Cardiovascular Mystery Series

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Soft tissues, hard times: a mordant affair 1

Karl T. Weber

A stern wind embraced Denmark’s capital this Saturday morning, January 15, 1972. Copenhagen had already been severely chilled by yesterday’s passing of King Frederik IX, descendant of first King Gorm. Nonetheless, there was widespread confidence in Margrethe, Frederik and Ingrid’s oldest, who today would become Denmark’s first reigning Queen — an event made possible by a plebiscite in 1956 that unanimously amended the Act of Succession. Nicole Jacobsen, resident in internal medicine, considered Margrethe a symbol of national freedom and women’s equality. Buoyed by this historic event, she began morning rounds. Mrs. T., a 52 year old, had been admitted with a two month history of weakness, constipation and headache. Typical rheumatoid erosions of hands and feet had appeared 20 years earlier; tender masses now involved affected joints. Blood pressure normal; aortic ejection murmur; and soft, tender masses of feet and hands. Elevated blood urea nitrogen (BUN) and creatinine (Cr); hypercalcemia, normal phosphorus, slightly elevated alkaline phosphatase, and increased urinary calcium excretion. Extensive periarticular calcifications on X-ray. Nicole ascribed respective symptoms and signs to hypercalcemia and calcification of dystrophic tissues. But why and why aortic sclerosis? Parathyroid function normal; no evidence of malignancy. From Mrs. T’s daughter, Nicole uncovered that over the past 18 months mother had subscribed to an arthritic remedy handed down from Viking folklore. This daily regimen called for several tablespoons of cod liver oil served with large glasses of milk. Nicole made the diagnosis of vitamin D intoxication.

Mr. S., a 67 year old farmer, presented with nausea and vomiting for weeks. Thirty years ago, recurrent bouts of dyspepsia within an hour of meals prompted his physician to prescribe Bertram W. Sippy’s powders. This included calcium carbonate and sodium bicarbonate, given hourly, alternating with milk on the half hour. S. consumed 2 lbs of these powders per week. Dehydrated and orthostatic; white conjunctival masses and grayish, granular corneal deposits; aortic ejection murmur; and a non-tender, mass over right shoulder and wrist. Elevated BUN and Cr; hypercalcemia and mild alkalosis without hypercalcuria or hypophosphatemia; normal alkaline phosphatase. Nicole diagnosed milk-alkali syndrome with hypercalcemia and metastatic calcification of tissues. But why calcium deposition in normal tissues? She reasoned that intravascular volume depletion and reduced renal perfusion had prevented hypercalcuria.

Mr. R., a 32 year old with a long history of renal failure and hypertension on intermittent peritoneal dialysis, presented with severe pain of right thumb and left 4th and 5th fingers. BP 160/110; hard, pulseless radial and ulnar arteries with cyanotic, cool hands; glass-like particles of conjunctiva near palpebral fissure; and soft masses over left shoulder involving axillary folds. A bout of severe pruritus with scratching at this site led to papillary dermatitis from which he could extrude white granules in a creamy colored substance. BUN and Cr markedly increased; normal calcium, increased serum phosphorus and alkaline phosphatase. Calcification of radial, ulnar and digital arteries on X-ray. Why intense vascular calcification?

Answer

Commissioned by son Harald Blue-Tooth around 983, Gorm’s gravesight in Jutland is marked by an 8 ft high memorial, the Jelling Stone. During Gorm’s reign, Vikings kept a basin of cod liver oil by the inner door of their home. Family and visitors were encouraged to swig a ladleful as they entered and departed; declarations of its

1 A brief mystery which sets the stage for the accompanying mini-review, seeking to integrate basic laboratory and clinical sciences and diverse expressions of disease, while highlighting the role of the generalist (that is, the integrator).

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Putative powers have endured for centuries. Patients with rheumatoid arthritis receiving >50,000 units vitamin D daily, together with a high calcium diet, are susceptible to calcium deposition in inflamed tissue. Vitamin D intoxication, destruction of bone, or prolonged excess dietary calcium/alkali intake lead to chronically elevated serum calcium–phosphorus product (>5.8 mmol/l) and metastatic calcification of normal tissues. A local (tissue) factor, which Hans Selye referred to as a chemical mordant that prepares tissues for calcium uptake, is also important. This is particularly evident in chronic renal failure with secondary hyperparathyroidism, where calcium appears in the media of medium sized arteries resembling medial calcific sclerosis of Monckeberg. Elastin fibers of such vessels are particularly susceptible to calcification. Vitamin D and/or parathyroid hormone mediated enhancement of metalloproteinase activity could contribute to elastin fiber degradation, and together with alkaline pH of tissue, predispose to calcium deposition. Contributions of diet to calcific aortic sclerosis remains uncertain.