in all but one case there was a slight but definite decrease in heart rate (Tables I and II). In no instance did these changes persist during the entire period of altered peripheral blood flow.

The vasoconstrictor action of ergotamine tartrate is here confirmed in human beings by plethysmographic studies. In 2 instances, however, a vasodilator action was noted, which is in accord with previous observations.^{4, 6, 15} The rise in systemic blood pressure and the decrease in heart rate following the injection were too slight and not constant or persistent enough to account for the prolonged changes in blood-flow. Further, the same degree of change was observed in those patients manifesting an increase in flow as in those with a decrease. Nevertheless, since cardiac outputs were not measured, an effect of the drug on the heart cannot be ruled out entirely.

There was no significant difference in the vascular response of subjects with liver disease from that of normals to the subcutaneous injection of ergotamine tartrate. Approximately the same degree of vasoconstriction, as indicated by the percentage decrease in peripheral blood-flow, results in both groups. This conclusion, of course, can at present only be applied to the effect of single therapeutic doses. However, it is probable that where conservative doses of ergotamine tartrate produce cardiovascular complications, an explanation may be found in previously existing disease of the vessels, unusual degrees of vasoconstriction, or unusual concentration of the blood elements, as in polycythemia.¹⁶

Summary. Single doses of ergotamine tartrate (0.5 mg.), injected subcutaneously, produce definite vasoconstriction as indicated by a decrease in peripheral blood-flow. Less commonly, vasodilata-

¹⁵ Bouckaert, J. J., and Moraes, A., *Compt. rend. Soc. de Biol.*, 1932, **110**, 993.

¹⁶ Lichtman, S. S., Letter, *J. A. M. A.*, 1936, **107**, 148.

tion is produced, with increased blood-flow. No significant difference in blood-flow change after ergotamine was noted between normals and subjects with liver disease.

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Effect of Some Short Acting Barbiturates on the Patency of the Glottis.

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Experiments were conducted on normal cats with the following barbituric acid derivatives: sodium N-methyl-cyclohexanyl barbiturate (evipal), sodium iso-amyl ethyl barbiturate (amytal), sodium iso-amyl ethyl thio-barbiturate (sodium thio-ethamyl*), sodium N-ethyl-1-methyl butyl barbiturate (nembutal), and sodium N-ethyl-1-methyl butyl thio-barbiturate (pentothal). In each case a 2% aqueous solution, freshly prepared, was injected intravenously at a constant rate of a milligram per second. The quantities injected ranged between the minimum anesthetic dose and the minimum lethal dose.

It was noticed that most of the animals would cough, sneeze, or hiccup considerably during the course of anesthesia and that these animals would quickly develop cyanosis and dyspnea regardless of whether a large or small dose had been administered. Inspection of the glottis in these cases showed spastic adduction of the vocal cords. In the cases where there was no spontaneous coughing, inspection of the glottis showed hyper-active adducted vocal cords and lifting the epiglottis would elicit complete spastic closure of the glottis; cyanosis then developed rapidly and unless tracheal intubation was

TABLE I.

Barbiturate	No. of animals	Spontaneous laryngospasm	Hyperactive laryngeal reflex, followed by laryngospasm
Sodium thio-ethamyl	37	36	1
Evipal	10	7	3
Amytal	10	4	5
Nembutal	10	6	4
Pentothal	11	8	3

* Parke, Davis & Co.