N. W. Carter

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MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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RESPONSES TO DISORDERS IN ACID-BASE BALANCE

Case 1.

A 46 year old white male was known to have been an insulin dependent diabetic since age 34 years. He was a binge-type alcoholic and had several previous episodes of keto-acidosis related to drinking and failure to take insulin. About 5 days before the present admission, he began to drink; history of food intake and insulin administration unreliable. Two days PTA he became weak and on the day PTA he noted some shortness of breath. Blood pressure 130/70, R-24, P-100, Temp 98°. No important physical findings.

Start of Therapy		5 hrs of Therapy	
Glucose	398	Glucose	220
BUN	16	BUN	24
Na	126	Na	143
Cl	81	Cl	106
K	6.7	K	7.5
CO_2	7.5	CO_2	11
Serum Ketones	1:6	Serum Ketones	1:2
		pH	7.05

During first 5 hours he received 500 units insulin, 2 L normal saline and 2 L Ringer's lactate. At 5 hours he became markedly orthopnic and chest x-ray showed pulmonary edema. Therapy for pulmonary edema was instituted and there was a good response. Blood pH was not repeated until 7 hours later at which time it was 7.35 and the pulmonary edema had cleared.

Case 2.

A 25 year old ex-service man had had many social-family problems since discharge from service 3 months PTA. For about the month prior to admission he had from 2-5 episodes of hyperventilation terminating with carpo pedal spasm and laryngospasm. Except for marked weakness, there were no significant physical findings. Several episodes of hyperventilation and tetany were observed on the ward.

Admission Chemistry

Na	138	CO_2	36
K	2.2	pH	7.66
Cl	90	pCO_2	30

24-hr. Urine - Na = 95 mEq; K = 40 mEq

Large doses of KCl (120-200 mEq daily) did not correct the hypokalemia while hyperventilation continued. It was necessary to use light pentothal anesthesia to control his hyperventilation at which time KCl administration quickly corrected the potassium deficiency.

Case 3. (From Reference #109)

An interesting report of an 18 year old girl who took NH_4Cl tablets to effect weight loss. The fourth and third days PTA she took 82 gms (153 mEq) of NH_4Cl. Her signs and symptoms, probably the result primarily of the profound acidosis induced, are of interest.

During the 2 days PTA she took no more NH_4Cl. However, she noted headache and nausea. Vomiting occurred once or twice. She was noted to appear drowsy and eventually confused.

At the time of admission she was disoriented, alternately stuporous and agitated. Except for hyperactive deep tendon reflexes, the remaining exam was not remarkable. Soon after admission she lapsed into a comatose state.

Initial Laboratory Findings - Hgb 15.4 gms WBC 27,400 with 72% neutrophils. Urinalysis; pH 4.82, Sp Grav 1.010, Protein 1+, Glucose 2+, Acetone negative. Sediment; occ. granular cast.

Blood

Na	144	Cl	137	BUN	37
K	5.2	pH	6.78	Glucose	237
CO_2	2.4	pCO_2	13.7		

She was treated with $NaHCO_3$, receiving in the first 2 hours about 361 mEq. At that point blood pH = 7.32 and she began to respond. She continued to hyperventilate. With continued therapy with $NaHCO_3$ she recovered completely, but did go through a period of hypokalemia (2.2 mEq/L) and developed a high CO_2 content (33 mEq/L).

Intracellular pH Measurements

1. The HCO_3^- - H_2CO_3 system:

$$pH_i = 6.10 + \log \frac{[HCO_3^-]}{0.03 \times pCO_2}$$

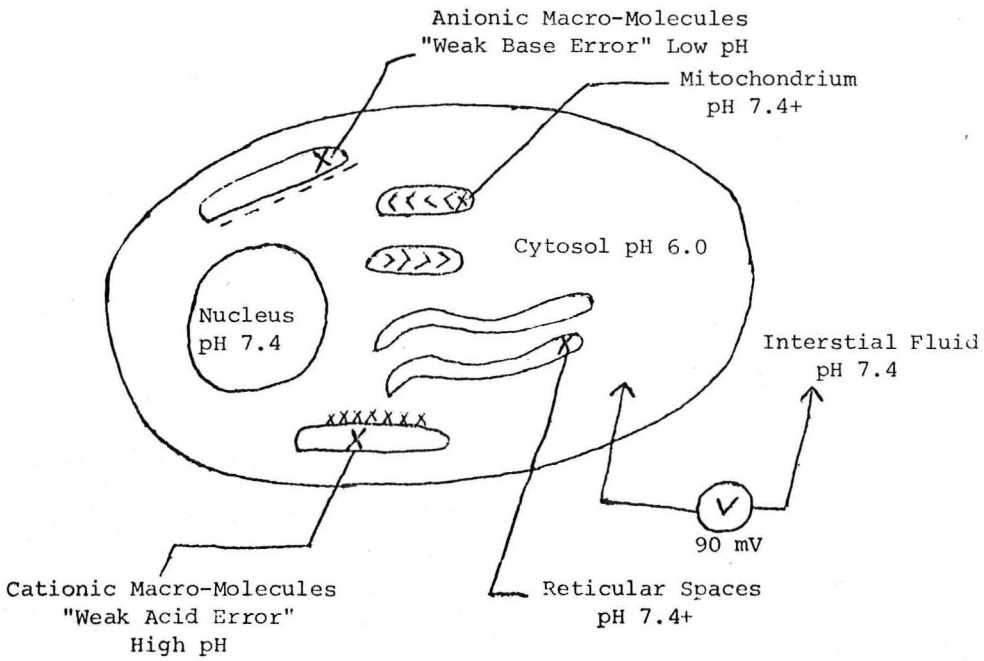
2. The DMO system:

$$pH_i = 6.13 + \log \frac{DMO^-}{DMOH}$$

3. pH sensitive glass electrodes, micro:

$$pH_i = pH_e - \frac{Em}{61.5}$$

where pH_i = intracellular pH; pH_e = extracellular pH; Em = transmembrane potential in millivolts; 61.5 is a constant for 2.3026 $\frac{RT}{F}$ at 37°C



Muscle Electrolyte Composition in Chronic Acid-Base Disturbances in the Rat

	Blood pH	Sodium mEq/100 gm FFDT	Potassium mEq/100 gm FFDT
Control	7.40	4.20	46.7
Metabolic Acidosis (NH_4Cl)	7.25	3.43	47.3
Respiratory Acidosis (10% CO_2)	7.28	3.31	43.0
Metabolic Alkalosis (K^+ Deficiency)	7.65	19.3	27.0

A Clinical Aid

From: Kassirer, J.P. and Bleich, H.L. Rapid estimation of plasma carbon dioxide content. New Eng. J. Med. 272:1067, 1965.

1. Take the difference between measured blood pH and 7.40; multiply by 100.
2. If blood pH is less than 7.40, add number found in Step 1 to 40. If blood pH is greater than 7.40, subtract number found in Step 1 from 40.
3. Substitute number found in Step 2 for H^+ in following formula:

$$pCO_2 \cong H^+ \times \frac{(CO_2 \text{ Content})}{25}$$

Example: Blood pH = 7.16; CO_2 content = 20 mEq/L

1. $7.40 - 7.16 = 0.24 \times 100 = 24$.
2. $40 + 24 = 64$.
3. $pCO_2 \cong 64 \times \frac{20}{25} = 51$ mm Hg. (True pCO_2 = 53 mm Hg).
4. Error in pCO_2 estimate becomes larger at the extremes of blood pH.

1. Waddell, W.J. and Bates, R.G. Intracellular pH. Physiol. Rev. 49:285, 1969.

This is the most up to date review of the subject (from 1956). The senior author is of course a champion of the DMO method for measurement of pH_i. Dr. Bates, National Bureau of Standards, is one of the foremost authorities on the measurement of pH. See next reference.

2. Caldwell, P.C. Intracellular pH. In: International Review of Cytology. Eds. Bourne, G.H. and Danielli, J.F. New York Academic Press 5:229, 1956.

A thorough review of pH_i including methods, results and discussion of the implications. Complete to 1956.

3. Waddell, W.J. and Butler, T.C. Calculation of intracellular pH from the distribution of 5,5-Dimethyl-2,4-oxazolidinedione (DMO). Application to skeletal muscle of the dog. J. Clin. Invest. 38:720, 1959.

Presentation of the DMO method for measurement of intracellular pH of muscle. Normal dog muscle pH_i was given as 7.04.

4. Caldwell, P.C. Studies on the internal pH of large muscle and nerve fibers. J. Physiol. 142:22, 1958.

Using rather large glass pH sensitive electrodes (80 to 100 μ diam) pH of crab muscle (150-350 μ diam) was found to be 7.0. Likewise the giant axon of the squid had an internal pH of 7.0.

5. Kostyuk, P.G. and Sorokina, Z.A. On the mechanism of hydrogen ion distribution between cell protoplasm and the medium. Membrane Transport and Metabolism. Academic Press, New York 1960, p. 193.

Using micro-electrodes (1.0 μ diam) found pH of frog muscle in vitro to be 7.0.

6. Carter, N.W., Rector, F.C., Campion, D.S. and Seldin, D.W. Measurement of intracellular pH of skeletal muscle with pH-sensitive glass microelectrodes. J. Clin. Invest. 46:920, 1967.

7. Carter, N.W., Rector, F.C., Campion, D.S. and Seldin, D.W. Measurement of intracellular pH with glass microelectrodes. Fed. Proc. 26:1322, 1967.

The bulk-phase pH of muscle cells was found to be about 6.0 and in electrochemical equilibrium with the outside pH.

8. Adler, S., Roy, A. and Relman, A.S. Intracellular acid-base regulation. I. The response of muscle cells to changes in CO_2 tension or extracellular bicarbonate concentration. J. Clin. Invest. 44:8, 1965.

9. Adler, S., Roy, A. and Relman, A.S. Intracellular acid-base regulation II. The interaction between CO_2 tension and extracellular bicarbonate in the determination of muscle cell pH. J. Clin. Invest. 44:21, 1965.

These two papers:
1) Exploit DMO to its utmost
2) Show that cell pH is effected by metabolic acidosis and alkalosis (A point questioned on technical grounds)
3) Discuss the limitations of DMO method on basis of cell heterogenerty. (See Ref. #2)
4) Show that in vitro, acidosis gives rise to a cellular loss of K^+ and gain of Na^+ (Rat Diaphragm).

10. Relman, A.S. Intracellular acid-base equilibrium: The reaction of muscle cells to metabolic and respiratory changes in extracellular acidity. Trans. Assoc. Amer. Phys. 76:176, 1963.

A good summary of the above two papers.

11. Robin, E.D., Vester, J.W., Wilson, R.J. and Andrus, M.H. The internal pH of mitochondria with observations on the functional significance of mitochondrial membranes. J. Clin. Invest. 39:1022, 1960 (abstract).

pH of mitochondria measured by HCO_3^-/H_2CO_3 and $\frac{NH_3}{NH_4^-}$ partition. In the former method $pH_m = 6.58$; with the ammonia system $pH_m = 6.25$. Compare with DMO results.

12. Addanki, S. and Sotos, J.F. Observations on intramitochondrial pH and ion transport by the DMO method. Ann. New York Acad. Sci. 147:756, 1969.

Find high pH_{im} (7.4-7.5) in non-transporting state when transporting Ca^{++} pH_{im} rises to 8.3-8.5.

13. Ghosh, A.K. Studies on the effect of permeant anions on the reversal of Ca^{++} induced mitochondrial alkalinity at different pH values. Ann. New York Acad. Sci. 147:849, 1969.

An interesting paper which concludes that although mitochondria are alkaline, values of pH_{im} determined by DMO method are falsely high because DMO is transported into mitochondria.

14. Irvine, R.O.H., Saunders, S.J., Milne, M.D., Crawford, M.A. Gradients of potassium and hydrogen ion in potassium-deficient voluntary muscle. Clin. Sci. 20:1, 1970.

The often quoted paper showing an acidification of K^+ deficient muscle. Intracellular pH measured by DMO method.

15. Eckel, R.E., Botschner, A.W. and Wood, D.H. The pH of K-deficient muscle. Am. J. Physiol. 196:811, 1959.

Using the HCO_3^-/CO_2 method, and interesting variations thereof, found no change in muscle pH_i in K deficiency.

16. Miller, R.B., Tyson, I., and Relman, A.S. pH of isolated resting skeletal muscle and its relation to potassium content. Am. J. Phys. 204:1048, 1963.

A comparison of measurement of intracellular pH (rat diaphragm) by the DMO and bicarbonate methods. Bicarbonate method always higher by 0.2+ units.

By these methods, intracellular pH showed no significant change after intracellular K^+ depletion.

17. Eckel, R.E. and Sperlakis, N. Membrane potentials in K-deficient muscle. Am. J. Physiol. 205:307, 1963.

Unlike our results, the Em (control) was -80.8 mV (low) and in K^+ deficiency fell to -60.7 mV. From the indirect method of HCO_3^-/CO_2 partition, found intracellular pH unchanged in K^+ deficiency. Chief idea of Eckel is that cationic amino acid makes up the difference between intracellular K^+ loss and Na^+ in K^+ deficiency. Despite dubious data for Em and "intracellular pH", amino acid concept may be correct.

18. Struyvenberg, A., DeGraeff, J. and Lameijer, L.D.F. The role of chloride in hypokalemic alkalosis in the rat. J. Clin. Invest. 44:326, 1965.

19. Orloff, J., Kennedy, T., Jr. and Berliner, R.W. The effect of potassium in nephrectomized rats with hypokalemic alkalosis. J. Clin. Invest. 32: 538, 1953.

Two experiments showing that the acute replacement of K^+ in K^+ deficiency results in an acidification of the extracellular fluid.

20. Campion, D.S., Carter, N.W., Rector, F.C., and Seldin, D.W. Intracellular pH in chronic potassium deficiency in the rat. Clin. Res. 16:379, 1968 (abstract).

By direct measurement with a glass electrode intracellular pH in control animals was 5.95 and in severely K^+ depleted animals (serum $[K^+]$ = 1.4 mEq/L) the intracellular pH was 5.84.

$-Em = 61.5 \times (pH_e - pH_i)$
$110 = 61.5 \times (7.65 - 5.84)$

Buffering - Acid and Alkaline Loads:

21. Brown, E.B. and Clancy, R.L. In vivo CO_2 buffer curves of skeletal and cardiac muscle. Am. J. Phys. 211:1309, 1966.

22. Cohen, R.D., Simpson, B.R., Goodwin, F.J. and Strunin, L. The early effects of infusion of sodium bicarbonate and sodium lactate on intracellular hydrogen ion activity in dogs. Clin. Sci.. 33:233, 1967.

23. Kim, W.H. and Brown, E.B. Potassium transfer with constant extracellular pH. J. Lab. Clin. Med. 71:687, 1968.

Three papers, all making use of DMO to estimate pH_i and thereby form conclusions about cell buffering. Obviously if a pH_i given by the DMO method is meaningful, then the statements regarding buffering are meaningful.

24. Rogers, T.A. and Wachenfeld, A.E. Effect of physiologic acids on electrolytes in rat diaphragm. Am. J. Physiol. 193:623, 1958.

An attempt to show that organic acids have a different effect on muscle electrolyte composition than does mineral acid. The results are probably dependent more on overall experimental design than on the different acids used.

25. Fenn, W.O., Rogers, T.A. and Ohr, E.A. Muscle electrolytes in acid and alkaline solutions. Am. J. Physiol. 194:373, 1958.

Frog muscle in vitro - Although not emphasized by the authors, K^+ was lost from muscle in both alkalotic and acidotic situations. Their main point was that in response to external pH changes intracellular concentrations of Na^+ and K^+ were being set by some active process, not by passive Donnan equilibrium.

26. Thompson, A.M. and Brown, E.B. Tissue carbon dioxide concentrations in rats during acute respiratory acidosis. J. Appl. Physiol. 15:49, 1960.

Shows a remarkable rise in CO_2 content of skeletal muscle, heart and brain when rats were exposed to 30% CO_2. This suggests that there is considerable buffering capacity for H_2CO_3. However, the very high values reported here are probably due to a filure to correct for ECF CO_2 in the tissue analyses.

27. Schwartz, W.B., Jenson, R.L. and Relman, A.S. The disposition of acid administered to sodium depleted subjects: The renal response and the role of the whole body buffers. J. Clin. Invest. 33:587, 1954.

In NH_4Cl loaded humans, balance data disclosed that from 12 to 18% of the load was buffered by blood; 19 to 44% by interstitial fluid; 43 to 69% by the intracellular compartment. This latter was accomplished primarily by the exchange on intracellular K^+

28. Swan, R.C., and Pitts, R.F. Neutralization of infused acid by nephrectomized dogs. J. Clin. Invest. 34:205, 1955.

HCl infusions in nephrectomized dogs show that about 40% of acid load buffered extracellularly. Intracellular buffering was accompanied by a loss of both Na^+ and K^+ from cells.

29. Tobin, R.B. Plasma, extracellular and muscle electrolyte responses to acute metabolic acidosis. Am. J. Phys. 186:131, 1956.

In nephrectomized cats infused with HCl, the acid load resulted in an outward shift from muscle of Na^+ and to a lesser extent of K^+. However, the ECV increment in Na^+ was 30% greater than the amount lost from muscle and the increment in ECV K^+ was only 0.1 that lost from muscle.

30. Schwartz, W.B., Orning, K.J. and Porter, R. The internal distribution of hydrogen ions with varying degrees of metabolic acidosis. J. Clin. Invest. 36:373, 1957.

Acid loads were about equally buffered in dogs between intracellular and extracellular sites. (57.6 ± 11.6 S.D.% intracellular).

31. Elkinton, J.R., Singer, R.B., Barker, E.S. and Clark, J.K. Effects in man of acute experimental respiratory alkalosis and acidosis on ionic transfers in the total body fluids. J. Clin. Invest. 34:1671, 1955.

Both alkalosis and acidosis appeared to be involved mostly with exchanges of Na^+ and (H^+ + HX) between the extracellular and intracellular compartment.

32. Carter, N.W., Seldin, D.W., and Teng, H.C. Tissue and renal response to chronic respiratory acidosis. J. Clin. Invest. 38:949, 1959.

Little change in muscle or bone electrolytes occurred with chronic respiratory acidosis in rats (10% CO_2 for 10 days). Only when Na^+ and K^+ were withheld in the diet could a small but significant fall in muscle K^+ be observed. Moreover, this acidosis did not lead to a sustained increase in acid excretion as does NH_4Cl induced acidosis.

33. van Gordsenhoven, G. M.-T., Gray, O.V., Price, A.V. and Sanderson, P.H. The effect of prolonged administration of large doses of sodium bicarbonate in man. Clin. Sci. 13:383, 1954.

In humans with peptic disease given $NaHCO_3$ for as long as 3 weeks up to 140 gms/day, a modest increase in plasma CO_2 and pH occurred. There was expansion of ECV with release of Cl^- from cells. No loss of K^+. No renal damage.

34. Cooke, R.E. et al. The role of potassium in the prevention of alkalosis. Am. J. Med. 17:180, 1954.

In acute experiments in rats, massive $NaHCO_3$ loading (15 mM/Kg B.W.) caused a marked excretion of K^+ (5 mM in first 12 hrs.) reduced skeletal muscle K^+ but did not cause a sustained systemic alkalosis.

35. Swan, R.C., Axelrod, D.R., Seip, M. and Pitts, R.F. Distribution of sodium bicarbonate infused into nephrectomized dogs. J. Clin. Invest. 34:1795, 1955.

Initially, 3/4 of the infused $NaHCO_3$ remains in extracellular fluid. Some of this is eventually neutralized, presumably by lactic acid. About 1/4 of the administered $NaHCO_3$ leaves the ECV and is neutralized intracellularly, perhaps by an exchange of Na^+ for H^+.

36. Singer, R.B., Clark, J.K., Barker, E.S., Crosley, A.P. and Elkinton, J.R. The acute effects in man of rapid intravenous infusion of hypertonic sodium bicarbonate solution. Medicine 34:51, 1955.

The immediate volume of distribution of $NaHCO_3$ is the ECV. These authors, however showed little intracellular exchange. Apparently some Na^+ was exchanged for H^+ in the intracellular phase, but also saw slight shifts of K^+ out of cells.

37. Brown, E.B., Jr. Physiological effects of hyperventilation. Phys. Rev. 33:445, 1953.

An interesting review with many important older references. Use primarily for a discussion of hyperventilation tetany.

38. Darrow, D.C. Tissue electrolyte at low atmospheric pressures. Am. J. Phys. 142:61, 1944.

In cats with a mild respiratory alkalosis of about 24 hrs. duration, no significant changes in muscle, brain or heart [K^+] occurred.

39. Lars, H.S. et al. Potassium deficiency in bulbar poliomyelitis. J.A.M.A. 146:1017, 1951.

A report of three cases of bulbar polio where renal K^+ loss was almost certainly brought about by chronic hyperventilation ($\downarrow pCO_2$). Over long periods, a metabolic alkalosis may become superimposed on a chronic respiratory alkalosis.

Changes in Serum Potassium Concentration:

40. Scribner, B.H. and Burnell, J.M. Interpretation of the serum potassium concentration. Metabolism 5:468, 1956.

41. Burnell, J.M., Villamil, M.F., Vyeno, B.T. and Scribner, B.H. The effect in humans of extracellular pH change on the relationship between serum potassium concentration and intracellular potassium. J. Clin. Invest. 35:935, 1956.

Concluded that for every 0.1 unit extracellular pH change there was an average inverse change of 0.6 mEq/L in serum potassium concentration.

42. Burnell, J.M. and Scribner, B.H. Serum potassium concentration as a guide to potassium need. J.A.M.A. 164:959, 1957.

From the paper: "In using the serum potassium concentration as a guide to potassium need, it is helpful to remember that acidosis increases and alkalosis decreases the serum potassium concentration independently of the potassium stores. Rapid correction of acid-base disturbances will be accompanied by rapid changes in the serum potassium concentration, which reflect rapid changes in the need for potassium".

43. Scribner, B.H., Fremont-Smith, K. and Burnell, J.M. The effect of acute respiratory acidosis on the internal equilibrium of potassium. J. Clin. Invest. 34:1276, 1955.

In dogs, respiratory acidosis results in hyperkalemia. In these acidotic dogs, infusion of KCl does not cause cellular uptake of K^+ as it does in a normal dog.

44. Fenn, W.O. and Asano, T. Effects of CO_2 inhalation on potassium liberation from the liver. Am. J. Physiol. 185:567, 1956.

The rise in $[K^+]_s$ incident to respiratory acidosis involves the "adrenal-sympathico-hepatic system" since the rise is prevented by cervical section of the spinal cord, adrenergic blocking agents, clamping of both the hepatic artery and portal vein and is usually diminished by adrenalectomy.

45. Ligour, J.C. and Nahas, G.G. Comparative effects of acidosis induced by acid infusion and CO_2 accumulation. Am. J. Phys. 198:1201, 1960.

In dogs, experimental acidosis by CO_2 retention produced a secretion of epinephrine and norepinephrine together with ↑ BP and ↑ blood sugar, whereas a similar arterial pH change brought about by lactic acid infusion did not effect catecholamine blood levels nor alter BP or blood sugar.

46. Hickam, J.B., Wilson, W.P. and Frayser, R. Observations on the early elevation of serum potassium during respiratory alkalosis. 35:601, 1956.

In 13 normal subjects, a mean increase of 1.2 mEq per L in serum potassium was achieved with 2 min. of hyperventilation. Arterial pH was elevated in all cases.

47. Lade, R.I. and E.B. Brown, Jr. Movement of potassium betwen muscle and blood in response to respiratory acidosis. Am. J. Physiol. 204:761, 1963.

In anesthetized dogs, breathing 30% CO_2 in O_2 was shown to be accompanied by a release of K^+ from muscle and an uptake of K^+ by the heart. Interestingly, a marked rise in $[K^+]_s$ which accompanied the cesation of CO_2 breathing did not come about by K^+ release from skeletal muscle, but was at least in part the result of K^+ release from the heart.

Effects on Bone:

48. Bergstrom, W.H. and Wallace, W.M. Bone as a sodium and potassium reservoir. J. Clin. Invest. 33:867, 1954.

In response to an acid load, sodium depleted rats were found to have decreased concentrations of sodium and potassium in their bones.

49. Levitt, M.F., Turner, L.B., Sweet, A.Y. and Pandiri, D. The response of bone, connective tissue and muscle to acute acidosis. J. Clin. Invest. 35:98, 1956.

50. Nichols, N. and Nichols, G. The effect of alloxan diabetes and acidosis on the mineral and water content of bone. J. Clin. Invest. 37:1676, 1958.

In acutely induced acidosis (NH_4Cl or HCl) in the rat, the bone apparently participates in buffering by the solution of both Ca^{++} and Na^+.

51. Forbes, G.B., Tobin, R.B. and Lewis, A. Response of bone sodium to acute changes in extracellular fluid composition (cat). Am. J. Physiol. 196:69, 1959.

Although the authors were able to show that acidosis was accompanied by removal of bone Na^+, the amount of bone Na^+ removed was not in any way related to the acid load nor degree of acidosis produced.

52. Goodman, A.D., Lemann, J., Jr., Lennon, E.J. and Relman, A.S. Production, excretion, and net balance of fixed acid in patients with renal acidosis. J. Clin. Invest. 44:495, 1965.

Found that maintenance of a positive acid balance in patients with renal acidosis was accompanied by a higher serum HCO_3^- concentration than expected. Thus some extra-renal buffering of acid was suspected. The suggestion was made that bone was the base source.

53. Nguyen, V.V. and Jowsey, J. The acute effects of hormones, vitamin D_3 and acidosis during in vivo perfusion of adult dog forelimbs. J. Bone and Joint Surg. 52-A:1041, 1970.

Direct infusion into arterial blood supplying bone (4 hr. duration) of either HCl or citric acid results in slight change in venous blood Ca concentration (+ 6-7%) when the effluent blood pH varies between 7.1-7.2. A rather large increment in phosphate in the effluent is seen.

54. Lemann, J., Jr., Litzow, J.R. and Lennon, E.J. Studies of the mechanism by which chronic metabolic acidosis augments urinary calcium excretion in man. J. Clin. Invest. 46:1318, 1967.

Conclude that the increase in Ca excretion incident to metabolic acidosis is the result of the kidney's decreased reabsorption of Ca^{++} resulting from a change in metabolic functions of the renal tubular cell brought about by acidosis. (Perhaps has some relation to NH_3 production).

55. Silberg, B., Calder, D., Carter, N. and Seldin. Urinary calcium excretion in parathyroidectomized rats during metabolic and respiratory acidosis. Clin. Res. 12:50, 1964 (abstract).

Although acid loads (NH_4Cl) insufficient to significantly alter blood pH, give rise to increased renal calcium excretion, severe acidosis produced with CO_2 have no effect on calcium excretion.

Effects on Metabolism and Metabolic Effects,

56. Gilbert, R. and Auchincloss, H. Arterial blood gases and acid-base balance at the exercise breaking point. Arch. Int. Med. 125:820, 1970.

One example of the degree of metabolic (lactic primarily) acidosis that a normal person can develop with severe exercise. Arterial blood pH can go as low as 7.15. (Trained persons can go below pH 7.0).

57. Huckabee, W.E. Relationships of pyruvate and lactate during anaerobic metabolism. I. Effects of infusion of pyruvate or glucose and of hyperventilation. J. Clin. Invest. 37:244, 1958.

Both infusion of $NaHCO_3$ and hyperventilation increased the blood concentrations of lactate and pyruvate in the absence of hypoxia.

58. Eichenholz, A., Mulhausen, R.O., Anderson, W.E. and MacDonald, F.M. Primary hypocapnia: a cause of metabolic acidosis. J. Appl. Physiol. 17:283, 1962.

Showed in experiments with dogs that if severe hypocapnia is sufficiently prolonged the excess production of lactic and pyruvic acids can deplete serum HCO_3^-, eventually resulting in a metabolic acidosis.

59. Plum, F. and Posner, J.B. Blood and cerebrospinal fluid lactate during hyperventilation. Am. J. Physiol. 212:864, 1967.

In anesthetized dogs: 1) could not duplicate the experiments of Eichenholz et al. even after 6 hrs. of hyperventilation. No acidosis was produced. 2) Hyperventilation increased CSF lactate, and presumably brain lactate, to such a degree as to return CSF pH to near normal despite continued severe arterial alkalosis.

60. Hastings, A.B. "Ah Sweet Mystery." A biochemist's myopic viewpoint. Diabetes II:361, 1962.

In rat liver slices, changed medium $[HCO_3^-]$ and keeping pH constant by altering pCO_2 resulted in increasing glycogen production with increasing $[HCO_3^-]$ (and pCO_2). However, if medium $[HCO_3^-]$ was kept constant, but pH varied - the highest pH (but lowest pCO_2) was associated with the largest rate of glycogen synthesis.

61. Longmore, W.J., Hastings, A.B. and Mahowald, T.A. Effect of environmental CO_2 and pH on glycerol metabolism by rat liver in vitro. J. Biol. Chem. 239:1700, 1964.

pH and CO_2 content had no effect on the conversion of glycerol to glucose + CO_2 nor on the incorporation of glycerol into phospholipids. Same effects on glycogen formation as stated in the previous reference.

62. Gevers, Wieland and Dowdle, E. The effect of pH on glycolysis in vitro. Clin. Sci. 25:343, 1963.

In rat liver, kidney and adipose slices glycolysis is stimulated by alkaline pH; but this effect is blocked by physiological concentrations of $PO_4^{\equiv}$ in the media. Rat diaphragm glycolysis is also stimulated by alkaline pH, but the effect is not blocked by $PO_4^{\equiv}$.

63. Longmore, W.J., Landau, B.R., Baher, E.S., Hastings, A.B., Lym, D.M. and Williams. Effect of pH and CO_2 concentration on glucose metabolism by rat adipose tissue in vitro. Am. J. Physiol. 215:582, 1968.

Glucose utilization altered by medium pH and not by ECF changes in $[HCO_3^-]$ or pCO_2.

64. Trivedi, B. and Danforth, W.H. Effect of pH on the kinetics of frog muscle phosphofructokinase. J. Biol. Chem. 241:4110, 1966.

Examines, in vitro, the relation of pH to PFK and demonstrates that the activity is very sensitive to H^+ activity at around pH 7.0.

65. Vi, M. A role of phosphofructokinase in pH-dependent regulation of glycolysis. Biochem. Biophys. Acta 124:310, 1966.

The inhibitory affect of ATP on PFK is markedly pH sensitive being blocked by raising pH and excentuated by lowering pH. Studies carried out with cell-free extracts of rat diaphragm using CO_2 tension to adjusted pH of medium.

66. Huszak, I. and Domonkos, J. Effect of hydrogen-ion concentration on carbohydrate metabolism of brain tissue. J. Neurochem. 4:238, 1959.

It appears that in brain (in vitro, cat) increasing medium pH causes increased glucose utilization, and increased lactate and pyruvate production.

67. Adler, S. The role of pH, P_{CO_2} and bicarbonate in regulating rat diaphragm citrate content. J. Clin. Invest. 49:1647, 1970.

Extracellular acidification caused, or was associated with a decrease in muscle citrate concentration and alkalinization was associated with an increase in cell citrate. Acidification caused increased metabolism of citrate. But, at any pH, $[HCO_3^-]_{ECF}$ directly correlated with citrate content of muscle.

68. Goorno, W.E., Rector, F.C. and Seldin, D.W. Relation of renal gluconeogenesis to ammonia production in the dog and rat. Am. J. Physiol. 213: 969, 1967.

Gluconeogenesis was found to be increased in cortical kidney slices from animals with induced metabolic acidosis - depressed from animals receiving $NaHCO_3$ - and not effected in slices from animals with respiratory acidosis.

69. Kamm, D.E., Frusz, R.E., Goodman, A.D. and Cahill, G.F., Jr. Acid-base alterations and renal gluconeogenesis: effect of pH, bicarbonate concentration. J. Clin. Invest. 46:1172, 1967.

In kidney slices (rat) from normal animals, low medium pH increased gluconeogenesis. Slices from rats made acidotic (metabolic or respiratory) likewise showed increased glucose production. pH rather than pCO_2 or $[HCO_3^-]$ thought to be the most important variable effecting renal gluconeogenesis.

70. Alleyne, G.A.O. and Scullard, G.H. Renal metabolic response to acid-base changes. I. Enzymatic control of ammoniogenesis in the rat. J. Clin. Invest. 48:364, 1969.

71. Alleyene, G.A.O. Renal metabolic response to acid-base changes. II. The early effects of metabolic acidosis on renal metabolism in the rat. J. Clin. Invest. 49:943, 1970.

In rats, very early after an acid load, renal gluconeogenesis is increased, presumably in connection with increased NH_3 production.

72. Mackenzie, C.H., Mackenzie, B. and Beck, P. The effect of pH on growth, protein synthesis and lipid-rich particles of cultured mammalian cells. J. Bioph. & Bioch. Cyt. 9:141, 1961.

Rat liver cells grow well in medium pH range 7.38-7.87. On lowering pCO_2 cell growth declined rapidly; raising pCO_2 had less effect (to about pH 7.0). Cell death on the alkolotic side was shown not to be the result of decrease Ca^{++} or Mg^{++} in the medium.

73. Mackenzie, C.G., Mackenzie, J.B. and Reiss, O.K. Increase in cell lipid and cytoplasmic particles in mammalian cells cultured at reduced pH. J. Lipid Res. 8:642, 1967.

Most interesting that a medium pH of 6.9 did not seem to effect protein synthesis (cell growth) of cultured rat liver cells or fibroblast. However, the triglyceride level of both cells was increased in the acid medium by 2X. The "acidosis" was induced by CO_2.

74. Goldstein, E., Green, G.M. and Seamans, C. The effect of acidosis on pulmonary bactericidal function. J. Lab. Clin. Med. 75:912, 1970.

Showed that in rats made acidotic with NH_4Cl (pH below 7.20), the lungs normal capacity to kill bacteria was greatly reduced.

Effects on Blood Vessels:

75. Haddy, F.J. and Scott, J.B. Metabolically linked vasoactive chemicals in local regulation of blood flow. Physiol. Rev. 48:688, 1968.

Reviews many studies, which in summary appear to show that increased hydrogen ion activity (↓pH) tends to lower vascular resistance in skeletal muscle, intestine, coronary, renal and cerebral circulations. A rise in pH probably has the opposite effect. Activity of visceral smooth muscle is decreased with ↓pH and augmented by ↑pH.

76. Kittle, C.F., Aoki, H., Brown, E.B. The role of pH and CO_2 in the distribution of blood flow. Surgery 57:139, 1965.

A study in lightly anesthetized dogs confirmed that cerebral blood flow was very sensitive to pCO_2 of blood - ↑pCO_2 = ↑blood flow. The authors also thought there was little influence of arterial pH on cerebral and coronary blood flow. Likewise, coronary blood flow appeared to respond, less convincingly, to ΔpCO_2. Least convincing was a change of renal blood flow with pCO_2 - ↑pCO_2 = ↓blood flow, again with little effect seen from blood pH.

77. Carrier, O. Jr., Cowsert, M., Hancock, J. and Guyton, A.C. Effect of hydrogen ion changes on vascular resistance in isolated artery segments. Am. J. Physiol. 207:169, 1964.

Small isolated femoral arterial branches from the dog were perfused with Tyrode's solution of different pH's. Titrating downward from pH 7.4, resistance decreased to pH 7.15. Thereafter it began to increase but even at pH 6.8 it was 50% lower than at pH 7.4. Titrating upward, resistance decreased from pH 7.4 to 7.56 (after an initial 35% increase at pH 7.5). By pH 7.8 the resistance was higher than at pH 7.5. pCO_2 was said to have been held constant (normal) in these experiments.

78. Downing, S.E., Mitchell, J.H. and Wallace, A.G. Cardiovascular responses to ischemia, hypoxia and hypercapnia of the central nervous system. Am. J. Physiol. 204:881, 1963.

In dogs, the brain was perfused with hypercapnic blood which resulted in a peripheral sympathetic release which increased peripheral resistance and heart rate. The pH of the perfusate was extremely low, however; range 6.62-6.80. Of interest, perfusion with blood plus added HCO_3^- (pH 7.80-8.08) also gave the same response, presumably by the elevation of pCO_2.

79. Nahas, A.G. and Poyart, C. Effect of arterial pH alterations on metabolic activity of norepinephrine. Am. J. Physiol. 212:765, 1967.

Both metabolic and respiratory acidosis inhibit all the actions of norepinephrine. Alkalosis does not potentiate the effects of the drug. In alkalotic experimental dogs, norepinephrine produced cardiac arrythmia.

80. Simmons, D.H. and Olver, R.P. Effects of acute acid-base changes on renal hemodynamics in anesthetized dogs. Am. J. Physiol. 209:1180, 1965.

Renal vascular resistance was pCO_2 dependent but not pH dependent. Increased pCO_2 (with constant pH) decreased resistance while lowering pCO_2 increased resistance. However, only very small changes in blood pH (0.2 unit) were examined with nearly constant pCO_2. The resistance changes with pH change (down in acidosis; up in alkalosis) were not thought significant.

81. Bersentes, T.J. and Simmons, D.H. Effects of acute acidosis on renal hemodynamics. Am. J. Physiol. 212:633, 1967.

In anesthetized dogs, both respiratory and metabolic acidosis of a "mild" degree (pH $\sim$ 7.0) produced intra-renal vasodilatation; more severe acidosis resulted in vasoconstriction. Thus renal vascular resistance is both pH and pCO_2 dependent.

82. Sharpey-Schafer, E.P., Semple, S.J.G., Halls, R.W. and Howarth, S. Venous constriction after exercise: Its relation to acid-base changes in venous blood. Clin. Sci. 29:397, 1965.

Venous constriction after exercise was found not mediated by neural pathways, but rather was most likely the direct result of lowered pH in venous blood resulting from acids produced by the contracting muscle. Interesting, no increase in venous tone resulted from reactive hyperemia due to acute muscle ischemia (2 min. duration).

83. Harvey, R.M., Enson, Y., Lewis, M.L., Greenough, W.B., Ally, K.M. and Panno, R.A. Hemodynamic effects of dehydration and metabolic acidosis in Asiatic cholera. Trans. Ass. Am. Phys. 79:177, 1966.

Salt replacement in acidotic hypovolemic patients resulted in pulmonary congestion thought to be the result of a disproportionate venous return to the heart as a consequence of increased venous tone caused by the acidosis.

84. Schwartz, W.B. and Kassiner, J.P. Medical management of chronic renal failure. Am. J. Med. 44:795, 1968.

Authors suggest that therapy is not needed for low $[HCO_3^-]_s$ and acidosis unless the patient is symptomatic. This neglects the possible ill effects arising from increased venous tone, and perhaps on the continued titration of bone

Heart:

85. McElroy, W.T., Jr., Gerdes, A.J. and Brown, E.B., Jr. Effects of CO_2 bicarbonate and pH on the performance of isolated perfused guinea pig hearts. Am. J. Physiol. 195:412, 1958.

Changes noted - consistent with other experiments, were felt to be the result of changes in pH of the perfusing solution and not pCO_2 alone nor $[HCO_3^-]$.

86. Goodyear, A.V.N., Eckhardt, W.F., Ostberg, R.H. and Goodkin, M.J. Effects of metabolic acidosis and alkalosis on coronary blood flow and myocardial metabolism in the intact dog. Am. J. Physiol. 200:628, 1961.

In anesthetized dogs, infusion of HCl resulted in arterial pH of 7.16-7.29 and resulted in a ↓C.O., ↓coronary blood flow. Infusions of $NaHCO_3$ (pH 7.49-7.65) produced opposite effects as well as raising blood lactate and pyruvate levels. pCO_2 not controlled in the $NaHCO_3$ infusion.

87. Bendixen, H.H., Laver, M.B. and Flacke, W.E. Influence of respiratory acidosis on circulatory effect of epinephrine in dogs. Cir. Res. 13:64, 1963.

Respiratory acidosis did decrease the effect of epinephrine on augmenting the contractile force of the heart, but the effect of lowered pH on the ability of epinephrines to raise BP and heart rate was not altogether predictable.

88. Opis, L.H. Effect of extracellular pH on function and metabolism of isolated perfused rat heart. Am. J. Physiol. 209:1075, 1965.

Concluded that there was decreased mechanical activity at pH 7.1 but that Krebs cycle activity was unaltered by pH changes from 7.1 to 8.0. Glycolysis and acetate oxidation were increased by pH's above 7.4.

89. Wang, H. and Katz, R.L. Effects of changes in coronary blood pH on the heart. Circ. Res. 17:114, 1965.

In open chested dogs, infusions of DMOH plus $NaHCO_3$ (CO_2 release) into coronary arteries caused fall in coronary blood flow and contractile force. Opposite effects were found with infusions of THAM and Na_2CO_3 (alkanizing effects). Suggests pH mediation.

90. Carson, S.A.A., Chorley, G.E., Hamilton, F.N., Lee, D.C. and Morris, L.E. Variation in cardiac output with acid-base changes in the anesthetized dog. J. Appl. Physiol. 20:948, 1965.

Metabolic acidosis results in decreased C.O. However, simple increase in pCO_2 (respiratory acidosis) appeared to increase C.O.

91. Delcher, H.K. and Shipp, J.C. Effect of pH, pCO_2 and bicarbonate on metabolism of glucose by perfused rat heart. Biochim. Biophys. Acta 121:250, 1966.

The effects noted on glucose metabolism; alkaline = ↑glucose uptake, ↑lactate production and ↑glycogen breakdown; Acid = opposite effects except that glycogen levels unchanged - appeared due to changes in H^+ activity and not specifically to changes in $[HCO_3^-]$ or pCO_2.

92. Delcher, H.K. and Shipp, J.C. Effect of pH, pCO_2 and bicarbonate on metabolism of glucose by perfused rat heart. Biochimica Biophys. 121: 250, 1966.

Effects similar to those previously reported. Appear to be pH mediated.

93. Kohlhardt, M., Wirth, K., and Dudeck, J. The influence of metabolic alkalosis and metabolic acidosis on the contractility of the isolated heart. Pflugers Arch. ges Physiol. 296:352, 1967.

Alkalosis (up to pH 7.8) increased $\frac{dp}{dt}$ by 36.8%. Further increase of pH to 8.2 had little additional effect.
Acidosis (pH 7.0) decreased $\frac{dp}{dt}$ by 27%. An acidosis to pH 7.2 had a negative inotropic effect, but the change in $\frac{dp}{dt}$ was not significant.

94. Scheuer, J. and Berry, M.N. Effect of alkalosis on glycolysis in the isolated rat heart. Am. J. Physiol. 213:1143, 1967.

Perfusion to pH 8.2-8.5 (either metabolic or respiratory) produced 3-fold increase in lactate production and increased exogenous glucose and endogenous glycogen utilization. In the hearts glucose 6-phosphate and fructose 6-phosphate decreased while fructose 1,6-diphosphate and dihydroxyacetone phosphate increased. Creatinine phosphate increased - No change in adenosine compounds or inorganic phosphate. Results consistant with a stimulation of the phosphofructokinase reaction.

95. Vaughan-Williams, E.M. and Whyte, J.M. Chemosensitivity of cardiac muscle. J. Physiol. 189:119, 1967.

The membrane potential was measured in isolated rabbit atria in control baths and acid and alkaline baths (both metabolic and respiratory). Acidosis caused a fall in membrane potential and alkalosis a slight rise. Changes were thought brought about by external H^+ activity and not by changes in $[HCO_3^-]$ or pCO_2.

96. Wildenthal, K., Mierzwiak, D.S., Myers, R.W. and Mitchell, J.H. Effects of acute lactic acidosis on left ventricular performance. Am. J. Phys. 214:1352, 1968.

Effects on heart appear to be pH mediated. A negative inotropic effect was observed at pH 7.1-6.8 which was preceded by a transient positive inotropic effect presumably due to catecholamine release.

97. Katz, A.M. The early "pump" failure of the ischemic heart. Am. J. Med. 47:497, 1969.

Suggests that an intracellular acidosis (in this case, the result of ischemia) may effect the affinity of the contractile proteins for each other.

98. Nakamaru, Y. and Schwartz, A. Possible control of intracellular calcium metabolism by sarcoplasmic reticulum of skeletal and cardiac muscle. Biochem. Biophys. Res. Comm. 41:830, 1970.

Suggests that acidosis may inhibit Ca^{++} release from sarcoplasmic reticulum thus reducing the number of contractile groups. Based upon in vitro experiments.

Central Nervous System:

99. Winters, R.W., Lowder, J.A. and Ordway, N.K. Observations on carbon dioxide tension during recovery from metabolic acidosis. J. Clin. Invest. 37:640, 1958.

An examination in patients of the continued hyperventilation that exist after correction of arterial pH. Although continued intracellular acidosis in brain cells is a possible explanation, more complex mechanisms seem to play an important role in controlling respiration following systemic metabolic acidosis.

100. Robin, E.D., Whaley, R.D., Crump, D.H. Acid-base relations between spinal fluid and arterial blood with special reference to control of ventilation. J. Appl. Physiol. 13:385, 1958.

There is considerable lagg in the change in spinal fluid $[HCO_3^-]$ following changes in blood $[HCO_3^-]$.

101. Pierce, N.F., Fedson, D.S., Brigham, K.L., Mitra, R.C., Sach, R.B. and Mondal, A. The ventilatory response to acute base deficit in humans. Time course during development and correction of metabolic acidosis. Ann. Int. Med. 72:633, 1970.

Fast changes in [HCO_3^-] (Down: 13 mM/L/14 hr or Up: 9 mM/L/3 hr) resulted in inappropriate venalitory responses. Thus blood pH was inordinately low as [HCO_3^-] rapidly fell or high as [HCO_3^-]. was elevated.

102. Fisher, V.J. and Christianson, L.C. Cerebrospinal fluid acid-base balance during a changing ventilatory state in man. J. Appl. Phys. 18:217, 1963.

During hyperventilation changes in pCO_2 in cisternal fluid were rapid although to some extent lagging arterial pCO_2. Lumbar CSF pCO_2 changes lagged behind cisternal changes by 15-20 min.

103. Lee, J.E., Chu, F., Posner, J.B. and Plum, F. Buffering capacity of cerebrospinal fluid in acute respiratory acidosis in dogs. Am. J. Physiol. 217:1035, 1969.

In respiratory acidosis, the spinal fluid receives HCO_3^- from some unknown source which allows a near maintenance of CSF pH. This increment of HCO_3^- into the spinal fluid is blocked by hypoxia, but was not blocked by the addition of either Diamox or ouabain to the CSF compartment. See below.

104. Vates, T.S., Bonting, S.L. and Oppelt, W.W. Na-K activated adenosine triphosphatase and formation of cerebrospinal fluid in the cat. Am. J. Physiol. 206:1165, 1946.

A reduction in volume formation of CSF can be effected by the addition of ouabain to the CSF compartment.

105. Maren, T.H. and Broder, L.E. The role of carbonic anhydrase in anion secretion into cerebrospinal fluid. J. Pharm. and Exp. Therap. 172: 197, 1970.

A carbonic anhydrase system, inhibited by IV Diamox, appears to be in part responsible for secretion of HCO_3^- and Cl^- into the CSF.

106. Posner, J.B., Swanson, A.G. and Plum, F. Acid-base balance in cerebrospinal fluid. Arch. Neurol. 12:479, 1965.

107. Posner, J.B. and Plum, F. Spinal-fluid pH and neurologic symptoms in systemic acidosis. New Eng. J. Med. 277:605, 1967.

Severe acidosis can cause delirium and unconsciousness, but only when the spinal fluid pH is far below normal. In many instances of low blood pH, the spinal fluid pH is nearly normal and such patients are without neurologic symptoms. But when acid-base changes are the result of changes in pCO_2 (respiratory) changes in CSF pH tend to deviate from normal by the same degree as blood pH. Range of Normal spinal fluid pH 7.26-7.36.

108. Bulger, R.J. et al. Spinal-fluid acidosis and the diagnosis of pulmonary encephalopathy. New Eng. J. Med. 274:433, 1966.

Two cases where blood pH was nearly normal or high, but pCO_2 (arterial) was high. Spinal fluid [HCO_3^-] although elevated was not sufficiently high to prevent the high CSF pCO_2 from causing a marked fall in CSF pH. An encephalopathy probably resulted from the low CSF pH.

109. Relman, A.S., Shelburne, P.F. and Talman, A. Profound acidosis resulting from excessive ammonium chloride in previously healthy subjects. New Eng. J. of Med. 264:848, 1961.

See Case 3 above.
Report of 2 cases of severe metabolic acidosis.