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Calcinosis universalis as related to scleroderma

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CALCINOSIS UNIVERSALIS AS RELATED TO SCLERODERMA

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Introduction

This paper is a partial review of the literature on the subject of calcinosis universalis as a complication or a companion finding with the collagen disease scleroderma. The finding of these two "entities" since 1911 has been called the Thibierge-Weissenbach syndrome. The literature written in English since that time has been reviewed and only those papers which contributed something more than case reports were included. Like many diseases or syndromes which are not too well understood as to etiology and treatment a great deal has been written, but with nothing concrete in either vein. Many different treatments have been tried, and in some cases good results have been obtained, but many times the series have been so small that they can be of little value statistically. More often than not the same therapy tried by other researchers has failed to produce the same results. As a guide to the reviewing of the literature on the subject I used some of the better reviews such as that of Durham (22), O'Leary and others (53) and the most recent by Talbott (88). No attempt has been made to review the literature not in English. Also included in this paper is a case report of a patient with the syndrome. The patient was not followed for any length of time because she was not a resident of this

state and thus could not be kept in a state-owned hospital. No specific new type of therapy was tried on the patient because of her residency status but her record should be added to the literature because she fits into a rather set pattern of this syndrome.

* * *

What is calcinosis universalis and how is it related to scleroderma? The theories on etiology and the pathogenic and clinical findings are as follows:

Calcinosis universalis was first reported by Weber 1878 according to Lutz (46). However it was not until 1911 that Thibierge and Weissenbach described calcinosis associated with scleroderma. Calcification is the result of many different causes as shown by the excellent paper by Curtis (17) on soft tissue calcification which includes:

Etiology of soft tissue calcification

A. Calcification due to tissue injury

1. Calcification associated usually with localized injury and a known injurious agent--the so-called dystrophic calcification.

   a. Mechanical and physical trauma

   b. New growths, benign and malignant

   c. Parasites

   d. Foreign bodies

A. 1. e. Circulatory disorders, venous and arterial

f. Infectious processes

g. Congenital defects

2. Calcification associated with widespread tissue injury and unknown injury

a. Scleroderma and/or Raynaud's syndrome

b. Dermatomyositis

c. Lupus erythematosis

d. Rheumatoid arthritis

e. Acrodermatitis chronica atrophicans

f. Mixed collagen diseases

B. Calcification due to abnormality of calcium and/or phosphorus regulation remote from the site of the deposits. Abnormal levels of serum calcium and/or serum phosphorus belong in this group.

1. Hyperparathyroidism

2. Renal insufficiency

3. Vitamin D intoxication

4. Destructive bone disease

a. Metastatic carcinoma

b. Osteomyelitis

c. Leukemia

d. Multiple myeloma

e. Paget's disease of bone

5. Pseudohyperparathyroidism

According to Curtis the Thibierge-Weissenbach syndrome is calcification of widespread injured tissue. He does not consider the possibility of alterations in calcium phosphorus balance in this disease. Olson's (54) 1917 classification of causes of calcification was not as complete as that of Curtis but it included:

1. Unknown
2. Affection of the sebaceous glands
3. Chronic inflammatory condition e.g. tuberculosis
4. Calcareous granuloma
5. Cysticercus disease
6. Calcification of subcutaneous veins and/or arteries
7. Calcareous metastases in the skin
8. Fatty tissue calcification
9. True osteoma in subcutaneous or scars
10. Gout

O'Leary reported an etiology of scleroderma was caused by a Raynaud-like etiology such as vascular necrosis. He did not think the possibility of a thyroid dysfunction should be considered because in his series of 103 cases he had both hyper- and hypofunctioning thyroids. In most of these cases the full-blown disease of scleroderma was preceded by a Raynaud-like phenomenon. As stated above the thyroid had been blamed as

the seat or origin of the disease. Castle (12) wrote that any of the ductless glands could be the origin of the disease including adrenals, thyroid, or pituitary associated with the nervous system. He states that severe nervousness and emotion must be given serious consideration. Castle points out that many cases have hematrophy, indicating nervous origin but whether central ganglion or tropho-neuroses or something affecting cutaneous branches had not been determined at that time.

Howard (33) 1937 quotes a 1913 theory by Hunter that scleroderma is apparently a chronic interstitial inflammation of the skin and it is probably dependent on a chronic local arthritis. The calcinosis is secondary to the fibrotic changes in the skin and thus analogous to the calcium deposits in the sclerosed valves of chronic endocarditis or the cicatrices of an old tuberculous lesion. This is also the view taken by Thibierge and Weissenbach.

Brody (6) believes calcinosis with scleroderma is based on a number of things: 1. Trauma and exposure 2. Angiotrophoneurosis 3. Primary disturbance of connective tissue, local or general 4. Hyperparathyroidism 5. Disturbance of calcium phosphorus metabolism 6. Endocrinopathies other than parathyroids e.g. hyperthyroidism or hypogonadism 7. Physio-chemical changes

local and general. He believes the disease starts with vasospasm. This affects the nutrition of the part and the involved tissue degenerates and collagen tissue proliferates. As collagen tissue increases the blood vessels are obliterated, fat disappears and fibrous tissue replaces it. The skin becomes atrophic and finally the skin appendages disappear. Tissues that are physiologically active have a high CO_2 content and those inactive have a low CO_2 content; calcium is deposited in the presence of low CO_2 content. The calcium that is deposited comes from the blood. The parathyroids increase absorption of bone but the calcium absorption from intake is increased. Thus Brody proposes that parathyroidectomy would decrease serum calcium and there would be less calcium available for deposition. He also states that when scleroderma occurs without calcinosis the process is so slow that local anemia is produced slowly, tissue death is very slow, and we get fibrosis. He believes that scleroderma and Raynaud's are just degrees of disease and it depends on the rapidity of development as to whether calcification occurs.

Bauer and others (3) state they found no chronic inflammation, infarction, hemorrhage, or tissue necrosis to precede pathological calcification in studies of calcinosis universalis. He states finely divided calcium

particles were distributed around the periphery of fat which appeared histologically normal. He suggests that calcium may be combined with fatty acids and retention is due to a local cellular condition. Lutz quotes Litchtwitz who says precipitation of colloids in degenerated tissue may bring about a reduction in soluble crystalloids whereby the more insoluble salts such as calcium are precipitated.

Banks (2) points out vascular changes may be found in a number of listed diseases. He states this is purely chance and that diagnosis should be made on clinical criteria and not on laboratory criteria. Clinically we have one disease and laboratory studies indicate we have another, thus we have these bizarre findings in different diseases.

Medvei (48) agrees with Brody that this syndrome is a combination of factors which cause changes in the connective tissue and an alteration of calcium metabolism.

Wheeler (71) agrees with Brody that decreased CO_2 content causes more alkalinity and calcium precipitation. He also states calcium is precipitated if serum calcium goes up and serum phosphorus goes down or vice versa. Normal calcium is laid down in bone with release of phosphate ions and in tissue injury calcium is precipitated because of phosphate ion release.

Mufson (52) states he too thinks that Raynaud's disease and scleroderma are of the same origin and differ only in intensity. He says the primary physiological disturbance is in the tonus of the precapillary vessels. With closure the blood is shunted by arteriovenous anastomosis. Under a skin microscope the capillaries have a beaded appearance, blood flow is slow, and the vein walls are indistinct, fuzzy and dilated. Elastic tissue disappears and collagen fibers increase. The temperature is lowered. These changes he states are body-wide but best manifested in the skin. The author thought all cases show a commensalistic type of personality which makes them susceptible to threats of death and the loss of a loved object such as father, husband, etc. All had a threat to their security. He states these people are in a non-psychotic group. He states that when a patient is able to cope with this loss and channel his anxiety he can have a remission. The author demonstrated this by injecting histamine intra-arterially into the femoral artery. As the leg got warm the patient was asked to relate about a father who had recently died to visitors in the room. The foot immediately began to blanch. The audience left and the leg again became red. He believes scleroderma begins with emotional trauma. Faiture to resolve these prob-

lems is followed by the sequelae of Raynaud's disease and/or scleroderma.

In contrast to this Donhauser (19) in reporting generalized calcinosis associated with a case of primary lymphosarcoma says calcification is due to two things: first, impairment of tissue vitality by injury or preexisting pathologic condition and second, infection by some hematogenous organism or toxins.

Another interesting paper by Su (67) reported three cases of scleroderma after the patients had been chewing betel nuts. He states many papers have reported secondary oral changes in scleroderma. He states the etiology is due to mechanical irritation, neurotropic vascular disorders and hormonal changes. So, in his cases the etiological agent was the betel nut which has 14-18% tannic acid and the crude calcium powder paste around the nut. Continued use of the nut which contains arecoline which affects the vascular nerves fills all the criteria as an etiologic agent for scleroderma.

Gilston (28) suggests the etiology may be stress. He states there is a high incidence at middle life, the time when there may be metabolic dysfunction and emotional factors. Allergy and infection may also play a large part.

Estes (25) states the criteria for Ray-

naud's disease are Raynaud's phenomenon (episodic color changes of the extremities), the trophic lesions must be bilaterally symmetrical, absence of gangrene except of the finger tip type, absence of underlying primary causative disease, and duration of symptoms more than two years. They state the sclerodactylia found must be differentiated from generalized scleroderma. However other authors state the former is just an early form of the latter, or that the disease has not progressed to the generalized form as yet.

In his book Talbott states the etiology of the disease scleroderma is a hypersensitivity. He reports that a number of diseases such as typhoid, bronchopneumonia, lobar pneumonia, tuberculosis, bacteremia, scarlet fever, measles, malaria, tonsillitis and syphilis have preceded the disease. He states emotional factors are important since many cases are associated with Raynaud's syndrome. He also agrees with Mufson that vascular changes do occur and the only endocrines that can be implicated are the parathyroids. He adds that serum calcium and phosphorus are usually normal. He agrees with Brooks as to the way calcification occurs.

Clinical Findings in the Thibierge-Weissenbach syndrome

At the onset of the disease (Talbott) the first stage is a non-pitting edema. Lutz also states at this time there is diffuse pain and there is an onset of gradual weakness. Initially there is an intolerance to cold and paresthesias occur. The disease is most common in menopausal women--the incidence according to O'Leary three to one, female to male. With a careful history the patient will usually reveal a history of Raynaud-like syndrome which occurred from two to ten years prior to the hardening changes of the skin. The second stage according to Talbott is that of fibrosis when skin folds are obliterated and fingers are immobilized in flexion. The last stage is that of atrophy of the skin and hardening with calcinosis. Talbott states any differentiation between localized and diffuse calcinosis is an artificial one. In the last stage the patient acquires a mask-like face and is completely expressionless. The X-ray findings are diagnostic with the revelation of the multiple calcium plaques throughout the body, especially in the extremities. The patients usually have gastrointestinal complaints and difficulty swallowing. An upper GI series usually reveals the fixed esophagus which expands very little if at all. Many times the presenting complaint is draining sinuses at pressure

points from which calcium placques or calcific material has been draining. Late in the disease the patient has the markedly deformed fingers and toes similar to the arthritic.

Laboratory studies in these patients do not show any variations out of the normal limits of the serum calcium and phosphorus. The serum globulins are usually increased and greater than the albumins. The sedimentation rate is increased. Excluding these few findings none of the other tests are abnormal excepting an occasional variant as would be found with any disease.

Pathological findings

The calcium deposits occur usually in the extremities or over pressure areas such as the gluteal areas. The studies of Durham (22) reveal that there is hypertrophy of the collagenous intercellular tissues. This hypertrophy causes pressure on the vessels and epidermic structures. The papillae swell first and then shrink. He states the calcium deposits are made up of calcium phosphate and carbonate. In the cases Durham studied the ages ranged from four to sixty-four. He noted there was a definite deficiency of capillary loops in the finger tips as also found in Raynaud's disease. Wilens (72) reported two years earlier that calcification occurred in fatty tissue in the cases of calcinosis associated

with scleroderma but that the fatty tissue was not degenerating in type. In Wilens' one case study the patient did not have a Raynaud-like phenomenon. He stated he did not know if the hyaline degeneration was due to decreased blood and food to the tissue, or if hyaline degeneration caused a decrease in blood. Brooks (7) quotes Verse that calcareous granules are within the living fibrous mass. This too is conflicting with the theory that degeneration antedates the calcification process in this disease. Ramsdell (57) states the disease is related to the thyroid and parathyroid dysfunction. However, he states the dysfunction has not been clearly demonstrated. He does state that with hypothyroidism there is a retention of calcium in the soft tissues and with hyperthyroidism there is an increased calcium excretion. Atkinson (1) states there is an abnormal phosphate metabolism but does not elaborate as to why he came to this conclusion. Moran (51) reported biopsy of two patients with calcinosis, neither of which had had a Raynaud's disease or scleroderma. Tissue necrosis was present in one patient but not in the other. This one patient again corroborates the idea that calcification does occur in normal tissue and not in degenerating tissue. Wheeler states that idiopathic calcinosis universalis should be dropped in contrast to

the case report of Lutz who cites it as a distinct entity. In a review of 66 cases Wheeler found calcinosis followed or was a complication of scleroderma in 24 cases and that it followed or complicated dermatomyositis in 24 cases and ten cases were undifferentiated between the two diseases, scleroderma and dermatomyositis. He states dermatomyositis usually occurs in people from age 15 to 40 and they have a very poor prognosis, while scleroderma occurs in older people generally from 31 to 40 on up and the prognosis is usually fairly good. Another very descriptive report of the microscopic pathology by Talbott and others states that the epidermis is very thin and the rete pegs are broad and flat. The dermis is extremely avascular, the elastic fibers are decreased and the deeper collagen fibers are undergoing hyalinization. There is an increase in the amorphous material. Careful examination of the sympathetic nervous system may reveal sclerosis, chronic inflammation, and vascular or segmental degeneration with accumulation of lipochromic granules. He suggested that the degenerative changes in the walls of the blood vessels supplying the nerves were responsible for the disease scleroderma. Talbott mentioned the increase in amorphous material. In an earlier study by Seville (64) with electron microscope there is a great increase in

amorphous material which can be removed by trypsin or ether. This leaves the collagen fibrils which are practically all normal in width. He suggests the amorphous material is ground substance which is changed in scleroderma.

Another interesting finding which has been found to be associated with the Thibierge-Weissenbach syndrome according to Rosen and others (59) is the presence of doubly refractory lipoid bodies in the urinary sediment. These refractile bodies have previously been reported in glomerulonephritis, amyloidosis, luetic nephrosis, thrombosis of the renal veins, intercapillary glomerulosclerosis, periarteritis nodosa and lupus. He states this indicates severe arteriolar sclerotic changes. Leinwand and others (43) report that patients with scleroderma have more caclium in the skin than normal.

Differential Diagnosis

According to Atkinson a differential diagnosis would have to include the following: 1. Calcified epithelioma 2. Sebaceous cyst 3. Multiple minute calcareous nodules as seen in the pre-tibial area of older women 4. Moveable sphericle of Ehlers-Danlos syndrome 5. Calcification of scars 6. Very rare

cases of calcification in old sclerodermatous lesions 7. True bony nevi have been reported. Langmead (40) earlier reported that scleroderma was not a sclerosing disorder of skin but that it affected muscles, bones, joints, blood vessels and skin. His theory of calcification is first, formation of fibrosis, then hyaline or colloid degeneration, then calcification. He states an obliterative endarteritis can explain the Raynaud's syndrome. He reviewed the two diseases dermatomyositis and myositis fibrosa and believes these two with scleroderma have a single moribund process. Talbott states that in a differential early in the disease one must consider all of the collagen diseases. He also states one must include myasthenia gravis, Addison's disease, malignant hypertension, primary and secondary hyperparathyroidism, acute and chronic glomerulonephritis, carcinoma of the esophagus, hypervitaminosis D, idiopathic ulcerative colitis, regional ileitis, and myositis ossificans.

Incidence

Scleroderma is not a rare disease but it is uncommon. Durham (22) reviews the history of 645 cases reported in the literature from 1894-1926. Of these cases only 23 showed an associated calcinosis. In a

clinical study of 103 cases of scleroderma O'Leary had only two cases of associated calcinosis. Ingram (34) reported 150 cases of calcinosis circumscripta associated with scleroderma. Beigelman (4) in reviewing 15 cases of scleroderma had 4 cases which had an associated calcinosis.

A reference by Ingram to the term calcinosis circumscripta has been abandoned by most writers. It was supposedly associated with an older age group and had a much better prognosis than the calcinosis universalis which was associated with an age group from four to twenty years. Calcinosis circumscripta was said to occur in an age group forty years and older. It is generally agreed now that this was an artificial classification. Ingram reports that in his patients aged 35 to 50 82% were women. This is a little higher than the incidence ratio of female to male which was 3:1.

Statistics including some case reports and experimental work

In one of the rather unusual reports of a case Langmead (39) reported a case of the Thibierge-Weissenbach syndrome in a 4½ year old Mongol who had a bluish rash associated with his disease. This is the first time this was reported. An autopsy report on a 67 year old white female by Durham (21) showed such extensive

calcification of the arteries that they cracked on bending. Her serum calcium had been 7.4 mgm.% and she had had the disease for 37 years. Langmead (41) in 1930 reported a case of an 18 year old white female who had a loss of muscle power in arms and legs and later developed scleroderma with associated dermatomyositis. He states this is quite rare, but since that time there have been a number of cases of the two diseases asso-iated and a differentiation between the two had been impossible. Kessler's (37) case of a 61 year old white female had "rheumatism" at age 11 and onset of scleroderma at age 54. Calcification began at age 56. This seems a long lapse of time to blame "rheumatism" (rheumatic fever) as the etiologic agent. Epstein and others (24) report on a 56 year old white female from which they biopsied a mass composed of calcium carbonate and calcium phosphate. They reported serum calcium and phos-phorus were normal. Howard (32) reports a 34 year old female presented with a Raynaud's phenomenon. Her fin-ger tips would break down and drain a calcium exudate. She also demonstrated a 12% eosinophilia. She later developed a full blown T-W syndrome. Another interesting case reported by Gould (29) was a 31 year old colored female who had consumed one gallon of vinegar and one and one-half pounds of magnesium sulfate to lose

weight. She dropped from 221 pounds to 135 pounds in one year so in this case the calcinosis was thought due to the formation of fatty soaps first and then calcification. In a case reported by Comroe (14) an autopsy report of a 62 year old male with universal calcification revealed only benign prostatic hypertrophy, pyelonephritis and normal parathyroids and bone. No underlying disease to account for the calcinosis could be found. Milne (49) reported a 29 year old female developed T-W syndrome after a septic sore throat. The history of her disease was only three years old. Ellman (23) reported a case similar to that of Kessler's, a 28 year old female who had rheumatic fever age 11 and calcific nodules began to appear at age 14. Also at age 14 she was bothered by Raynaud's phenomenon. Moore (50) reported on a 46 year old female who had onset of Raynaud's phenomenon at age 36. This became worse and she developed characteristic scleroderma. She had a fall and developed a mass in her shoulder which on aspiration produced calcareous material. She did not develop any calcification in her hands and wrists as most others do. Peters (55) reports on a 57 year old female who developed swelling of interphalangeal joints and muscle and joint pain for seven years. She then developed subcutaneous calcification (generalized). No skin biopsy

was done but this author calls this idiopathic calcinosis. Rae (56) reports on a 48 year old white female who had Raynaud's syndrome for fifteen years since birth of her first child. Three years prior to the author's paper the patient began to notice calcific deposits. Could stress have been an etiologic factor here? Halper (30) reports on a 70 year old female who had Raynaud's syndrome since age 33. He states the etiology of the disease is in the vasomotor center of the diencephalon. Treble (69) reported a case like that of Langmead. In 1930 diagnosis of T-W syndrome was made on a 39 year old female who at age 28 was diagnosed as dermatomyositis. This case, as most of the others did, revealed normal calcium and phosphorus levels. Douglas (20) gives a case report on a 26 year old female who began to develop scleroderma at age 6 with the onset of Raynaud's syndrome. She came to the hospital because an ulcer on her heel would not heal. She had diffuse calcinosis and a biopsy proved the scleroderma. A sympathectomy helped to heal the leg ulcer but did not improve the scleroderma. Cole (13) in reporting one case stated that calcinosis does occur with scleroderma but that it is very rare with, if it exists with, Raynaud's disease. He states if the patient has Raynaud's attacks and calcinosis the disease is scleroderma although it

may take years to develop. He states we still should call the disease idiopathic because we do not know the mechanism by which the calcium is laid down. In a review of 15 cases Beigelman stated that 12 had a Raynaud's phenomenon before scleroderma was diagnosed. He was one of the first authors to call scleroderma collagen disease. McLean (47) reported the case of a 34 year old female who became progressively weak at age four. She developed some fatty cysts which lasted from age twelve to twenty-one. She was put on a rigid low fat diet from age sixteen through twenty-six and now the cysts are calcifying. There was not report of a skin biopsy but this case could be dermatomyositis preceding scleroderma. It is possible in this case scleroderma never developed because calcification does occur with dermatomyositis alone. Scott (63) reported a case of idiopathic calcinosis universalis in an 11 year old female who developed calcific nodules on both knees after a fall. She did not have calcification anyplace else. I wonder if a case like this is properly named. Calvert (10) reported on a woman aged 53 who had had Raynaud's phenomenon since age 33. She developed gangrene of one foot and angiograms of the other foot showed obliteration of the left posterior tibial artery. This author calls this acrosclerosis because it was confined

to the extremities, especially the lower. This again seems to be a degree of a generalized disease. The last case report I want to mention other than my own is that of Harrison (31) who did calcium tolerance studies on a 60 year old female with T-W syndrome for three years. He found no abnormal retention of calcium and thus no defect in calcium and phosphorus metabolism.

Some of the experimental work done with this disease includes a paper by Bauer and others, in which they studied calcium intake and fecal and urinary output in a case of calcinosis with scleroderma. When their studies were compared with control volunteers it was found the output was greatly decreased in the T-W syndrome. They tried treating their patient with NH_4Cl, producing acidosis and the calcium was greatly increased in the excreta. Stephens (66) and others in an interesting paper on experiments done on young white rats reported the following: The rats were fed several diets, in different groups. One diet was high in calcium, another high in phosphate, some were acid diets and others alkaline diets or combination of these diets. One group was fed alternating acid and alkaline diets. The rats were sacrificed after thirteen days and sections were made of heart, lung, liver, stomach, spleen, pancreas, muscle, and skin. They reported the following

results: First, alternating acid and alkaline diets with high calcium did not produce calcification. Second, an acid diet, high in phosphorus produced calcification. Third, neutral or alkaline diets high in either phosphorus or calcium did not produce calcification. Fourth, an excess of calcium and/or phosphorus and acid was needed for calcification to occur. Fifth, iron deposits were found wherever calcium deposits occurred. One wonders if an acid diet in humans with an excess calcium or milk intake could produce this calcification. Burge's (8) work to explain pathologic calcification was done on the gastrocnemius muscle of frogs. By using ammonium molybdate paper on a cut muscle the phosphate was found to be higher at the cut end. He put on two electrodes, one at the injured end of the muscle and one at the uninjured end, and a demarcation current was demonstrated. The cut end put in $CaCl_2$ solution stopped the demarcation and the demarcation current was restored with the cut end put into disodium phosphate. This same experiment was repeated using a moistened paper in the solutions instead of muscle. It is also known that the contracted part of a muscle is negatively charged and the relaxed part is positive. This suggests the negativity is due to the hydrolysis of creatine phosphate and adenylpyrophosphate. The author

suggests this as the reason for calcification in soft tissue. Cornbleet (15) worked with ten cases of known scleroderma. He did fecal and urinary calcium studies. Then he started administering large doses of Vitamin D, 2-300,000 units daily. This was carried out as long as three months and the patients had some symptomatic relief. Where there were calcium deposits these were decreased in size before any bony changes were noted. The fecal calcium remained stabile but the urine calcium was greatly increased. The authors did not propose this theory for general use. Their hypothesis is that scleroderma is initially due to a toxin which injures the collagen syncitium and that these injured tissues take up calcium. Massive doses of Vitamin D produce a negative balance apparently at the expense of the calcium deposited in the collagen and muscle. Rothman (60) found in his clinic that patients with scleroderma had no retention of calcium on a tolerance test of calcium, He also found the skin content of calcium to be within normal limits. He does not think calcium metabolism plays a part in this disease because a poor diet of calcium in one of his patients produced a rapid deteriorization. In their laboratory they did find there was an increase in gamma globulin indicating an allergic or infectious process. Lansbury and others (42) in reporting

an "anti-stiffness" factor derived from molasses, sugar cane and cream state that this regulates phosphorus metabolism. They state it is a fat soluble vitamin, which may be a steroid. When it is eliminated from the diet of animals such as guinea pigs they develop stiffness and calcinosis. The authors thought this might be of therapeutic value, but in a trial of seven patients one had good results and six others had only minimal improvement over a period of seven months. However, the author states there evidently is a species variation so humans do not get the same benefits that guinea pigs do. Other experimental work has been carried out as to trials of therapy and these will be discussed under the therapy section.

Therapy for the Thibierge-Weissenbach Syndrome

Many different types of therapy have been tried and in the hands of some clinitians good results have been obtained, but in general most therapies have afforded only symptomatic relief. Many of the different types of treatment are aimed at whatever the clinitian thought the causative or etiological agent of the disease. The following are some of the medications, diets, and operative procedures which have been used in the treatment of the T-W syndrome.

Craig (16) treated a five year old patient with

disodium phosphate 1 dram q.i.d. and 3 times weekly. In six weeks the calcium masses had almost entirely disappeared. Skossogorenko (65) treated a patient for seven months with NH_4Cl with an interruption of 7-10 days. His patient was greatly improved, tendons become softer and the calcium deposits became smaller. The urine calcium was greatly increased. Kennedy (35) (36) was the first to use the ketogenic diet in this disease. He used it on a 6 year old patient for one year, who by that time was controlled on a diet free of milk. The diet consisted of 14 gm. CHO, 25 gm. protein, and 155 gm. fat. Brooks, in treating his patients, used a combination of ketogenic diet and producing acidosis by NH_4Cl and a low calcium diet. He got only symptomatic relief. Leriche (44) thinks the treatment of choice is a parathyroidectomy. He quoted the work done on dogs with hyperparathyroidism in which they had high serum calcium levels in the beginning but later in the disease the serum levels were within normal limits. Yet the hyperparathyroidism still existed. This was his rationale for parathyroidectomy and he had 90% improvement in 13 cases. He also did sympathectomies for 13 cases with scleroderma. He had improvement in two-thirds of his cases. Some of the group had both procedures and were completely cured. Ramsdell quotes Gar-

lock as having treated 32 patients with unilateral parathyroidectomies and resection of both inferior thyroid arteries. Ramsdell states that retention of calcium in soft tissues is associated with hypothyroidism and yet on his patient he did a unilateral thyroid and parathyroidectomy and his patient made a rapid recovery. He states that at times the absorption of calcium was so rapid that the lesions broke down and a milky calcium substance drained out. Lutz and Rothstein (61) treated his patients with a ketogenic diet, NH_4Cl, disodium phosphate with no good results from any of these treatments. Byron (9) tried to repeat Ramsdell's work with a hemithyroidectomy and removal of two parathyroids but his patient developed symptoms of hypothyroidism so the author gave thyroid extract. He states he feels he had a failure because he did not wait long enough for his results. Livingston (45) had a patient, a 48 year old woman who was treated with a total thyroidectomy and no parathyroids were found in the tissues. The patient was greatly improved symptomatically but there was no change in calcification. She had less joint pain and her skin was less tense. Rothman found benedryl of value in the edematous stage of scleroderma and the patients got some relief from IM bismuth but he found endocrine and Vitamin D therapy of no value. Freund (27)

treated his patient with alpha tocopheral phosphate 300 mgm. q day and the calcium deposits began to resorb. He states his patient felt better and the skin was much softer. Treble treated a patient with 40 gm. of glycine daily for some weeks with no benefit. Frank (26) treated a 25 year old female with ACTH 25 mgm. q.i.d. with no change after seven days. He then started 300 mgm. cortisone, 200 mgm. the next day and 100 mgm. daily for maintenance. The author states the skin returned to normal with cortisone but the Raynaud's syndrome, while relieved early, soon returned to pre-treatment status. Briggs (5) treated 2 patients with large doses of ACTH. The first, a four year old female, received 2000 mgm. of ACTH in six weeks and she had complete remission. The other patient, a 13 year old who had calcinosis for 10 years, did not respond at all. Beigelman tried ACTH and cortisone on his 15 cases with no relief from symptoms at all. He also tried AT 10, testosterone, peripheral vaso-dilators, stellate ganglion blocks, sympathectomy, heavy metals, thyroid, stilbestrol, and relaxin with no good results with any of them. Douglas believes after treating one patient that there is some symptomatic relief from using ACTH. Solomon (62) treated three patients with cortisone as Briggs did, except that he did not start with ACTH, and found

the skin to be softer and lung volume studies revealed these values to be increased. All of the patients had remissions of their diseases after three to six months but the symptoms were no worse than those at the onset of therapy. Catchpole's (11) studies of the effect of cortisone on peripheral blood flow did not show any increased flow in the extremities. However patients did feel better. Klein (38) tried EDTA (Ethylenediamine tetraacetic acid) on a 45 year old female who had been treated with cortisone, gold, and butazoladine with no effects for 10 years. The patient was started on 1.2 gm. calcium diet for 10 days and then a sodium salt of EDTA called sodium versonite 3 gm. of 20% solution in 500 cc. of 5% dextrose in water was started. The patient's average calcium excretion prior to therapy was 165 mgm. per 24 hdr. During therapy this went up to 293 mgm. per 24 hr. The patient did not get tetany and she also received massage and active exercises. She received three different courses of treatment with this dosage on alternate weeks. There was absorption of the calcium, the skin softened, and hair grew in the skin. X-ray evidence showed almost complete resorption of the calcium deposits. After treating 14 patients, Zion and others (73) came to the conclusion that only those patients who were treated within six months of the onset of the disease were helped by cortisone. However, cortisone has been continued in the other patients in the hope that

cortisone will prevent the progression of the disease. Calvert reported a case deriving no benefit from ACTH or cortisone or a sympathectomy in a patient who had had the syndrome for 20 years. In a recent paper Delaney (18) reported on the effects of Diamox (acetazoleamide) on calcinosis universalis. Diamox is a carbonic anhydrase inhibitor so that sodium is excreted from the kidney. It has also been recently noted that phytic acid 1. increases fecal calcium excretion and decreases urinary calcium excretion, 2. increases fecal magnesium excretion and decreases urinary magnesium excretion and 3. increases phosphate intake and therefore serum phosphate is increased, urinary phosphate excretion is increased. A five year old patient was treated with 250 mgm. diamox q 6 hr. and urinary calcium went up to 514 mgm. per 24 hr. with a control of 370 mgm. per 24 hr. With the addition of phytic acid the urinary calcium decreased but it was still above the control. A marked acidosis resulted as shown by the CO_2 combining power. The patient was also placed on a controlled calcium diet but he developed diarrhea so full evaluation of the therapy was not made. Tuchman (70) has treated some patients with ultrasonics on the theory that scleroderma is a vasospastic disease. He states one patient got relief from 0.6 watt per sq. cm. in cervical

area above C-1 and T-2 and he got relief on flexion and extension of his hands. He also reports a patient who had the disease for ten years was greatly improved after four weeks. Another recent paper by Rodman and others (58) reports treating a patient with prednisone 30 mgm. q day and the patient got symptomatic relief. She was able to wrinkle her skin but biopsy failed to reveal any changes in the skin. Therapy had been carried on for 4½ months at the time of this writing with no bad side effects. Talbott states the best therapy consists of 300,000 units Vitamin D daily and one of the steroids, cortison, hydrocortisone or prednisone. He also recommends sympathectomy if vasodilation is produced early in the disease. However, he states in general most of the therapy is only for symptomatic relief.

Case Report

Patient: M. D. Widowed white woman Age 71 Hosp No. 9686 The patient was admitted 3/6/56 and dismissed 3/14/56 because she was not a resident of this state.

Chief complaint: The patient was admitted because she had subcutaneous calcium deposits in her arms, hips, and legs for 30 years and has had severe back pain for six months.

Present illness: The patient states the pain is across her hips and if she lies on right side the pain moves to

her neck. She had no pain or numbness down her legs. She states her legs are somewhat stiff.

Past History by Systems:

Skin: The patient has had calcified areas in skin (hips and thighs mostly) for 30 years. She states they have never been painful unless they break down and drain. She could not recall any history of Raynaud's phenomenon.

Weight: There is a history of 12 pounds weight loss in the past three months.

EENT: Not contributory.

Gastro-intestinal: There was no history of difficulty in swallowing. The patient has a good appetite.

Cardio-respiratory: No history was given that was contributory to the disease.

Genito-urinary: There is no history of nocturia, burning, frequency, or hematuria. The patient has been menopausal since age 51. Gravida ⫶⫶ Para ⫶⫶

Past illnesses: Measles, mumps, and pertussis as a child. The patient had erysipelas 40 years ago.

Family history: was not contributory.

Physical examination

The patient is a well-nourished, well developed white woman who appeared to be the stated age of 71.

Skin: There are numerous plaques under the surface of the skin mostly on the forearms, buttocks and posterior

thighs. They vary in size from a few mm. to 4 cm. across. They are hard and rough and freely moveable under the skin. Several areas of drainage over the plaques were found on the buttocks.

EENT: No abnormality was noted.

Heart, Lungs and Breast: did not reveal any abnormality.

Abdomen: The patient was rather obese but no fluid wave or area of dullness could be demonstrated.

Pelvic: No calcified areas were found. First degree cystocoele was noted.

Back: There is a decided shelf at the superior margin of the sacrum.

Neurological: No abnormality found.

Extremities: The arms are rather flabby to about mid-forearm area at which point the subcutaneous adipose tissue is cut off giving the distal portion of the extremity a thinner appearance. The skin is tightened over the fingers. The patient has extreme valgus deformity of all the toes.

Impression on admission: 1. Spondylolisthesis

2. Collagen disease with calcinosis

Laboratory findings:

Skin tests for tuberculosis, histoplasmosis, and coccidiomycosis were negative. Mazzini and Eagle were

negative.

E.S.R. 54 mm/hr. Hbg 10.5 gm. R.B.C. 3.24 million with hypochromic and anisocytosis. WBC 5300 28 segs 10 staff 1 eosinophil 50 lymphocytes 11 monocytes

Urinalysis: straw colored, sp. gr. 1.021 pH 5

PCV 34 TSP 7.8 Albumin 3.1 Globulin 4.7 Serum calcium 9.5 mgm.% Serum inorganic phosphate 3.84 mgm.% prothrombin time 15 seconds Serum alkaline phosphates 1.68 Serum bilirubin 12 mgm.% total 64 mgm.% Thymal turbidity 4.4 units Cephalin flocculation 2+ in 24 hr. 3+ in 48 hdr. NPN 39 mgm% LE preparation was negative. Serum uric acid 5.0 mgm%

X-rays Reported

Chest: osteoporosis of spine with cardiomegaly with arteriosclerotic heart disease and bilateral basilar congestion.

Survey films: Biconcave deformities of T12 and almost complete obliteration of the vertebral bodies. Wedging of L1 and L4. Impression 2nd degree spondylolisthesis of L5 and S.

K. U. B. film shows many subcutaneous calcifications, none in the kidneys. Impression: consistent with scleroderma.

Skull: Numerous condensations spread throughout the vault.

Esophagus: Slight rigidity and areas of gaping and loss of normal peristolic activity and mucosal pattern. Barium appeared to remain along the wall of the esophagus.

Legs: Numerous calcifications consistent with scleroderma.

Hands: Osteoporosis with soft tissue calcification.

Dermatology Consultation Reported

Suggest possibility of scleroderma

Biopsy of subcutaneous nodules on posterior surface of left thigh 3/10/56

Report: Marked blunting of rete pegs. Collagen bundles prominent and some degeneration. Minimal number of skin appeandages. No evidence of pigmentation of the basilar area of epidermis. Findings are consistent with scleroderma but not diagnostic.

Electrophoretic pattern: Marked increase in gamma globulin.

Hospital course: The patient did not improve or get worse. She was dismissed for reasons stated above on the following drugs:

Premarin 0.625 mgm. daily
Methyl testosterone 5 mgm. daily } for osteoporosis

Ascorbic acid 300 mgm. t.i.d.

Dismissal diagnosis was scleroderma with universal cal-

cification.

(Comment) This patient did not have a history of a Raynaud-like phenomenon and she could not recall the onset of her scleroderma or the calcification. The physical examination is almost a stereotype of the many cases reported in the literature. As in the other cases the laboratory studies do not reveal any unusual values not reported in similar case reports. This patient did show some liver dysfunction.

Discussion

It has often been said that when little is known about a subject a great deal is usually written about it. In the etiology of scleroderma we could say that no one thing is a causative agent, but it takes a combination of an allergic disorder associated with sympathetic vasospasm of the arterioles of the skin. Since it occurs predominantly in women of a middle age group, usually forty years old and over, an endocrine factor may be of the utmost importance. There is always a proliferation of the collagen fibers in case of scleroderma and some studies report that there is an increase in the tissue calcium in the patient with scleroderma. Most of the patients report a Raynaud's phenomenon or syndrome at the onset of the disease so we cannot exclude the emotional make up of the patient who is af-

fected by scleroderma. Calcification seems to occur in tissue that is not degenerating but in which the normal physiology has been distorted. One author stated it was due to the low CO_2 content which may change the pH and thus allow the laying down of calcium. The parathyroids have been blamed but not many patients got relief of symptoms from parathyroidectomies. More than one author believes that calcinosis is not a distinct entity, but is merely a stage of the disease of scleroderma. These same authors think that Raynaud's syndrome is just the first atage of the condition which will be scleroderma. Whether or not calcification occurs depends on the rapidity at which the disease develops and how rapidly the blood supply to the periphery is reduced.

The disease is not a common one with probably no more than 1000-1500 cases reported. In the case reports reviewed we have various etiological agents, from the chewing of betel nuts to consumption of vinegar and magnesium sulfate to lose weight. Many of the cases do report the onset of the disease following an infectious process such as septic sore throat or rheumatic fever.

Some of the experimental work revealed some interesting results such as in the experiment with the frog muscle. We still are not sure if this is what happens

in human beings when calcification occurs.

In the reviews on therapy a method which was successful for one group could not be repeated by others. The ketogenic diet of Kennedy sounds good and he had good results, but few others had success with the same treatment. The reports of thyroidectomies and parathyroidectomies had good results but again they have not been repeated with good success. Some authors had excellent results with ACTH and others got only symptomatic improvement. An interesting report by Klein on the use of EDTA should be followed up with the hope that it might be of some use as a standard therapy.

The case reported in this paper does not add any new therapy or unusual means of onset but is reported because it should be added to those of the literature.

Summary

This paper is a review of all the papers in English since the description of the Thibierge-Weissenbach syndrome. The theories on the etiology of the disease scleroderma and the mechanism of how calcium is laid down in soft tissues are discussed. Various papers were cited in which the suggestion is offered that calcium is laid down in normal tissue and not in that which has undergone degeneration and possible necrosis. The

various pathological findings were reviewed as well as the incidence of the disease. The skin usually shows flattening of the rete pegs with marked increase in collagen fibers with almost complete loss of elastic fibers in the dermis and marked decrease in vascularity. The various case reports that were reviewed showed the marked variety of diseases which had primarily affected the patients before the onset of scleroderma. A review was given of the various types of treatments tried. They are too numerous to repeat in the summary. It is the general consensus of opinion now that symptomatic relief can be afforded by the steroids. One case report was reviewed of a 71 year old white woman. No specific therapy was tried on her for her underlying disease.

Conclusions

From the review of the literature stated above it can be concluded that:

1. Raynaud's syndrome almost always precedes the onset of scleroderma.

2. Universal calcification is the final stage in the disease of scleroderma.

3. The etiology of scleroderma is still unknown. A number of systems such as vasomotor, sympathetic, endocrine including adrenals and thyroids and parathyroids, and the psyche because of the emotional factors

involved are suggested as causing the basic disease of scleroderma. It seems to be a disease of stress.

4. Calcification does occur in normal tissues which have not undergone degeneration.

5. Treatment of choice would be ACTH, cortisone and Vitamin D in large doses for symptomatic relief. Drugs like EDTA should be further investigated.

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