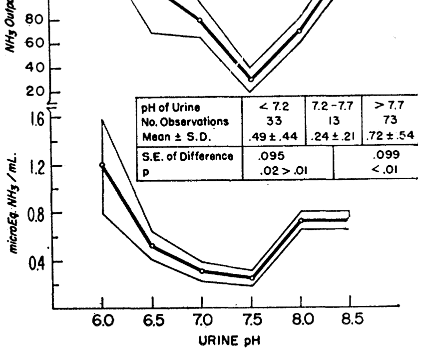
Reports

Relation of Ammonia Excretion to Urine pH in the Guinea Pig

In 1856 Claude Bernard (*1*) observed that the urinary *p*H of carnivorous animals is markedly lower that that of herbivorous animals. Some years later Walter (*2*) described the excretion of ammonia in various animals that had been rendered acidotic and stressed the protective and base-saving features of this mechanism. Since then, numerous studies on the patterns of ammonia excretion in man, dog, and rat, especially during acidosis, have been published. On the other hand, very few studies on these patterns in the rabbit have been made and, as far as we are aware, none in the guinea pig. The current theories of ammonia excretion are, therefore, largely based on studies in species that normally excrete an acid urine.

In spite of much work in this field, three major questions await conclusive answers. What is the physiological stimulus for ammonia excretion? What is the relative importance of enzymatic and physicochemical factors in the mechanism of ammonia excretion? What is its physiological significance? During studies on ammonia excretion in the guinea pig, we have made observations that are surprising when they are considered in the light of present concepts of ammonia formation and excretion.

The ammonia output of guinea pigs (1 to 4 microequivalent/30 min kg) is low compared with that of rats or dogs and varies with age, sex, and dietary habits. In acute experiments (*3*) guinea pigs were rendered acidotic or alkalotic; and urine, collected under oil, was analyzed for *p*H (*4*) and ammonia content (*5, 6*). The urinary ammonia concentration was expressed as microequivalents per milliliter and the output as microequivalents per 30 minutes, per kilogram of body weight. Data from seven acute experiments are plotted on Fig. 1, using the urinary *p*H as abscissa and ammonia concentration or output as ordinate (*7*). The graph shows that both the concentration and the relative output of ammonia in the urine rise, not only during acidosis as in man, dog, and rat, but also during alkalosis. The same is true if the relative ammonia output for each animal per 30 minutes is plotted against the *p*H. The correlation between deviations of *p*H from the normal range and increased ammonia output is not strict but is statistically significant. A similar pattern has been observed in a few experiments with rabbits.



pH of Urine	< 7.2	7.2 - 7.7	> 7.7
No. Observations	33	13	73
Mean ± S.D.	.49 ± .44	.24 ± .21	.72 ± .54
S.E. of Difference	.095		.099
p	.02 > .01		< .01

Fig. 1. The relation of ammonia excretion to urine *p*H in the guinea pig.

The increased ammonia concentration in alkaline urines cannot be explained as a function of urine flow, as could an increased output. It must, therefore, be assumed that there is increased ammonia production or transfer into alkaline, as well as acid, urine.

These observations suggest reconsideration of current hypotheses regarding the stimulus. Decreased plasma bicarbonate or *p*H or increased titratable acidity or decreased *p*H of the urine have been proposed as the proximate stimulus for the increase in ammonia output during acidosis. None of these, however, could cause the marked increase in ammonia output observed during alkalosis. Information now available does not indicate whether the same or different stimuli act during acidosis and alkalosis.

Ammonia excretion is currently considered to be the resultant of two independent mechanisms, one being enzymatic, the other being physicochemical in nature. Investigations during the past few years indicate that glutaminase activity in the kidneys is one of these factors (*8*). Transport of ammonia from tubular cells into urine, be it by passive diffusion (*9*) or active exchange for sodium (*10*), is held to be the second limiting factor for ammonia excretion. Our experiments demonstrate that ammonia excretion in the guinea pig is nearly as efficient in the alkaline as in the acid range. It seems improbable, therefore, that physicochemical transport is the limiting factor in ammonia excretion in the guinea pig. If it were, different mechanisms in the acid and alkaline ranges would have to be postulated.

At urine *p*H's of 8, 8.5, and 9 the fractions of ammonia present in an un-ionized form as free ammonia are respectively 4, 11, and 29 percent (*11*). Back diffusion of the ammonia during the flow of the urine from the distal tubules to the bladder should, therefore, also be taken into account in studies on ammonia excretion in the alkaline range. This aspect has not yet been explored.

R. RICHTERICH-VAN BAERLE
LEON GOLDSTEIN
EARL H. DEARBORN

Department of Pharmacology, Boston University School of Medicine, Boston, Massachusetts

References and Notes

1. Claude Bernard, *An Introduction to the Study of Experimental Medicine*, translated by H. C. Green (Macmillan, New York, 1927), p. 152.
2. F. Walter, *Arch. exptl. Pathol. Pharmacol.* 7, 148 (1877).
3. The animals were anesthetized with pentobarbital and ether, and a stomach tube and bladder catheter were inserted. They were given $NaHCO_3$ or HCl by stomach tube. The experiments lasted 2 to 6 hours, and 6 to 15 urine samples were collected during each experiment.
4. Determinations of *p*H were done with a Cambridge Research *p*H meter using the syringe-type glass electrode.
5. A modification of the microdiffusion method of D. Seligson and H. Seligson [*J. Lab. Clin. Med.* 38, 324 (1951)] was used. The working range of this method in our hands was between 0.5 and 100 microequivalents of ammonia nitrogen.
6. This investigation was supported by a research grant, RG-3795, from the National Institutes of Health, U.S. Public Health Service.
7. Owing to individual variations in the level of ammonia excretion, the average ammonia excretion in each experiment was assigned a value of 100, and the individual values were expressed as percentages of this figure.
8. F. C. Rector, D. W. Seldin, J. H. Copenhaver, *J. Clin. Invest.* 34, 20 (1955).
9. A. P. Briggs, *J. Lab. Clin. Med.* 28, 174 (1942).
10. C. Ryberg, *Acta Physiol. Scand.* 15, 114 (1949).
11. The *pK* for the reaction $NH_4^+ \leftrightharpoons H^+ + NH_3$ was taken as 9.4 [E. J. Conway, *Microdiffusion Analysis and Volumetric Error*, C. Lockwood (London, ed. 2, 1947)], p. 88.

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Taming and Susceptibility to Audiogenic Convulsions

Several recent papers have reported that taming influences both growth and behavior in the albino rat. Tamed animals are described as larger, heavier, and more resistant to the effects of physical and emotional stress than untamed ones. They have also been characterized as