CARBON DIOXIDE DISSOCIATION CURVES BEFORE AND AFTER THE INTRAVENOUS INJECTION OF PITRESSIN

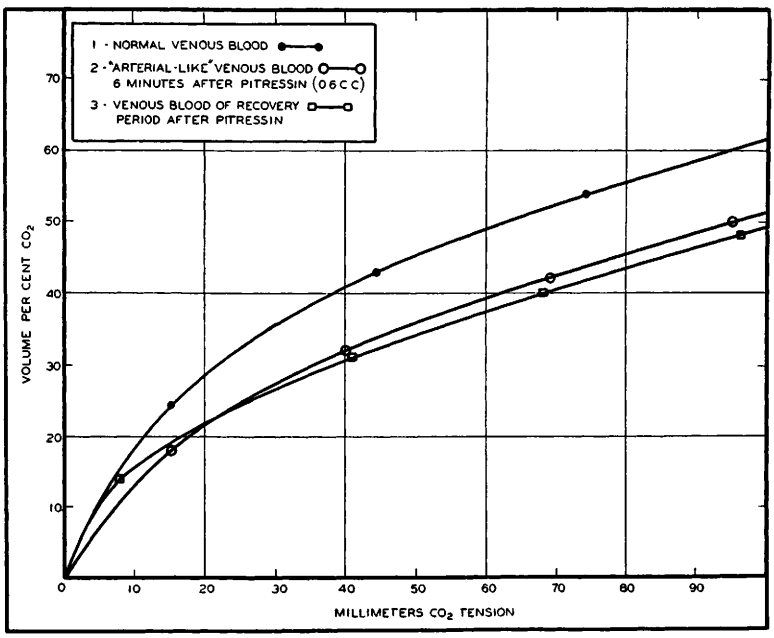

FIG. 2.

due to the presence of lactic acid, which has been shown to increase to a value 3 times the basal level after the injection of pitressin.

From the above findings it seems justifiable to conclude that the high percentage of oxy-hemoglobin in venous blood after the injection of pitressin cannot be attributed to any interference with the power of the blood to yield its oxygen at a given tension.

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Effect of Pitressin and Pitocin on Oxygen Consumption of Excised Tissue.

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A direct action of pituitrin and pitressin on the tissue cells so as to render them incapable of taking up oxygen was one of the possible explanations suggested by Geiling and DeLawder for the sig-

nificant metabolic changes produced in man and animals by these drugs.[1, 2, 3] To test the validity of this suggestion the present work was carried out.

Ahlgren[4] using Thunberg's methylene blue method found that minute concentrations of various posterior pituitary preparations increased tissue respiration. Himwich, Finkelstein and Humphreys,[5] working with the Warburg apparatus, showed on the other hand that the oxygen consumption of excised tissues of white rats is definitely decreased under the influence of pituitrin and pitressin. However, the doses used by them were entirely disproportionate to the amounts generally employed in the intact animal. Accordingly, similar experiments have been carried out with dosages covering a range to include large and small concentrations of post-pituitary preparations (pitressin, pitocin and inactivated pitressin). Even the smallest dose used in this work is relatively large when compared to the effective amount used in the intact dog or in man.

Experimental. White rats weighing approximately 250-300 gm. were used. Liver, heart and diaphragm tissues were excised directly after the animal had been killed by decapitation and their oxygen consumption in the presence of varying quantities of the post-pituitary preparations was immediately determined in Warburg vessels with Barcroft manometers at 37.5°C.[6]

Fresh Ringer-buffer-glucose and saline-buffer-glucose solutions, as recommended by Richardson,[7] were used as nutrient media. A thin slice of tissue not more than 0.5 mm. in thickness was placed in the Warburg vessel with 3 cc. of the medium—Ringer-buffer-glucose solution for liver tissue and saline-buffer-glucose solution for diaphragm and heart (ventricle) tissue. Normal potassium hydroxide (0.2 cc.) was used to absorb the carbon dioxide formed. The post-pituitary extracts, in varying quantities, were added directly to the media in the vessels. Oxygen consumption was measured

[1] Geiling, E. M. K., and DeLawder, A. M., *Bull. Johns Hopkins Hosp.*, 1932, **51**, 1.

[2] Geiling, E. M. K., and DeLawder, A. M., *Bull. Johns Hopkins Hosp.*, 1932, **51**, 335.

[3] Grollman, Arthur, and Geiling, E. M. K., *J. Pharmacol. and Exp. Therap.*, 1932, **46**, 447.

[4] Ahlgren, G., *Skandin. Arch. f. Physiol.*, 1925, **47** (supplement), 1.

[5] Himwich, H. E., Finkelstein, R., Humphreys, K. E., PROC. SOC. EXP. BIOL. AND MED., 1931, **29**, 233.

[6] Warburg, O., *Biochem. Z.*, 1923. **142**, 317.

[7] Richardson, H. B., *Physiol. Rev.*, 1929, **9**, 61.

during a period of 2 hours, after which the tissues were dried and weighed.

Pitressin (20 pressor units per cc.) was freed of chloretone before using. A small quantity of a highly purified preparation of pitocin containing 30 oxytocic units per cc. was kindly supplied by Dr. duVigneaud. The pitressin was inactivated by heating with alkali and it was then neutralized with HCl, the NaCl formed being removed by dialysis. An assay showed that 95% of the pressor activity was destroyed.

Results. The accompanying tables show that with a sufficiently small quantity of pitressin the oxygen consumption of excised liver and diaphragmatic tissues is increased, whereas with progressively larger amounts of the drug this effect becomes less pronounced, until finally a sufficiently large dose causes a definite decrease in oxygen consumption. This latter fact is in agreement with the results of Himwich and associates. The results obtained on heart tissue are in the main similar, though less conclusive, except that they show a definite depression of metabolism in the case of the largest amount used. From the data it appears that the various tissues of the body have different threshold levels of activity. Thus the amount of pitressin which suppressed the oxygen consumption of muscle (diaphragm and heart) produced an increase with liver (parenchymatous tissue). With the inactivated pitressin there was a gradual decrease in oxygen consumption as the dosage was increased.

The results with pitocin are inconclusive; but there is a similarity in the results as compared with the inactivated pitressin in the same dosage range.

TABLE I.

O_2 Consumption of Excised Tissues in cu. mm. per mg. per minute.

Dose	Pitressin (A)			Inactivated Pitressin (B)		
	Liver	Diaphragm	Heart (Ventricle)	Liver	Diaphragm	Heart (Ventricle)
Normal	0.0140					
4/50 cc.	0.0082					
Normal	0.0137					
3/50 cc.	0.0134					
Normal	0.0092	0.0144	0.0119	0.0102	0.0129	0.0177
2/50 cc.	0.0132	0.0106	0.0091	0.0065	0.0053	0.0065
Normal	0.0095	0.0102	0.0167	0.0102	0.0129	0.0177
1/50 cc.	0.0127	0.0085	0.0165	0.0075	0.0062	0.0093
Normal		0.0085	0.0078		0.0129	0.0177
1/100 cc.		0.0106	0.0084		0.0095	0.0138

TABLE II.
O_2 Consumption of Excised Tissues in cu. mm. per mg. per minute.

Doses	Pitocin. Liver	Diaphragm	Heart (Ventricle)
Normal	0.0079	0.0071	0.0089
2/50 cc.	0.0063	0.0057	0.0058
1/50 cc.	0.0057	0.0058	0.0071
1/100 cc.	0.0061	0.0072	0.0070

One hesitates to place any definite interpretation on the effects produced on isolated tissues by the larger doses of pitressin, especially since the inactivated material similarly reduces the oxygen consumption. Of course, alkali treatment may do more than merely render inactive the small amount of hormone present in the pitressin fraction, which is a mixture of organic substances. There may be formed new products which depress the metabolism of the tissues. Furthermore the tissues of the rat may be much less reactive to posterior pituitary preparations than are those of human beings or dogs. Hence it may be that excised human or dog tissues under similar conditions would show depression of respiration with very much smaller dosages. On the other hand, the data presented show clearly that there is an increase in oxygen consumption of excised tissues with the smaller concentrations of pitressin. It would thus seem that the initial lowering of metabolism produced by relatively small doses of the drug when injected into the intact animal does not find an explanation in the experiments here reported.