PRODUCT MONOGRAPH

Pr PHOSLO®
(Calcium Acetate)

Oral Tablets

Phosphate Binder

Manufactured for:
Fresenius Medical Care North America
Waltham, MA 02451 USA

Distributed by:
Fresenius Medical Care Canada, Inc
Richmond Hill, ON, L4B 4W6 Canada
1-888-709-4411

Date of Preparation: February 20, 2007
Control Number: 112003

NAME OF DRUG

PhosLo

Calcium Acetate
667 mg Tablets

THERAPEUTIC CLASSIFICATION

Phosphate Binder

ACTIONS AND CLINICAL PHARMACOLOGY

When taken with meals, PhosLo (calcium acetate) combines with dietary phosphate to form insoluble calcium phosphate, which is excreted in the feces. PhosLo is highly soluble at neutral pH, making the calcium readily available for binding to phosphate in the proximal small intestine. Calcium acetate is a more efficient phosphate binder than other calcium salts. When phosphate binding in the proximal small intestinal lumen occurs, the calcium available for absorption decreases, thus reducing the risk of hypercalcemia in these patients.

The absorption of phosphorus plays a critical role in the development of metabolic bone diseases in patients with chronic renal failure. The retention of phosphate plays a pivotal role in causing secondary hyperparathyroidism associated with osteodystrophy and soft tissue calcification. The majority of patients with advanced renal insufficiency (glomerular filtration rate less than 30 mL/min) exhibit phosphate retention with hyperphosphatemia.

The rate of removal of phosphate by dietary manipulation or by dialysis is insufficient to prevent hyperphosphatemia in most dialysis patients. Dialysis patients absorb 40% to 80% of dietary phosphorus. Therefore, the fraction of dietary phosphate absorbed from the diet needs to be reduced. Phosphate binders in most renal failure patients on maintenance dialysis are effective in accomplishing that.

INDICATIONS AND CLINICAL USE

PhosLo (calcium acetate) is indicated for the control of hyperphosphatemia in end stage renal failure.

CONTRAINDICATIONS

PhosLo (calcium acetate) is contraindicated in patients with hypercalcemia.

WARNINGS

PhosLo (calcium acetate) should not be given concurrently with calcium supplements because patients with end stage renal failure may develop hypercalcemia.

Progressive hypercalcemia due to overdose of calcium salts administered to patients with chronic renal impairment may be sufficiently severe to require emergency measures. Chronic hypercalcemia may lead to vascular calcification and other soft tissue calcifications. The serum calcium concentration should be monitored twice weekly during the early dose adjustment period and regularly thereafter. **The serum calcium times phosphate (CaXP) product should not be allowed to exceed 5.33 $mmol^2/L^2$.** Radiographic evaluation of the suspect anatomical region may be helpful in early detection of soft tissue calcification.

PRECAUTIONS

General:
Excessive dosage of PhosLo (calcium acetate) could induce hypercalcemia; therefore, early in the treatment during dosage adjustment, serum calcium should be determined twice weekly, and monitored regularly thereafter. Should hypercalcemia develop, the dosage should be reduced or the treatment discontinued immediately depending on the severity of hypercalcemia. Calcium salts should not be given to patients on digitalis because hypercalcemia may precipitate cardiac arrhythmias. Therapy with phosphate binders should always be started at low doses and should not be increased without careful monitoring of serum calcium. An estimate of daily dietary calcium intake should be made initially and the intake adjusted as needed. Serum phosphorous should also be determined periodically.

Use in Pregnancy:
The safety and efficacy of PhosLo (calcium acetate) in pregnant women has not been established; therefore, PhosLo (calcium acetate) should be prescribed during pregnancy only if the benefits outweigh potential risks. Animal reproduction studies have not been conducted with PhosLo (calcium acetate), nor is it known whether PhosLo (calcium acetate) can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity.

Use in Children:
The safety and efficacy of PhosLo (calcium acetate) in children have not been established.

Drug Interactions:
PhosLo (calcium acetate) may decrease the bioavailability of tetracyclines. PhosLo (calcium acetate) should not be taken with non-prescription antacids because these drugs contain calcium.

ADVERSE REACTIONS

The most frequent adverse reaction to PhosLo (calcium acetate) was hypercalcemia, which occurred in 15% of the patients in clinical studies. Mild hypercalcemia(Ca > 2.63 mmol/L) may be asymptomatic or manifest itself as constipation, anorexia, nausea and vomiting. More severe hypercalcemia (Ca > 3 mmol/L) is associated with confusion, delirium, stupor and coma. The serum calcium concentration should be monitored, and the dose should be adjusted accordingly. Decreasing dialysate calcium concentration could reduce the incidence and severity of hypercalcemia induced by PhosLo (calcium acetate).

In clinical studies, 7% of patients experienced nausea (including vomiting) and gastrointestinal disturbance during PhosLo (calcium acetate) therapy. Frequently this was a consequence of hypercalcemia.

The long-term effect of PhosLo (calcium acetate) on the progression of vascular or soft tissue calcification has not been determined.

Information to be provided by the physician to the patient:
The patient should be informed about compliance with dosage instructions, adherence to instructions about diet and avoidance of the use of non-prescription antacids. Patients should be informed about the symptoms of hypercalcemia (See ADVERSE REACTIONS Section).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Administration of PhosLo (calcium acetate) in excess of the appropriate daily dosage can cause severe hypercalcemia (See ADVERSE REACTIONS Section). Mild hypercalcemia is easily controlled by reducing the PhosLo (calcium acetate) dose or temporarily discontinuing therapy. Severe hypercalcemia can be treated by acute hemodialysis and discontinuing PhosLo (calcium acetate) therapy.

DOSAGE AND ADMINISTRATION

The recommended initial dose of PhosLo (calcium acetate) for the adult dialysis patient is 2 tablets with each meal. The dosage may be increased gradually to bring the serum phosphate value below 1.94 mmol/L, as long as hypercalcemia does not develop. Most patients require 3 - 4 tablets with each meal. Tablets should be swallowed whole and not chewed.

STORAGE CONDITIONS

PhosLo (calcium acetate) can be stored at controlled room temperature (15° – 30°C).

HOW SUPPLIED

In tablet form for oral administration. Each white round tablet (stamped "BRA200") contains 667 mg of calcium acetate USP equal to 169 mg calcium, and 10 mg of the inert binder, polyethylene glycol 8000 NF. Tablets should be swallowed whole and not chewed.

DIN 02229437 Bottles of 200

PHARMACEUTICAL INFORMATION

Drug Substance:
Calcium Acetate, USP. The calcium acetate used is a white, anhydrous powder; $Ca(CH_3COO)_2$; MW = 158.17 grams. Solubility is 37.4% at 0°C. The pH of a solution of 2 g in 40 mL water is 6.3 – 9.6.

Composition:
Each white round tablet (stamped "BRA200") contains 667 mg of calcium acetate USP equal to 169 mg (8.45 mEq) calcium, 10 mg of the inert binder, polyethylene glycol 8000 NF, and 0.8 mg of the inert tablet lubricant, mineral oil

Stability and Storage Conditions:
The product is stable for at least two years. PhosLo (calcium acetate) should be stored at controlled room temperature (15° – 30°C).

Availability of Dosage Forms:
In tablet form for oral administration. Each white round tablet (stamped "BRA200") contains 667 mg of calcium acetate USP (anhydrous; $Ca(CH_3COO)_2$; MW = 158.17 grams) equal to 169 mg (8.45 mEq) calcium, and 10 mg of the inert binder, polyethylene glycol 8000 NF.

INFORMATION FOR THE PATIENT

The patient should be informed about compliance with dosage instructions, adherence to instructions about diet and avoidance of the use of non-prescription antacids. Patients should be informed about the symptoms of hypercalcemia (See ADVERSE REACTIONS Section).

PHARMACOLOGY

The pharmacologic effect of the oral ingestion of calcium acetate with a meal is the binding to and faecal excretion of dietary phosphate (as calcium phosphate). This leads to a reduction of phosphate absorption and can prevent or correct hyperphosphatemia in patients with end stage renal disease. Phosphate binding *in vivo* can be operationally

defined as the degree to which phosphate absorption is inhibited by a phosphate binder. For a binding agent to be effective *in vivo* it must precipitate phosphate at a gastrointestinal site proximal to the site of phosphate absorption. In humans, phosphate absorption occurs mainly in the small intestine. In the early part of this segment, the highly acidic output from the stomach is neutralized. A major difference between calcium acetate and calcium carbonate is calcium acetate's greater solubility at neutral pH. Therefore, the observed experimental superiority of calcium acetate as a phosphate binder is probably due to the greater solubility, and hence, greater availability for phosphate binding of the calcium ions from calcium acetate in the early small intestine.

Calcium absorption is inversely correlated to phosphate binding. *In vivo*, calcium carbonate is associated with higher levels of calcium absorption than calcium acetate and poorer phosphate binding. Dr. John Fordtran, of Baylor University, evaluated the safety of calcium acetate for the control of phosphate absorption in 6 volunteers with end stage renal failure. The study was conducted as a double blind cross-over design with the objective to measure the absorption of phosphate and calcium after ingestion of a meal with defined phosphate and calcium content.

The subjects were treated with 50 mEq of calcium as one of two calcium compounds (calcium acetate or calcium carbonate) or placebo administered with the meal. In this study, the subjects followed a rigorous protocol in which their gastrointestinal tracts were cleansed by a gastrointestinal lavage. Four hours later a meal of defined calcium and phosphate content was eaten with a phosphate binder. Twelve hours after the meal, the subject's gut was again cleansed by a second lavage. The rectal effluent from this lavage and any stool excreted since the meal were analyzed for phosphate and calcium. On a separate day, the identical procedure was performed with the omission of the test meal in order to provide an estimate of the phosphate and calcium appearing in the rectal effluent that was not attributable to the ingested meal. The phosphate binders were calcium acetate, calcium carbonate, or placebo (in a cross-over design).

The results demonstrated that calcium acetate was a significantly better binder of dietary phosphate than either calcium carbonate or placebo. As a result, a smaller dose of calcium acetate was expected to be clinically sufficient to control serum phosphate levels in patients with end stage renal failure than would be the case with calcium carbonate.

Additional studies have shown that for efficient phosphate binding the calcium acetate must be given with a meal. The authors also demonstrated that the dose may be taken before or after the meal or may be split (one half before and one half after) with equivalent phosphate binding efficacy.

TOXICOLOGY

The proposed use for calcium acetate for phosphate binding in patients with end stage renal disease is based on a dose of 6 to 12 grams of compound per day, composed of 1.5 to 3 grams of calcium and 4.5 to 9 grams of acetate. At 6 grams, this is equivalent to ingesting 5 cups of milk and 5 tablespoons of vinegar (but without the acid (H+) content).

The low oral toxicity of the compound has been well established. For example, in the rat, the LD50 for acute oral administration is 4.28 grams per kilogram. By extrapolation, this is equivalent to about 300 grams for a 70 kg human.

Acute Toxicity:

Rat Oral: The acute oral toxicity of calcium acetate in rats was defined by Smyth, et al., as part of a major range-finding toxicity study. Rats were dosed by lavage in a concentration of 0.1 gram per millilitre. The LD 50, based on the hydrated form of the salt, was 4.28 g/kg with a range of 3.86 to 4.76. This dose would extrapolate to about 300 grams per 70 kilogram human.

Long-term Toxicity:

Rat Oral: The effect of 28 days dietary exposure to calcium acetate (about 1.5 g/kg/day) has been evaluated in a long-term experiment (110 weeks) by Poirier, et. al. in 25 animals. These observations were made in conjunction with a study of the effect of calcium acetate on the carcinogenicity of cadmium chloride. No significant difference was found in the growth curves or body weights between control and calcium acetate-treated animals. Necropsy evaluation of tissues made one and two years after a one-month dietary exposure revealed no significant difference that could be associated with calcium acetate.

The effect of long-term (18 month) continuous oral dietary exposure to calcium acetate in rats has been evaluated (Kasprzak, et al.). These observations were made in the course of a study of the interaction between calcium and lead on renal carcinogenicity. The experimental diet contained 3% calcium acetate monohydrate to provide a dose of 1.5 g/kg/day. The equivalent dose level in humans would be approximately 100 grams.

Of the 30 animals given the control diet, all survived to 58 weeks, and 29 survived until 79 weeks. Of the 30 animals given calcium acetate, 29 survived to 58 weeks and 27 to 79 weeks. The growth rate of animals fed calcium acetate was slightly slower than control animals. This difference became significant at 4 weeks ($p < 0.05$).

At 79 weeks there was a difference of 7% in body weight between groups. Feeding calcium acetate was not associated with any significant affect on the weights of kidneys and livers, or increased incidence of tumors.

CARCINOGENICITY

The following long-term toxicity studies also provide data related to carcinogenicity.

Calcium Acetate-Chronic Toxicity Studies

Species	Route	Dose	Duration	Ref.
Mouse	I.P.	72 mg/kg	3X/wk for 8 wks	76
Rat	Oral	1.5 g/kg/day	28 days	62
Rat	Oral	1.5 g/kg/day	18 months	42

MUTAGENICITY

No mutagenicity studies were performed because calcium acetate is "generally recognized as safe" under CFR Title 21, Chapter 1, Part 582, and because the oral dosage recommended is within the range found in a normal diet.

REPRODUCTION AND TERATOLOGY

No segment I, II, or III reproduction studies were performed because calcium acetate is listed as "generally recognized as safe" under CFR Title 21, Chapter 1, Part 582, and because the oral dosage recommended is within the range found in a normal diet.

DEPENDENCE AND LIABILITY

No dependence and liability studies were performed because calcium acetate is listed as "generally recognized as safe" under CFR Title 21, Chapter 1, Part 582, and because the oral dosage recommended is within the range found in a normal diet.

Manufactured for: **Fresenius Medical Care North America**
Waltham, MA 02451 USA

REFERENCES

1. ALFREY AC, LEGENNDRE GR, and KAEHNY WD. 1976. Dialysis encephalopathy syndrome. N. Eng. J. Med. 294:184-188.

2. APPLETON GVN, DAVIES PW, BRISTOL JB, and WILLIAMSON RNC. 1987. Inhibition of intestinal carcinogenesis by dietary supplementation with calcium. Br. J. Surg. 74:523-525.

3. APPLETON GVN, BRISTOL JB, and WILLIAMSON RNC. 1986. Increased dietary calcium and small bowel resection have opposite effects on colonic cell turnover. Br. J. Surg. 73:1018-1021.

4. ARENA JM and DREW RH (eds). 1986. Poisoning: Toxicology, Symptoms, Treatments. Charles C. Thomas, Illinois. pp. 539-541.

5. BAKIR AA, HRYHORCZUK DO, BERMAN E, and DUNEA G. 1986. Acute fatal hyperaluminemic encephalopathy in undialyzed and recently dialyzed uremic patients. ASAIO Trans. 32:171-176.

6. BELIZAN JM, VILLAR J, PINEDA O, GONZALES AE, SAINZ E, GARRERA G, and SIBRIAN R. 1983. Reduction of blood pressure with calcium supplementation in young adults. J. Am. Assoc. 249:1161-1165.

7. BERKOW R, (Ed) 1982. The Merck Manual. Merck Sharp & Dohme Research Laboratories, NJ. pp. 1515-1529.

8. BIERENBAUM ML, FLEISCHMAN AI, and RAICHELSON RI. 1972. Long term human studies on the lipid effects of oral calcium. Lipids. 3:202-206.

9. BIERENBAUM ML, WOLF E, BISGEIER G, and MAGINNIS WP. 1988. Dietary calcium: A method of lowering blood pressure. Am. J. Hypertens. 1:149S-152S.

10. BO-LINN GW, DAVIS GR, BUDDRUS DJ, MORAWSKI SG, SANTA ANNA C, and FORDTRAN JS. 1984. An evaluation of the importance of gastric acid secretion in the absorption of dietary calcium. J. Clin. Invest. 73:640-647.

11. BRICKER NS, SLATOPOLSKY E, REISS E, and AVIOLI LV. 1969. Calcium, phosphorus, and bone in renal disease and transplantation. Arch. Intern. Med. 123:543-553.

12. BRICKER NS. 1970. On the pathogenesis of the uremic state. N. Eng. J. Med. 286:1093-1099.

13. CARLSON LA, OLSSON AG, ORO L, and ROSSNER S. 1971. Effects of oral calcium upon serum cholesterol and triglycerides in patients with hyperlipidemia. Atherosclerosis 14:391-400.

14. COLE VV, HARNED BK, and HAFKESBRING R. 1941. The toxicity of strontium and calcium. Pharm. Exp. Therap. 71:1-5.

15. COLTON T. 1974. Statistics in Medicine. Little, Brown and Co. Boston, MA.

16. Consensus Conference. 1984. Osteoperosis. JAMA. 252: 799-802.

17. DAVENPORT HW. 1971. Physiology of the Digestive System, 3rd Edition Year Book Medical Publishers, Chicago, IL.

18. DAVIS GR, SANTA ANA CA, MORAWSKI SG, and FORDTRAN JS. 1980. Development of a lavage solution associated with minimal water and electrolyte absorption and secretion. Gastroenterology 78:991-995.

19. DAVIS SS, HARDY JG, and FARA JW 1986. Transit of pharmaceutical dosage forms through the small intestine. Gut 27: 886-892.

20. DRENICK, EJ. 1961. The influence of ingestion of calcium and other soap-forming substances on fecal fat. Gastroenterology 41:242-244.

21. DUPRE J, STILLER CR, and GENT M. 1987. Management of hyperphosphatemia in renal dialysis patients. Lancet 1:633-634.

21a. EMMETT M, SIRMON MD, KIRKPATRICK WG, NOLAN CR, SCHMITT GW, and CLEVELAND MvB. 1991. Calcium acetate control of serum phosphorous in hemodialysis patients. Am. J. Kid. Dis.17:544-550.

22. FISK CH and SUBBAROW Y. 1925. The colorimetric determination of phosphorous. J. Biol. Chem. 66:375-400.

23. FORDTRAN JS and LOCHLEAR TW. 1966. Ionic constituents and osmolality of gastric and small-intestinal fluids after eating. Am. J. Dig. Dis. 11:503-521.

24. FORDTRAN JS and LOCHLEAR TW. 1966. Ionic constituents and osmolality of gastric and small-intestinal fluids after eating. Am. J. Dig. Dis. (New Series) 11:503-519.

25. FOURNIER A, MORINIERE P, LUC SEBERT J, DKHISSI H, ATIK A, LEFLON P, RENAUD H, GUERIS J, GREGOIRE I, IDRISSI A, and GARABEDIAN M. 1986. Calcium carbonate, an aluminum-free agent for control of hyperphosphatemia, hypocalcemia, and hyperparathyroidism in uremia. Kidney Int. 29(suppl 18):S114-S119.

26. FROMET DN, MOLITORIS BA, and ALFREY AA. 1989. Mechanism of enhanced gastrointestinal absorption of aluminum by citrate. Kidney Int. 35:395 (abstract).

27. GARLAND C, BARRETT-CONNER E, ROSSOF AH, SHEKELLE RB, CRIQUI MH, and PAUL O. 1985. Dietary vitamin D and calcium and risk of colorectal cancer: A 19 year prospective study in men. Lancet 1:307-309.

28. GARLAND CF and GARLAND FC. 1980. Do sunlight and vitamin D reduce the likelihood of colon cancer? Int. J. Epidermiol. 9:227-231.

29. GLANTZ SA. 1981. Primer of Biostatistics. McGraw-Hill, New York, NY.

30. GLEASON MN, GOSSELIN RE, HODGE HC, and SMITH RP. 1969. Clinical Toxicology of Commercial Products, 3rd Edition. Williams and Wilkins Co., Baltimore, MD.

31. GRIESSEN M, SPEICH PV, INFANTE F, BARTHOLDI P, COCHET B, DONATH A, COURVOISIER B, and BONJOUR JPH. 1969. Effect of absorbable and nonabsorbable sugars on intestinal calcium absorption in humans. Gastroenterology 96:769-775.

32. GROBBEE DE and HOFMAN A. 1986. Effect of calcium supplementation on diastolic pressure in young people with mild hypertension. Lancet 2:703-707.

33. GUYTON, AC. 1986. Textbook of Medical Physiology. W.B. Saunders Co.

34. HENNINGS H, MICHAEL D, CHENG C, STEINERT P, HOLBROOK K, and YUSPA S. 1980. Calcium regulation of growth and differentiation of mouse epidermal cells in culture. Cell 19:245-254.

35. HODSMAN AB, SHERRARD DJ, ALFREY AC, OTT S, BRICKMAN S, MILLER NL, MALONEY NA, and COBURN JW. 1982. Bone aluminum and histomorphic features of renal osteodystrophy. J. Clin. Endocrin. Metab. 54:539-546.

36. Home and Garden Bulletin No. 72. 1977. Nutritive Value of Foods. Agricultural Research Service, USDA.

37. Intentionally left blank.

38. IND #30, 080. 1987. "Calcium Acetate". Braintree Laboratories, Inc.

39. INGLIS JK. 1980. Introduction to Laboratory Animal Science and Technology. Pergamon Press, Oxford, UK

40. JAFFE LF. 1982. Eggs are activated by a calcium explosion: Carcinogenesis may involve calcium adaptation and habituation. In: Ions, Cell Proliferation and Cancer. Boynton AL, McKeehan WL, and Whitfield JF (eds). Academic Press, New York, NY.

41. KASPRZAK KS, QUANDER RV, and POIRIER LA. 1985. Effects of calcium and magnesium salts on nickel subsulfide carcinogencity in Fisher rats. Carcinogenesis 6:1161-1166.

42. KASPRZAK KS, HOOVER KL, and POIRIER LA. 1985. Effects of dietary calcium acetate in lead subacetate carcinogenicity in kidneys of male Sprague Dawley rats. Carcinogenesis 6:279-282.

43. KASPRZAK KS and WAALKES MP. 1986. The role of calcium, magnesium, and zinc in carcinogenesis. In: Essential Nutrients in Carcinogenesis. Poirier LA, Newburne PM, and Pariza MW (eds). Plenum Press, New York, NY

44. KASPRZAK KS and POIRIER LA. 1983. Effects of calcium, magnesium and sodium acetates on tissue distribution on nickle (II) in strain A mice. In: Chemical Toxicology and Clinical Chemistry of Metals. Brown SS and Savory J (eds). Academic Press, New York, NY.

45. KASPRZAK KS and POIRIER LA. 1985. Effects of calcium (II) and magnesium (II) on nickel (II) uptake and stimulation of thymidine incorporation into DNA in the lungs of strain A mice. Carcinogenesis 6:1819-1821.

46. KASPRZAK KS, POIRIER LA. 1985. Effects of calcium and magnesium acetates on tissue distribution of carcinogenic doses of cadmium in Wistar rats. Toxicology 34:221-230.

47. LARSON EA, ASH SR, WHITE JL, and HEM SL. 1986. Phosphate binding gels: Balancing adsorption and aluminum toxicity. Kidney Int. 29:1131-1135.

48. LEHNINGER AL. 1975. Biochemistry. Worth Publishers, New York, NY.

49. LEVENSON R, HOUSMAN D, and CANTLEY L. 1980. Amiloride inhibits murine erythroleukemia cell differentiation; Evidence for Ca++ requirement for commitment. Proc. Natl. Acad. Sci. USA. 77:5948-5952.

50. LEWIS RJ. 1979. Registry of Toxic Effects of Chemical Substances. U.S. Dept. of Health, Education and Welfare.

51. LIPKIN M and NEWMARK H. 1985. Effects of added dietary calcium on colonic epithelial-cell proliferation in subjects at high risk for familial colonic cancer. N. Eng. J. Med. 313:1381-1384.

52. MCCARRON DA. 1985. Dietary calcium in the pathogenesis and therapy of human and experimental hypertension. In: Calcium in Biological Systems. Rubin RP, Weiss GB, and Putnet JW, Jr. (eds). Plenum Press, New York, NY. pp. 561-568.

53. Intentionally left blank.

54. MISCHEL MG, MOLITORIS BA, and ALFREY AA. 1989. Calcium citrate markedly augments aluminum absorption in man. Kidney Int. 35:399 (abstract).

55. MILLIKIN GA, and JOHNSON DE. 1984. Analysis of Messy Data. Volume 1: Designed Experiments. Lifetime Learning Publications. Belmont, CA.

56. NELSON RL, TANURE JC, and ANDRIANOPOULOS G. 1987. The effect of dietary milk and calcium on experimental colorectal carcinogenesis. Dis. Colon Rectum. 30:947-949.

57. NEWMARK HL, WARGOVICH MJ, and BRUCE WR. 1984. Colon cancer and dietary fat, phosphate, and calcium: A hypothesis. J. Natl. Cancer Inst. 72:1323-1325.

58. NOBUHARA Y, TAKEUCHI K, and OKABE S. 1986. Vinegar is a dietary irritant to the rat gastric mucosa. Jpn. J. Pharmacol. 41:101-108.

58a. NOLAN CR, CALIFANO JR, and BUTZIN CA. 1990. Influence of calcium acetate or calcium citrate on intestinal aluminum absorption. Kidney Int. 38:937-941.

59. PENCE BC and BUDDINGH F. 1988. Inhibition of dietary fat-promoted colon carcinogenesis in rats by supplemental calcium or vitamin D3. Carcinogenesis 9:187-190.

60. PIERIDES AM, EDWARDS WG, CULLUM UX, MCCALL JT, and ELLIS HA. 1980. Hemodialysis encephalopathy with osteomalacic fractures and muscle weakness. Kidney Int. 18:115-124.

61. POIRIER LA, THEISS JC, ARNOLD JC, ARNOLD LJ, and SKIMKIN MB. 1984. Inhibition by magnesium and calcium acetates of lead subacetate and nickel acetate induced lung tumors in strain A mice. Cancer Res. 44:1520-1522.

62. POIRIER LA, KASPRZAK KS, HOVER KL, and WENK KL. 1983. Effects of calcium and magnesium acetates on the carcinogenicity of cadmium chloride in Wistar rats. Cancer Res. 43:4575-4581.

63. RAMIREZ JA, EMMETT M, WHITE MG, FATHI N, SANTA ANA C, MORAWSKI SG, and FORDTRAN JS. 1986. The absorption of dietary phosphate and calcium in hemodialysis patients. Kidney Int. 30:753-759.

64. READ NW, MILES CA, FISCHER D, HALGATE AM, KONIE ND, MITCHELL MA, REEVE AM, ROCHE TB, and WALKER M. 1980. Transit of a meal through the stomach, small intestine, and colon in normal subjects and its role in the pathogenesis of diarrhea. Gastroenterology 79:1276-1282.

65. RUBIN RP, WEISS GB, and PUTNEY JW. 1985. Calcium in Biological Systems. Plenum Press, New York, NY.

66. RUBINI ME, COBURN JW, MASSRY SG, and SHINABERGER JH. Renal osteodystrophy: Some therapeutic considerations to long-term dialysis and transplantation. Arch. Intern. Med. 124:663-669.

67. SCHILLER LR, SANTA ANA CA, SHEIKH M, EMMETT M, and FORDTRAN JS. 1989. Effect of the time of administration of calcium acetate on phosphorous binding. N. Eng. J. Med. 320:1110-1113.

68. SHEIKH MS, SANTA ANA CA, NICAR MJ, SCHILLER LR, and FORDTRAN JS. 1987. Gastrointestinal absorption of calcium from milk and calcium salts. N. Eng. J. Med. 317:532-536.

69. SHEIKH MS, MAGUIRE JA, EMMETT M, SANTA ANA CA, NICAR MJ, SCHILLER LR, and FORDTRAN JS. 1989. Reduction of dietary phosphate absorption by phosphorous binders: A theoretical, in vitro and in vivo study. J. Clin. Invest. 83:66-73.

70. SCHILLER LR, SANTA ANA CA, SHEIKH MS, EMMETT M, and FORDTRAN JS. 1989. Effect of the time of administration of calcium acetate of phosphorous binding. N. Eng. J. Med. 320:1110-1113.

71. SLATOPOLSKY E, WEERTS C, LOPER-HILKER S, NORWOOD K, ZINK M, WINDUS D and DELMEZ J. 1986. Calcium carbonate as a phosphate binder in patients with chronic renal failure undergoing dialysis. N. Eng. J. Med. 315:156-161.

72. SLATOPOLSKY E, CAGLAR S, GRADOWSKA L, CANTERBURY JM, REISS E, and BRICKER NS. 1972. On the prevention of secondary hyperparathryroidism in experimental chronic renal disease using "proportional reduction" of dietary phosphorous intake. Kidney Int. 2:147-151.

73. SMYTH HF, CARPENTER CP, WEIL CS, POZZANI UC, and STRIEGEL JA. 1962. Range-finding toxicity data: List VI. Am. Indust. Hyg. Assoc. J. 23:95-107.

74. SMYTH HF, CARPENTER CP, WEIL CS, POZZANI UC, STRIEGEL JA, and NYCUM JS. 1969. Range-finding toxicity data: List VII. Am. Indust. Hyg. Assoc. J. 30:470-476.

75. SNEDECOR GW and COCHRAN WG. 1980. Statistical Methods. Iowa State University Press, Ames, IA.

76. STONER GD, SHIMKIN MB, TROXEL MC, THOMPSON TL, and TERRY LS. 1976. Test for carcinogenicity of metallic compounds by the pulmonary tumor response in strain A mice. Cancer Res. 36:1744-1747.

77. THOMAS ABR and DIETSCHY JM. 1981. Intestinal lipid absorption: Major extracellular and intracellular events. In: Physiology of the Gastrointestinal Tract, Vol. 2. Johnson LR (ed). Raven Press, New York, NY.

78. TRUMP BF and BEREZESKY IK. 1987. Ion regulation, cell injury and carcinogenesis. Carcinogenesis 8:1027-1031.

79. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, HEALTH CARE FINANCING ADMINISTRATION. 1986. End Stage Renal Disease Program Highlights.

80. WARGOVICH MJ, ENG VW, NEWMARK HL, and BRUCE WR. 1983. Calcium ameliorates the toxic effect of deoxycholic acid in colonic epithelium. Carcinogenesis 4:1205-1207.

81. WARGOVICH MJ, ENG VWS, and NEWMARK HL. 1985. Calcium inhibits the damaging and compensatory proliferative effects of fatty acids on mouse colon epithelium. Cancer Letters 23:253-258.

82. WASSERMAN RH. 1981. Intestinal absorption of calcium and phosphorous. Fed. Proc. 40:68-72.

83. WELCH H, PRICE CW, NIELSEN JK and HUNTER AC. 1944. The acute toxicity of commercial penicillin. J. Lab. Clin. Med. 29:809-814.

84. WHITEFILED JF. 1982. The roles of calcium and magnesium in cell proliferation: An overview. In: Ions, Cell Proliferation and Cancer. Boynton AL, McKeehan WL, and Whitfield JF (eds). Academic Press, New York, NY.

85. WILKINSON R. 1976. Absorption of calcium, phosphate and magnesium. In: Calcium, Phosphate and Magnesium Metabolism. Nordin BEC (ed). Churchill, Livingstone, NY. pp. 36-112.

86. WINER BJ. 1971. Statistical Principles in Experimental Design, 2nd Edition. McGraw-Hill, New York, NY.

87. WORLD HEALTH ORGANIZATION. 1974. Food additives. Miscellaneous: Calcium acetate, chloride, gluconate and sulfate. In: Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents. Geneva, Switzerland. pp. 416-416.

88. YACOWITZ H, FLEISCHMAN AI, and BIERENBAUM ML. 1965. Effect of oral calcium upon serum lipids in man. Brit. Med. J. 1:1352-1354.