Parkland Memorial Hospital
MEDICAL GRAND ROUNDS
May 6, 1965

# CALCINOSIS

Case #1. The patient, a 9-year-old [redacted] female, was first seen [redacted], 1958, at [redacted] The chief complaint was pain in the right hip for 6 weeks and pain in the left knee for 2 weeks with progressive weakness, low-grade fever, and lassitude. Physical examination showed decreased rotary motion of both hips. X-ray films of hips, knees, shoulders, hands, and chest taken during this period showed no calcification.

Roentgenograms taken in [redacted], 1959, revealed for the first time extensive calcification of the soft tissues around the knees. By September this had increased in the legs and was also present in the hands and arms. A biopsy of the skin and muscle of the left lower leg showed predominantly acanthosis in the subcutaneous tissue. There was lobulated deposition of calcium varying from fine granularity to grossly visible deposits with occasional giant cells surrounding the calcium deposits. The muscle showed focal areas of nonspecific degeneration but no inflammatory reaction.

Administration of edetate was begun in [redacted], 1959. The daily dose was 0.95 gm., and the total dose was 14.25 gm. Range of motion performed before and after therapy was unchanged. Post-therapy roentgenograms showed no loss of tissue calcium. Subjective improvement was noted, and patient appeared to be more active after therapy. Repeat roentgenograms on [redacted], 1960, showed a slight increase in the calcium deposits in the hands.

In [redacted], 1960, she had an episode of acute pain and inability to move the left leg, with extreme tenderness just above the popliteal space on the left. Flexion deformities of the knees and recurrent episodes of pain in the area of calcific deposits above the popliteal space bilaterally led to operation on March 13, 1961, with bilateral hamstring release and removal of extensive calcific deposits in the muscles and tendons.

Case #2. The patient, a 14-year-old [redacted] female, developed low-grade fever, headaches, and generalized weakness at age 8. She was seen at [redacted], 1958, and found to have wasting of the muscles of the shoulder girdle and thighs. A skin and muscle biopsy from the left lower leg showed extensive areas of calcification in fibrofatty tissues and heavy inflammatory-cell infiltration around these areas. No changes were noted in the muscle tissue. Radiographic examination revealed calcification of the entire right anterior tibial muscle and tendon, and diffuse calcification in the subcutaneous tissue of the left lower leg and about the hip muscles.

The patient was admitted to [redacted] 1960, for a course of edetate therapy. There were ulcerated areas over the knees, elbows, forearms, and buttocks from which spicules of chalky material extruded. The eyelids showed a heliotrope discoloration, and roughened violaceous skin was present over the elbows, knees, and metacarpophalangeal joints. Edetate was given in a daily dose of 1.4 gm., a total dose of 21.0 gm. This produced no change in the appearance of the roentgenograms or in the size of the visible or palpable lesions. Range of motion showed a slight increase in the upper extremities, without change in the lower extremities. The patient stated that she felt better. Range of motion measured on [redacted] 1961, was essentially unchanged. She is still having intermittent discharge of calcium from the area of the right forearm, right knee, and right elbow and has developed a flexion contracture of the right knee secondary to calcium deposits.

Case #3. The patient is a 16-year-old [redacted] girl who was well until age 11 when she developed malaise, easy fatigability, and low-grade fever with maximum elevations to 101 F. Physical examination on [redacted] 1960, revealed a thin, emaciated child with marked muscle wasting, especially of the upper extremities. There were flexion contractures of elbows and knees and limitation of motion of shoulders and hips. Skin and muscle biopsy of the right upper arm on [redacted] had shown considerable variation in the size of muscle fibers and frequent fatty tissue replacement. There were small irregular focal calcifications and a few scattered mononuclear-cell infiltrates around blood vessels in the dermis. Muscle fibers were thin, atrophic, and showed occasional vacuolization and condensation of the nuclei. The pathological diagnosis was "low-grade, chronic polymyositis."

Edetate was given in daily doses of 1.25 gm., with the total dose 18.75 gm. There was no change in the range of motion or in the contractures. Roentgenograms were unchanged. She was discharged [redacted] 1960. Deposits of calcium in the left forearm extruded through ulcerated areas on 3 further occasions.

# CLASSIFICATION OF CALCIFICATION

Due to tissue injury:

1. Calcification usually associated with localized injury and a known injurious agent (dystrophic, arterial, congenital).

   A. Physical trauma
   B. New growths (benign and malignant)
   C. Parasitic infection
   D. Foreign body
   E. Arterial (deposits in both the media and atheroma's)
   F. Infectious processes
   G. Congenital defects (CRST syndrome, myositis ossificans progressiva)

2. Calcification associated with widespread tissue injury of unknown origin.

   A. Scleroderma
   B. Raynaud's disease
   C. Polymyositis
   D. Other collagen diseases (R.A., S.L.E.)

3. Calcification due to abnormality of calcium and/or phosphorous regulation remote from the site of the deposit. Abnormal levels of serum calcium and/or serum phosphorous (metastatic).

   A. Hyperparathyroidism
   B. Renal insufficiency
   C. Hypervitaminosis D
   D. Destructive bone disease (metastatic carcinoma, osteomyelitis, leukemia, multiple myeloma, Paget's disease)
   E. Pseudohyperparathyroidism
(?) F. Tumoral calcinosis

## FUNCTIONS IN SOFT TISSUE CALCIFICATION

| Disease | Serum Ca | Serum P | Alkaline Phosphatase | Urine Ca | Renal Function |
|---|---|---|---|---|---|
| Collagen Diseases | N | N | N | N | N |
| Hyperparathyroidism | ↑ | ↓ | N or ↑ | ↑ | N or ↓ |
| Vitamin D Intoxication | ↑ | ↑ or N or ↓ | N or ↑ | ↑ | N or ↓ |
| Metastatic Bone Disease | ↑ | ↑ or N or ↓ | ↑ | ↑ | N |
| Multiple Myeloma | ↑ or N | ↑ or N | ↑ | ↑ or N | N or ↓ |
| Renal Failure | N or ↓ | ↑ | ↑ | N or ↓ | ↓ |
| Pseudohyperparathyroidism | ↓ | ↑ | N or ↓ | ↓ | N |
| CRST syndrome | N | N | N | N | N |
| Tumoral calcinosis | N | N or ↑ | N | N | N |

## CALCIUM REMOVAL BY EDTA

| Subject | Total Dose (Gm) | Theoretical* Maximum Ca Chelated (Gm) | Predicted (80%) Excretion of Ca (Gm) | Measured Excretion of Ca (Gm) |
|---|---|---|---|---|
| 1 | 14.3 | 1.5 | 1.2 | |
| 2 | 21.0 | 2.3 | 1.8 | |
| 3 | 18.8 | 2.0 | 1.6 | |
| 4 (D&M) | 12.8 | 1.4 | 1.1 | 1.1 |
| 5 (H&V) | 31.5 | 3.4 | 2.7 | 2.9 |
| 6 (H&V) | 19.6 | 2.1 | 1.7 | 1.7 |

*In vitro 1 gram of EDTA binds approximately 108 mg of Calcium.

# BIBLIOGRAPHY

I. Relationship of calcinosis universalis to dermatomyositis.

Walton, J.N. and Adams, R.D., Polymyositis. E.S. Livingston, Edinburgh, 1958.

Muller, S.A., Winkelman, R.K. and Brunsting, L.A., Calcinosis in dermatomyositis. Observations on course of disease in children and adults. AMA Arch. Derm. 79, 669, 1959.

Sunde, H., Dermatomyositis in children. Acta Paediat. 37, 287, 1949.

Wedgwood, R.J.P., Cook, C.D. and Cohen, J., Dermatomyositis. Report of 26 cases in children with a discussion of endocrinic therapy in 13. Ped. 12, 447, 1953.

Roberts, H.M. and Brunsting, C.A., Dermatomyositis in childhood. A summary of 40 cases. Postgrad. Med. 16, 396, 1954.

Everett, M.A. and Curtis, A.C., Dermatomyositis. A review of 19 cases in adolescents and children. Arch. Int. Med. 100, 70, 1957.

Arendt, E.C., Pattee, C.J. and Mitchell, H.S., Calcinosis universalis. Canad. Med. Assn. J. 73, 269, 1955.

Rudolf, C.C., Calcinosis universalis and dermatomyositis. J. Pediat. 4, 342, 1934.

Wallace, H.J., Calcinosis cutis. ?Old dermatomyositis. Proc. Roy. Soc. Med. 57, 317, 1964.

Leistyna, J.A. and Hassan, A.H.I., Interstitial calcinosis. Report of a case and a review of the literature. Am. J. Dis. Child. 107, 96, 1964.

Scott, R.B. and de Lilly, M.R., Idiopathic calcinosis universalis. Am. J. Dis. Child. 87, 55, 1954.

Sunderman, F.W., Jr. and Sunderman, F.W., Interstitial calcinosis. Am. J. Med. Sci. 234, 287, 1957.

Peters, J.H., Horn, R.H. and Greenman, L., Idiopathic calcinosis universalis cutis without disability. Ann. Int. Med. 32, 138, 1950.

Katzchellenbogen, I. and Sandbouk, M., Generalized calcinosis in childhood. Acta Derm. Vener. 43, 76, 1963.

II. General review of the literature indicating some of the conditions in which calcium deposition is to be found.

Barr, D.P., Pathological calcification. Physiol. Rev. 12, 593, 1932.

Cole, W.R., Calcinosis: General review and discussion of its relationship to Raynaud's disease and scleroderma. Guy Hosp. Rep. 102,56, 1953.

Harrison, R.J. and Feiwel, M., Thibierge-Weissenbach syndrome (scleroderma with calcinosis). Brit. J. Derm. 68, 138, 1956.

Farmer, R.G., Gifford, R.W. and Hines, E.A., Prognostic significance of Raynaud's phenomenon and other clinical characteristics of systemic scleroderma: a study of 271 cases. Circulation 21, 1088, 1960.

Christman, H.E., Calcareous concretions in Raynaud's disease. Am. J. Roent. 30, 177, 1933.

Farmer, R.G., Gifford, R.W., Jr. and Hines, E.A., Jr., Raynaud's disease with sclerodactylia. Circulation 23, 13, 1961.

Gifford, R.W.J. and Hines, E.A., Jr., Raynaud's disease among women and girls. Circulation 16, 1012, 1957.

Lafferty, F.W., Reynolds, E.S. and Pearson, O.H., Tumoral calcinosis. Am. J. Med. 38, 105, 1965.

Kilborn, P., Calcinosis: A review with report of four cases. Postgrad. Med. J. 33, 555, 1957.

Lutwak, L., Myositis ossificans progressiva. Am. J. Med. 37, 269, 1964.

Mortensen, J.D., Emmet, J.L. and Baggenstoss, A.H., Clinical aspects of nephrocalcinosis. Proc. Staff Meet. Mayo Clin. 28, 305, 1953.

Testelli, M.R., Massive calcification of the myocardium: a report of two cases, one associated with nephrocalcinosis. Amer. J. Cardiol. 14, 407, 1964.

Dennis, J.L., Hansen, A.E. and Carpening, T.N., Endocardial fibroelastosis. Pediatrics 12,130, 1953.

Eisenberg, E. and Bartholow, P.V., Jr., Reversible calcinosis cutis. New Eng. J. Med. 268, 1216, 1963.

De Sousa, A. and Chaves, J.P., Calcinosis. J. Bone and Jt. Surg. 35B, 423, 1953.

Forbes, I.J., Diffuse interstitial pulmonary fibrosis and honeycomb lung. Austral. Ann. Med. 7, 205, 1958.

Arans, W.L., Christensen, W.R. and Sosman, M.C., Nephrocalcinosis visible by x-ray associated with chronic glomerulonephritis. Ann. Int. Med. 42, 260, 1955.

Clendenning, W.E. and Auerbach, R., Traumatic calcium deposition in skin. Arch. Derm. 89, 360, 1964.

Lindberg, T., Intervertebral calcinosis in childhood. Ann. Paediat. (Basel) 201, 173, 1963.

Winterbauer, R.H., Multiple telangiectasia, Raynaud's phenomenon, sclerodactyly and subcutaneous calcinosis: a syndrome mimicking hereditary hemorrhagic telangiectasis. Bull. Hopkins Hosp. 114, 361, 1964.

III. Treatment of calcinosis with varying agents none of which are effective.

Leckert, J.T., McHardy, G.G. and McHardy, R.S., Edathamil (EDTA) therapy of interstitial calcinosis. S. Med. J. 53, 728, 1960.

Herd, J.K. and Vaughan, J.H., Calcinosis universalis complicating dermatomyositis--its treatment with $Na_2$EDTA. Report of two cases in children. Arthr. & Rheumat. 7, 259, 1964.

Davis, H. and Moe, P.J., Favorable response of calcinosis universalis to Edathamil disorders. Pediatrics 24, 780, 1959.

Briggs, J.N. and Illingsworth, R.S., Calcinosis universalis treated with adrenocorticotropic hormone and cortisone. Lancet ii, 800, 1952.

Klein, R. and Harris, S.B., Treatment of scleroderma, sclerodactylia and calcinosis by chelation (EDTA). Am. J. Med. 19, 798, 1955.

Fink, C.W. and Baum, J., Treatment of calcinosis universalis with a chelating agent. Am. J. Dis. Child. 105, 390, 1963.

IV. Experimental, clinical and theoretical studies on the formation and deposition of calcium in normal and pathological sites.

Urist, M.R., The bone-body fluid continuum. Perspect. Biol. Med. 6, 75, 1962.

Selye, H., Calciphylaxis. University of Chicago press, Chicago, 1962.

Weidmann, S.M., Calcification of skeletal tissues. Int. Rev. Connect. Tissue Res. 1, 339, 1963.

Howell, D.S., Concepts of calcification. Arthr. & Rheumat., 6, 736, 1963.

Wheeler, C.E., Curtis, A.C., Cawley, E.P., Grekin, R.H. and Zhevtlin, G., Soft tissue calcification,with special reference to its occurrence in the "collagen diseases." Ann. Int. Med. 36:1050, 1952.

Calcification in Biological Systems, ed. R.T. Sognnaes, Am. Assn. for Adv. Science pub. 64, 1960.

Bachra, B.N., Precipitation of calcium carbonates and phosphates. I. Spontaneous precipitation of calcium carbonates and phosphates under physiological conditions. Arch. Biochem. 103, 124, 1963.

Molner, Z., Additional observations on bone crystal dimensions. Clin. Orthop. 17, 38, 1960.

Subel, A.E., Burger, M. and Nobel, S., Mechanisms of nuclei formation in mineralized tissues. Clin. Orthop. 17, 103, 1960.

Robinson, R.A., Observations regarding compartments for tracer calcium in the body. In: Bone Biodynamics, p. 423. Little Brown Co., Boston, 1963.

Baló, J., Connective tissue in atherosclerosis. In: Int. Rev. Connect. Tiss. Research 1, 241, 1963.

Szlye, H., The experimental production of calcified deposits in the rotator cuff. Surg. Clin. N. Amer. 43, 1483, 1963.

Giaconelli, F., Spiro, D. and Wiener, J., A study of metastatic renal calcification at the cellular level. J. Cell Biol. 22, 189, 1964.

MacGregor, J., Blood-bone equilibrium. In: Bone Biodynamics, p. 409. Little Brown Co., Boston, 1964.

Urist, M.R., Moss, M.J., and Adams, J.M., Jr., Calcification of tendon. Arch. Path. 77, 594, 1964.

Urist, M.R., Recent advances in physiology of calcification. J. Bone Joint Surg. 46, 889, 1964.

Loewi, G. and Darlong, J., Calcinosis. Ann. Rheum. Dis. 23, 272, 1964.

Rubin, P.S. and Howard, J.E., Histochemical studies on role of acid mucopolysaccharides in calcifiability and calcification. In: Metabolic Interrelations: Transactions of the Second Conference, New York: Josiah Macy, Jr. Foundation, 2, 155, 1950.

Irving, J.T., Histochemical changes in the early stages of calcification. Clin. Orthop. 17, 92, 1960.

Levine, M.D., Rubin, P.S., Fallis, R.H., Jr. and Howard, J.E., Histochemical studies on calcinosis universalis with respect to possible relationship between normal and pathological calcification. In: Metabolic Interrelations: Transactions of the First Conference, New York: Josiah Macy, Jr. Foundation, 1, 41, 1949.

Johnson, W.C., Graham, J.H. and Helwig, E.B., Histochemistry of the acid mucopolysaccharides in cutaneous calcification. J. Invest. Derm. 42, 215, 1964.

Moss, M.J. and Urist, M.R., Experimental cutaneous calcinosis. Arch. Path. 78, 127, 1964.

Raisz, L.G., Bone resorption in tissue culture. Factors influencing the response to parathyroid hormone. J. Clin. Invest. 44, 103, 1965.

Copp, D. Harold, The hormones of the parathyroid gland and homeostasis. In: Bone Biodynamics, p. 441. Little Brown Co., Boston, 1964.

Taves, D.R. and Neuman, W.F., Factors controlling calcification in vitro: the calcium-phosphate ratio. Proc. Soc. Exp. Biol. Med. 116, 631, 1964.

Hastings, A.B., Calcification. In: Metabolic Interrelations: Transactions of the Third Conference, New York: Josiah Macy, Jr. Foundation, 3, 38, 1951.

Mitchell, H.H., Hamilton, T.S., Steggerda, F.R. and Bean, H.W., The chemical composition of the adult human body and its bearing on the biochemistry of growth. J. Biol. Chem. 158, 625, 1945.