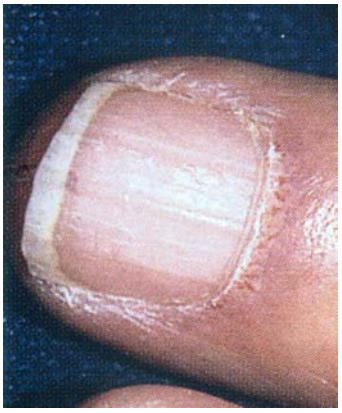
Case-based Learning Exercise

Raynaud's Phenomenon

submitted by RAF Clark

Case #1 (with answers) ***July 20, 2001***



36-year-old white female is referred to Dermatology for evaluation of a 5 year history of Raynaud's phenomenon (painful pallor of the fingers with cold exposure followed by cyanosis, hands appear mottled or red on rewarming). The problem had been fairly stable but she discovered on a medical Web site that Raynaud's phenomenon can be associated with scleroderma, a life threatening disorder. Upon careful questioning the patient admits to having mild difficulty swallowing. This is often manifest as a discomfort in the mid-chest and occurs most commonly after ingestion of a heavy food such as steak. She denies shortness of breath, diarrhea, or hypertension. Her weight has been stable for the past 5 years and she has not experienced undue fatigue. She takes no medication other than an occasional aspirin but does wear gloves often, even at night during the summer months. The patient appears well but is somewhat agitated. Mouth opens fully for inspection and a gag reflex can be easily elicited. Cutaneous exam reveals pallor of the fingers and toes with cyanosis of the nail beds. Nail folds have a moderate loss of capillaries with compensatory enlargement of capillary loops. The skin over the digits is supple. No matte telangiectasia nor hard cutaneous nodules are found on total body skin exam.

A. What is the most likely diagnosis and why?

Surveys have found that 4-15% of the general population has Raynaud's phenomenon (1). In most cases this symptom of vasospasm in the digits (Raynaud's disease) is mild and begins before the age of 25. Primary Raynaud's phenomenon, unlike Raynaud's phenomenon associated with underlying connective tissue disease, is not associated with remarkable changes in nail fold capillary bed (2, 3). The patient presented here has an undifferented connective tissue disease that may be an early stage of CREST syndrome (Calcinosis cutis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodatyly, Telangiectasia) or mixed connective tissue disease (MCTD). Raynaud's phenomenon, associated with diffuse cutaneous systemic sclerosis, usually proceeds to hand edema and then sclerosis within a year or two after onset (1).

1. White B: Systemic sclerosis and related syndromes. In: Primer on the Rheumatic Diseases. Edited by Klipper JH. Atlanta, GA, Arthritis Foundation, 1997, pp. 268.

Great general reference for rheumatologic disorders.

2. Spencer-Green G: Outcomes in primary Raynaud phenomenon: a meta-analysis of the frequency, rates, and predictors of transition to secondary diseases. Arch Intern Med 1998, 158:595-600.

Ten articles identified a total of 639 patients with primary Raynaud phenomenon who were followed up for 2531 patient-years. Eighty-one patients (12.6%) developed a secondary disorder, 80 of which were connective-tissue diseases. Transitions occurred at a mean rate of 3.2 per 100 patient-years of observation. The mean time to develop a secondary disorder was 2.8 years from study entry and 10.4 years from the onset of Raynaud phenomenon. At entry, the best predictor of transition was an abnormal nailfold capillary pattern (positive predictive value, 47%). Antinuclear antibodies in these patients had a positive predictive value of only 30%.

3. Luggen M, Belhorn L, Evans T, Fitzgerald O, Spencer-Green G: The evolution of Raynaud's phenomenon: a longterm prospective study. J Rheumatol 1995, 22:2226-2232.

Patients with suspected secondary RP were evaluated at baseline, 2.7 years, and 8.4 years after entry by history and examination, chest radiograph and barium esophagram, pulmonary function tests, antinuclear and anticentromere antibodies (ACA), cryoglobulins, and nailfold capillary microscopy (NCM). Thirty-two (50%) progressed to a definite CTD. Nailfold capillary abnormalities were the only baseline feature associated with the development of any definite CTD (OR = 8.3).

B. What tests are appropriate to confirm the diagnosis?

Serology for anti-nuclear antibodies, particularly anti-centiomere antibodies and anti-ribonuclearprotein antibodies, is essential in a patient suspected of having CREST syndrome (3) or mixed connective tissue disease (4), respectively. Antibodies for topoisomerase I (Scl-70) (5) or RNA polymerase (6) are specific for diffuse cutaneous systemic sclerosis with lung or renal involvement, respectively. Esophogeal manometry or some other appropriate test for esophageal peristalsis is indicated to confirm esophageal motility dysfunction as the underlying cause of dysphagia (7).

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4. Hoffman RW, Greidinger EL: Mixed connective tissue disease. Curr Opin Rheumatol 2000, 12:386-90.

A defining feature of mixed connective tissue disease (MCTD) is the presence of antibodies against the U1-ribonucleoprotein (RNP) complex, but other autoantibodies in MCTD have recently been described. Research has also further elucidated the immune responses directed against U1- RNP in humans and in murine models of disease. Hypotheses implicating modified self-antigens and/or infectious agents in the pathogenesis of MCTD have been advanced. Longitudinal study of patients with MCTD highlights the impact of pulmonary hypertension on disease outcome.

5. Diot E, Giraudeau B, Diot P, Degenne D, Ritz L, Guilmot JL, Lemarie E: Is anti-topoisomerase I a serum marker of pulmonary involvement in systemic sclerosis? Chest 1999, 116:715-20.
STUDY OBJECTIVE: To determine the value of the level of anti- topoisomerase I (anti-topo I) to evaluate lung involvement defined by abnormal high-resolution computed tomography (HRCT) score and pulmonary function tests (PFTs) in systemic sclerosis (SS). PATIENTS: Forty-eight patients with SS, 20 with lung involvement and 28 with no lung involvement. DESIGN: PFT measurement, HRCT scoring of lung involvement, and anti-topo I assay by enzyme-linked immunosorbent assay. Normal anti- topo I level was defined as < 30. RESULTS: There was a significant association between cutaneous extent and anti-topo I level (6.5% of patients with limited cutaneous scleroderma had abnormal anti-topo I levels vs 70.6% of patients with diffuse cutaneous scleroderma, p = 0.0001). In patients with diffuse cutaneous scleroderma, pulmonary involvement was associated with a higher percentage of abnormal anti- topo I level: 91.7% vs 20% (p = 0.010). In patients with diffuse cutaneous scleroderma, a significant association was found between the class of anti-topoII level and total lung capacity (median, 69 in patients with abnormal anti-topo I level vs 87 in patients with normal anti-topo I level, p = 0.010), between the class of anti-topo I level and HRCT score (median, 12 in patients with abnormal anti-topo I level vs 5 in patients with normal anti-topo I level, p = 0.05). CONCLUSION: Anti-topo I can be considered as a marker of lung involvement in patients with diffuse cutaneous scleroderma.

6. Bunn CC, Denton CP, Shi-Wen X, Knight C, Black CM: Anti-RNA polymerases and other autoantibody specificities in systemic sclerosis. Br J Rheumatol 1998, 37:15-20.

Sera from 735 patients with systemic sclerosis were classified according to antinuclear antibody (ANA) pattern as follows: centromere (25%), homogeneous (26%), fine speckled (21%), fine speckled with nucleolar (14%), coarse speckled (7%), nucleolar only (3%) and cytoplasmic only (3%). Immunoprecipitations using 35S-labelled HeLa cell antigen extract were performed using sera from 374 of these patients to detect the systemic sclerosis-specific antibodies to RNA polymerases I and III. The sera were selected to represent each ANA group, but focused on those giving fine speckled nucleoplasmic staining (with or without nucleolar staining) where all 86 sera positive for these antibodies were concentrated. Immunoprecipitates from a further 93 sera from patients with ANA-positive autoimmune diseases other than systemic sclerosis did not precipitate RNA polymerases. In addition, all sera were tested for antibodies to the extractable nuclear antigens topoisomerase I, nRNP, Ro, La and PM-Scl. Sera positive for antibodies to these antigens gave clear correlations with ANA patterns but, of the examples tested, none contained antibodies precipitating RNA polymerase I or III. Thus, sera containing antibodies to RNA polymerases I and III were exclusive of both anticentromere and anti-topoisomerase I, and formed a major serological subgroup (11.7%). Clinically, 77% were patients with diffuse cutaneous disease reflected by higher skin scores and a significantly higher incidence of renal involvement (33%) than patients with antibodies to topoisomerase I (3%).

7. Ling TC, Johnston BT: Esophageal investigations in connective tissue disease: which tests are most appropriate? J Clin Gastroenterol 2001, 32:33-36.

Forty-seven patients (39 women and 8 men) with suspected CTD were referred for esophageal manometry at the gastrointestinal physiology unit in the Royal Victoria Hospital, Belfast, U.K., over a 10-year period (1987-1997). The mean age was 51.7 years (range = 21-79

years). Chart review was conducted 1 to 10 years after manometry to confirm the final diagnoses: scleroderma was found in 11; CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia), 8; mixed connective tissue disease, 14; Raynaud's alone, 5; and other CTDs, 9. All 47 successfully underwent esophageal manometry. In addition to manometry, 24 underwent gastroscopy; 27, barium meal; and 3, esophageal pH studies. Clinically significant esophageal abnormalities were noted in 8 (33%) on gastroscopy, in 15 (56%) on barium meal, and in 31 (66%) on manometry. Gastroscopy had a significantly lower positivity rate than the others ($p < 0.05$). All three pH tests were abnormal. During manometry, abnormal findings were significantly more common in scleroderma-CREST when compared with other diagnoses (89% vs. 50%; $p < 0.02$). Thirty-three patients reported dysphagia. Abnormal manometry was more likely in these cases (82% vs. 33%; $p < 0.02$). A high percentage of patients with CTD have significant esophageal motility disorders. Investigations were more likely to be positive with scleroderma-CREST than other CTDs, even if dysphagia was present. Barium meal and manometry are more useful than OGD.

C. What therapy is appropriate?

Calcium channel blockers have been a main stay of therapy for Raynaud's phenomenon since 1985. In randomized controlled clinical trials (RCTs), nifedipine and diltiazem, but not verapimil, appear to be effective in this disorder (8-10). Recently, RCTs of other therapeutic strategies have been reviewed. These include prostaglandin analogues (11), serotonin antagonists, (12) and α-adrenergic receptor inhibitors (13). Of these, i.v. administration of iloprost, a prostaglandin analogue, appeared to be the most effective. A recent multicentered, randomized controlled clinical trial demonstrated that sustained-released nifedipine had a highly significant beneficial effect in primary Raynaud's phenomenon using digital blood pressure after cooling the fingers as an outcome measure (14).

8. Rhedda A, McCans J, Willan AR, Ford PM: A double blind placebo controlled crossover randomized trial of diltiazem in Raynaud's phenomenon. J Rheumatol 1985, 12:724-727.

A double blind placebo controlled crossover randomized study of the calcium channel blocking agent diltiazem in the treatment of Raynaud's phenomenon. Results showed a significant reduction in both frequency and duration of attacks of vasospasm in the hands. There was no detectable difference in response between patients with primary and those with secondary Raynaud's phenomenon. Study supports the use of calcium channel blocking agents in the treatment of intermittent digital vasospasm.

9. Kahan A, Weber S, Amor B, Menkes CJ, Hodara M, Degeorges M: Nifedipine and Raynaud's phenomenon associated with connective tissue diseases. Int Angiol 1985, 4:221-3.

Thirty patients were included in this study: Raynaud's phenomenon was associated with progressive systemic sclerosis (PSS) in ten patients, systemic lupus erythematosus (SLE) in five and rheumatoid arthritis (RA) in three; it was idiopathic (I) in twelve patients. Each patient received, in a double-blind manner and random order, on two consecutive weeks, nifedipine (20 mg three times daily) and placebo. Nifedipine proved to be effective: the mean number of digital vasospastic attacks per week decreased from 20.30 to 5.83 (p less than 0.01). The results in the SLE and RA groups were similar and were pooled. The improvement (in percent decrease) was

better in the idiopathic group (90.95) than in the SLE and RA group (78.63, p less than 0.02) and the PSS group (64.02, p less than 0.01).

10. Smith CR, Rodeheffer RJ: Raynaud's phenomenon: pathophysiologic features and treatment with calcium-channel blockers. Am J Cardiol 1985, 55:154B-157B.

Raynaud's phenomenon may be associated with severe pain, functional disability and digital infarction, particularly in patients with underlying vascular disease. The pathophysiologic features of Raynaud's phenomenon are complex although vasospasm contributes to the production of digital ischemia in most cases. Calcium-channel blockers have been shown to produce arteriolar vasodilation and an increase in peripheral blood flow. They have been used to treat patients with Raynaud's phenomenon in several prospective, randomized, double-blind, placebo- controlled trials. Low doses of verapamil were ineffective but both diltiazem and nifedipine produced subjective improvement in 60 to 90% of cases. Objective measures of digital blood flow were not improved. Patients without underlying vascular disease responded more readily to therapy than patients with scleroderma. Adverse effects were uncommon and seldom necessitated discontinuation of therapy. These data suggest that nifedipine and diltiazem provide effective short-term improvement in symptoms for most patients with Raynaud's phenomenon.

11. Pope J, Fenlon D, Thompson A, Shea B, Furst D, Wells G, Silman A: Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. Cochrane Database Syst Rev 2000, 2.

OBJECTIVES: To assess the effects and toxicity of the following agents:Prostaglandin analogues together with other agents proposed for the treatment of Raynaud's phenomenom (RP) in scleroderma. SEARCH STRATEGY: We searched the Cochrane Controlled Trials Register, and Medline up to 1996 using the Cochrane Collaboration search strategy developed by Dickersin et al.(1994). Key words included: raynaud's or vasospasm, scleroderma or progressive systemic sclerosis or connective tissue disease or autoimmune disease. Current Contents were searched up to and including April 7, 1997. All bibliographies of articles retrieved were searched and key experts in the area were contacted for additional and unpublished data. The initial search strategy included all languages. SELECTION CRITERIA: All randomized controlled trials comparing prostaglandin analogues versus placebo were eligible if they reported clinical outcomes within the start of therapy, and if the dropout rate was less than 35%. DATA COLLECTION AND ANALYSIS: Data were abstracted independently by two reviewers (DF, AT). Peto's odds ratios were calculated for all dichotomous outcomes and a weighted mean difference was calculated for all continuous outcomes. A fixed effects or random effects model was used if the data were homogeneous or heterogeneous, respectively. MAIN RESULTS: Seven randomized trials and 332 patients were included. Five of the seven trials were of parallel design. Five trials compared I.V. Iloprost and one trial studied p.o. Iloprost and another p.o. Cisaprost. Some trials were dose finding trials so various doses of Iloprost were used. Due to different efficacies of I.V. Iloprost, oral Iloprost and oral Cisaprost, the overall efficacy of these drugs was somewhat diluted. Intravenous Iloprost appears to be effective in the treatment of secondary Raynaud's phenomenon. REVIEWER'S CONCLUSIONS: Intravenous Iloprost is effective in the treatment of Raynaud's phenomenon secondary to scleroderma at decreasing the frequency and severity of attacks and preventing or healing digital ulcers. The effect seems to be prolonged after the intravenous infusion is given. Oral Iloprost may have less efficacy than

intravenous Iloprost. However, Cisaprost has minimal or no efficacy when given orally for the treatment of Raynaud's phenomenon secondary to scleroderma.

12. Pope J, Fenlon D, Thompson A, Shea B, Furst D, Wells G, Silman A: Ketanserin for Raynaud's phenomenon in progressive systemic sclerosis. Cochrane Database Syst Rev 2000, 2 OBJECTIVES: To assess the effects and toxicity of the following agent: ketanserin versus placebo proposed for the treatment of Raynaud's phenomenon (RP) in scleroderma. SEARCH STRATEGY: We searched the Cochrane Controlled Trials Register, and Medline up to 1996 using the Cochrane Collaboration search strategy developed by Dickersin et al.(1994). Key words included: Raynaud's or vasospasm, scleroderma or progressive systematic sclerosis or connective tissue disease or autoimmune disease. Current Contents were searched up to and including April 7, 1997. All bibliographies of articles retrieved were searched and key experts in the area were contacted for additional and unpublished data. The initial search strategy included all languages. SELECTION CRITERIA: All randomized controlled trials comparing ketanserin versus placebo were eligible if they reported clinical outcomes of interest. Trials with dropout rates greater than 35% were excluded. DATA COLLECTION AND ANALYSIS: Data were abstracted independently by two reviewers (DF, AT). Peto's odds ratios (OR) were calculated for all dichotomous outcomes, and a weighted mean difference (WMD) was carried out on all continuous outcomes. A fixed effects or random effects model were used if the data was homogeneous or heterogeneous, respectively. MAIN RESULTS: Three trials and 66 patients were included. The proportion improved was significantly better in the group on ketanserin with an odds ratio (OR) of 4.80 (95% CI 1.33, 17.37). However, when comparing ketanserin to placebo, the decrease in severity of RP attacks favoured placebo but this was not statistically significant. Side effects were significantly more common in the group using active treatment with an OR of 5.96 (95% CI 1.61, 22.06). Frequency of attacks did not change, but the duration of attacks decreased significantly in the ketanserin group. REVIEWER'S CONCLUSIONS: Ketanserin may have some efficacy in the treatment of Raynaud's phenomenon secondary to scleroderma. Overall, ketanserin is not significantly different from placebo for the treatment of Raynaud's phenomenon except for some decrease in the duration of attacks and more subjects improved on ketanserin compared to placebo. However, there were more side effects. It can be concluded that ketanserin treatment in Raynaud's phenomenon secondary to scleroderma is not clinically beneficial.

13. Pope J, Fenlon D, Thompson A, Shea B, Furst D, Wells G, Silman A: Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. Cochrane Database Syst Rev 2000, 2. OBJECTIVES: To determine the effects and toxicity of prazosin versus placebo proposed for the treatment of Raynaud's phenomenon (RP) in scleroderma. SEARCH STRATEGY: We searched the Cochrane Controlled Trials Register, and Medline up to December 1996 using the Cochrane Collaboration search strategy developed by Dickersin et al.(1994). Key words included: Raynaud's or vasospasm, scleroderma or progressive systemic sclerosis or connective tissue disease or autoimmune disease. Current Contents were searched up to and including April 7, 1997. All bibliographies of articles retrieved were searched and key experts in the area were contacted for additional and unpublished data. The initial search strategy included all languages. SELECTION CRITERIA: Randomized controlled trials comparing prazosin versus placebo were eligible if they reported clinical outcomes from the start of therapy. Trials with a greater than 35% dropout were excluded. Trials were included if patients with diffuse or limited scleroderma

were the subjects. If patients with other connective tissue diseases or primary Raynaud's were included, the trial was used if the data on the scleroderma patients could be extracted from the paper. DATA COLLECTION AND ANALYSIS: All data were abstracted by two independent and trained reviewers (DF, AT), and verified by a third reviewer (JP). Each trial was assessed independently by the same two reviewers for its quality using a validated quality assessment tool (Jadad 1996). Peto's odds ratios were calculated for all dichotomous outcomes and a weighted mean difference was carried out on all continuous outcomes. Fixed effects and random effects model were used if the data was homogeneous or heterogeneous, respectively. MAIN RESULTS: Two trials with a total of 40 patients were included. Prazosin has been found in two randomized controlled cross-over trials to be more effective than placebo in the treatment of Raynaud's secondary to scleroderma. However, the positive response is modest and side effects are not rare in those taking prazosin. REVIEWER'S CONCLUSIONS: Prazosin is modestly effective in the treatment of Raynaud's phenomenon secondary to scleroderma.

14. Maricq HR, Jennings JR, Valter I, Frederick M, Thompson B, Smith EA, Hill R: Evaluation of treatment efficacy of Raynaud phenomenon by digital blood pressure response to cooling. Raynaud's Treatment Study Investigators. Vasc Med 2000, 5:135-40

Previous studies have suggested that digital blood pressure response to cooling could provide a measure of the efficacy of treatments that are administered to patients with Raynaud phenomenon (RP). This method was used on 158 primary RP patients participating in a multicenter, randomized clinical trial that compared the efficacy of sustained-release nifedipine with temperature biofeedback in the treatment of RP. A pill placebo and electromyography served as controls. The response to local finger cooling was measured at 30 degrees, 20 degrees, 15 degrees and 10 degrees C in a temperature- controlled room under standardized conditions. The results showed that, at the 15 degrees C and 10 degrees C local cooling temperatures, the patients in the nifedipine group had a higher mean digital systolic blood pressure, a higher relative digital systolic blood pressure (RDSP), a smaller proportion of subjects with RDSP < 70% and a smaller proportion of subjects with a zero reopening pressure than the patients in the three other treatment groups. These results were statistically significant at 10 degrees C, the nifedipine group being significantly different from all others ($p < 0.05$); no significant difference was found between the three other treatment groups.