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Observations on Effects of Altitude on Renal Function.

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(Introduced by A. W. Hetherington.)
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At the present time there is a paucity of data available on the effect of reduced atmospheric pressure on the excretory function of the kidney. Alving *et al.*[1] studied the effects on renal function of intermittent, daily exposure of young men to simulated altitudes of 10,000 to 18,000 feet. Observations were made from the thirteenth to the forty-first day of exposure. They found that such exposure caused no change in glomerular filtration rate, but did cause an increase in maximum tubular excretory ability for diodrast (TmD).

We have been unable to find any specific data concerning the effect of simple acute hypoxia on unanesthetized experimental subjects as regards glomerular filtration rate, maximum tubular excretory ability; nor maximum tubular reabsorptive capacity. It is the influence of simple acute hypoxia on these phenomena with which this report is concerned.

Methods. Five well trained, unanesthetized, adult female dogs, 2 pure-bred Dalmatian coach hounds and 3 mongrels, were employed in these studies. The urine collection periods ranged from 10 to 15 minutes each with all standard precautions taken to insure adequate urine flow and bladder evacuation. Blood samples were obtained by external jugular puncture, and heparin was used as an anticoagulant. The renal function tests were performed at ground level and in an altitude chamber at simulated altitudes of 18,000 and 24,000 feet.

The glomerular filtration rate (GF) was measured by the clearance of creatinine (C_{cr}) in the mongrel dogs and by the clearance of inulin (C_{in}) in the Dalmatians. The maximum tubular excretory ability was measured with para-aminohippuric acid (TmPAH), and the maximum tubular reabsorptive capacity was measured with glucose (TmG). Inulin and para-aminohippuric acid were determined by the methods outlined by Smith *et al.*[2] creatinine by the method of Folin and Wu,[3] and glucose by the Folin method.[4]

The plasma levels of the various test substances were maintained following the injection of a primer dose by constant intravenous infusions started at least 20 minutes previous to the first urine collection period. Several consecutive urine collection periods were studied each day. To minimize the possible effects of acclimatization no animal was submitted to exposure to altitude more frequently than once per week. Because of the reported mutual interference of simultaneous TmPAH and TmG determinations,[5,6] only one of these measurements was performed on any one animal during a single exposure to altitude.

Results. The results obtained are summarized in Tables I and II. Although fluctuations in glomerular filtration rate were ob-

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2 Smith, H. W., Finkelstein, N., Alminosa, L., Crawford, B., and Graber, M., *J. Clin. Invest.*, 1945, **24**, 388.

3 Folin, O., and Wu, H., *J. Biol. Chem.*, 1919, **38**, 81.

4 Folin, O., *J. Biol. Chem.*, 1929, **82**, 83.

5 Houck, C. R., PROC. SOC. EXP. BIOL. AND MED., 1946, **63**, 398.

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TABLE I.
Effect of Altitude on TmPAH.

Dog		Ground level			18,000 feet			24,000 feet		
		Date	GF* cc/min	TmPAH† mg/min	Date	GF cc/min	TmPAH mg/min	Date	GF cc/min	TmPAH mg/min
No. 1	Wt 8.6 kg	3-11-47	55.0^{10}	9.1^{5}	3-18-47	43.8^{8}	13.1^{4}	4-11-47	67.8^{8}	8.2^{4}
No. 2	Wt 10.5 kg	20	44.9^{9}	22.6^{4}	27	47.7^{7}	15.3^{4}	4-8	43.3^{8}	25.8^{4}
		9-24	53.2^{3}		9-24	58.1^{4}		9-24	53.8^{4}	
		10-13	39.7^{7}	27.0^{7}						
		23	46.1^{7}							
No. 3	Wt 8.6 kg	3-7	41.8^{8}	20.1^{4}	3-14	98.5^{10}	37.7^{5}	4-7	58.6^{9}	65.1^{4}
					4-24	58.6^{4}				
No. 4	Wt 21.8 kg	4-21	105.9^{5}		9-15	64.2^{4}	88.9^{4}	9-15	63.6^{3}	204.3^{3}
		5-5	97.4^{5}							
		9-15	95.5^{4}	87.0^{4}						
		10-16	87.3^{4}							
		11-3	100.8^{4}							
No. 5	Wt 22.7 kg	5-19	99.8^{10}		23	88.0^{4}	83.2^{4}	23	61.0^{4}	78.7^{4}
		8-5	110.0^{5}							
		9-18	96.0^{3}	85.6^{3}						
		23	95.0^{4}	75.5^{4}						
		10-31	94.9^{9}							
		11-6	88.0^{3}							

Superscripts refer to the number of periods for which the figure quoted is the mean value.
* Glomerular filtration rate.
† Maximum tubular excretory ability for para-aminohippuric acid.

TABLE II.
Effect of Altitude on TmG.

Dog		Date	Ground level GF* cc/min	Ground level TmG† mg/min	18,000 feet GF cc/min	18,000 feet TmG mg/min	24,000 feet GF cc/min	24,000 feet TmG mg/min
No. 2	Wt 10.5 kg	10-1-47	42.8^{4}	157.9^{4}	44.3^{4}	126.6^{4}	46.4^{4}	143.7^{4}
		9	48.1^{4}	134.9^{4}	42.8^{4}	137.5^{4}	47.2^{4}	126.5^{4}
No. 4	Wt 21.8 kg	9-29	94.9^{4}	352.3^{4}	88.5^{4}	164.7^{4}	106.2^{4}	155.9^{4}
No. 5	Wt 22.7 kg	10-8	85.2^{3}	394.3^{3}	86.0^{3}	316.0^{3}	92.5^{4}	319.6^{4}

Superscripts indicate the number of periods for which the figure quoted is the mean value.
* Glomerular filtration rate.
† Maximum tubular reabsorptive capacity for glucose.

served, no obvious trend is exhibited by these changes. It is felt that all are attributable to individual variability of response to altitude. In 4 of the dogs at 18,000 feet and in 3 of them at 24,000 feet, no significant changes in TmPAH occurred. In dog No. 3 at 18,000 feet and in dogs Nos. 3 and 4 at 24,000 feet, significant increases in the TmPAH were observed. These changes were 88%, 222%, and 135%, respectively.

TmG was somewhat decreased by exposure to altitude. At 18,000 feet there was in 1 animal a relatively small decrease of approximately 20%, in another a larger decrease of approximately 55%, and in another no change in TmG in two sets of experiments. Although there were quite marked changes in TmG at 18,000 feet as compared to ground level, there were no appreciable differences observed between the values obtained at 18,000 and at 24,000 feet.

Discussion. Theoretically, decreased TmG and TmPAH could result from decreased availability of oxygen to the kidney tubules. In the present studies TmG did decrease at altitude but TmPAH did not. Indeed, there

is an apparent increase in some cases in the ability of the tubule cells to excrete PAH upon exposure of the animal to an atmosphere of sufficiently reduced oxygen tension. This observation agrees with that of Alving *et al.*[1] in the case of chronic, intermittent exposure to anoxia.

[7] Eiler, J. J., Althausen, T. L., and Stockholm, M., *Am. J. Physiol.*, 1943, **140**, 699.

[8] Heinbecker, P., Rolf, D., and White, H. L., *Am. J. Physiol.*, 1943, **139**, 543.

[9] Welsh, C. A., Rosenthal, A., Duncan, M. T., and Taylor, H. C., Jr., *Am. J. Physiol.*, 1942, **137**, 338.

An increase in the maximum tubular excretory ability has been effected by the administration of various hormone preparations,[7-9] indicating that hormonal influences are capable of causing alterations in the tubular transfer mechanism of the kidney. The possibility of such influences being operative here must be considered.

Conclusions. Upon exposure of animals to altitude, 1) glomerular filtration rate response varies widely with the individual, 2) TmPAH is increased or unaffected, and 3) TmG is decreased or unaffected.

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On Phenyletherase.*

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The enzymatic cleavage of the carbon-oxygen bond of phenyl ethers by rat tissues is reported in this paper. The methoxy-phenyl linkage occurs in a variety of biologically active compounds which include anti-fibrillatory compounds such as quinine, quinidine and α-fagarine[1] although here the methoxy radical apparently is not necessary[2] for the physiologic activity. This linkage also occurs in the anti-malarial compounds, atabrine and pentaquine; in the sedative papaverine; and in certain estrogen compounds such as dimethoxystilbestrol. The methoxy-phenyl linkage is present in the local anesthetic phenacaine. Barry, O'Rourke and Twomey[3] have shown that diphenyl ethers have potent antituberculous activity *in vitro*.

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[1] Moisset de Espanés, E., and Weksler, B., PROC. SOC. EXP. BIOL. AND MED., 1946, **63**, 195.

[2] Di Palma, J. R., and Lambert, J. J., *Science*, 1948, **107**, 66.

[3] Barry, V. C., O'Rourke, L., and Twomey, D., *Nature*, 1947, **160**, 800.

We have been unable to find earlier reports on enzymatic decomposition of ethers. The enzyme pectase catalyzes the cleavage of "methoxyl" groups of soluble pectin, a reaction studied extensively by Kertesz.[4,5] However, in pectin the methyl groups are attached to the carbohydrate as an ester and this bond is considerably weaker than an ether linkage. *p*-Nitrophenyl esters[6] are attacked at a much faster rate by esterase than are its ethers by the enzyme under consideration here.

It was found that the splitting of the methyl and ethyl ethers of *p*-nitrophenol (PNP) is carried out extensively by the intact rat and slightly by homogenates of liver and kidney. Following injection of these compounds in rats, appreciable or even large amounts of free and combined *p*-nitrophenol are excreted in the urine; it is well known that phenols are in large part excreted in the urine as conjugates of glucuronic and sulfuric acids. Since *p*-

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[5] McColloch, R. J., and Kertesz, Z. I., *J. Biol. Chem.*, 1945, **160**, 149.

[6] Huggins, C., and Lapides, J., *J. Biol. Chem.*, 1947, **170**, 467.