IV. Identification of Drugs and Devices to be Used in the Study

A. The well-known and extensively used uricosuric drug, probenecid, will be the only drug used in this study - (PDR, p. 1214, 1982)

B. No other drugs or special devices will be used.

V. Method and Materials

A. Objective and Rationale for the Study

1. We want to investigate the effect of probenecid on the dystrophic calcification present in the connective tissue disorders of progressive systemic sclerosis, the CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasis), polymyositis/dermatomyositis, and systemic lupus erythematosus.

2. Patients with the above disorders develop deposits of hydroxyapatite ($Ca_5OH(PO_4)_3$) in soft tissue. There are no abnormalities of the levels of serum calcium, phosphate, alkaline phosphatase, or parathyroid hormone. These deposits are often on the fingertips and over the extensor surfaces of the knees and elbows (calcinosis circumscripta) and occasionallly on other areas as well (calcinosis universalis). The deposits are unsightly and embarrassing to the patients. They are often painful and can interfere with the movement of joints. These lesions often drain. Infection of the surrounding soft tissue may ultimately result in the loss of skin and sometimes bone.

3. Because of the above problems, a safe and simple remedy is needed to remove dystrophic calcification.

B. Background

1. Currently there is no effective treatment for the dystrophic calcification of connective tissue disease (1).

2. The use of disodiumethylene diamine-tetraacetate by repeated infusions may cause calcinosis to transiently disappear, but the condition recurs quickly, and generally, this treatment fails. Repeated infusions are impractical (1).

3. Diphosphonates have generally been disappointing in the treatment of hydroxyapatite crystal deposits secondary to the connective tissue diseases listed above (2).

4. Aluminum hydroxide may improve calcinosis by decreasing phosphate levels, but it is not always effective and for some patients, it is unpleasant to take (2).

5. Because some patients with this malady were found to be in positive calcium balance, a diet low in calcium may be useful (1,2). Many patients are not in obvious positive calcium balance, however, and low calcium diets may not be palatable (2).

6. Systemic corticosteroids are usually ineffective in the treatment of dystrophic calcification (2). The long term use of these drugs causes cataracts, muscle wasting, glucose intolerance, osteoporosis, aseptic necrosis, hypertension, and hypokalemia as well as other side effects.

7. Surgical extirpation of these hydroxyapatite deposits is done for extremely painful lesions and/or lesions that consistently interfere with function (1). Surgery is rarely successful since the lesions tend to recur (1).

8. Probenecid can decrease the phosphate levels in hypoparathyroidism by a phosphaturic effect (3,4). Published data have not excluded a mild phosphaturic effect in normal people (2). An elevated [Ca^{++}] x $PO_4^{=}$] solubility product may increase the tendency for dystrophic

calcification to occur; lowering either factor might result in less deposition or perhaps dissolution. Dent and Stamp used probenecid to treat calcinosis circumscripta in a young woman with erosive arthritis (2). Skuterud et al, have treated the intramuscular and subcutaneous calcinosis of childhood dermatomyositis with probenecid (5).

C. Study Population

1. Patients included in this study must have the typical physical findings and radiographic findings of calcinosis circumscripta or calcinosis universalis (See Appendix A).

2. Patients will come from the Rheumatology Clinic, a division of the Internal Medicine Department, Naval Hospital, San Diego, California.

3. An attempt will be made to classify the associated connective tissue disorder which may be more easily treated with probenecid than calcinosis associated with another disorder.

D. Experimental Design

1. We would like to perform a pilot study to test the effectiveness of probenecid in the treatment of dystrophic calcification in at least 10 patients with this disorder. At this time, there are too few of these patients in the clinic to form a control group, but it should be remembered that other therapies are unsuccessful.

2. Patients will be given 2 gm. of probenecid in two divided doses daily. This dose is well-tolerated, and this dose successfully treated calcinosis previously.

3. At the beginning and every four months, serum parathyroid hormone, Mg^{++}, Ca^{++}, $PO_4^{\equiv}$, uric acid, 24-hour creatinine clearance, 24-hour urinary urate, will be tested.

4. Photographs and x-rays of the involved areas will be taken at the

beginning and every six months for a period of two years.

E. Possible Risks

1. Probenecid is relatively inexpensive, and it has few serious side effects.

2. Up to 5% gastric irritation

   a. Film coated tablets cause less nausea (6).

   b. There is less nausea when taken with meals.

   c. There is more gastric irritation with high doses (2 gm. is considered a mid-range dose).

3. Less than 5% show signs of hypersensitivity reaction, mainly skin rash.

4. It can precipitate an acute attack of gout in a patient with high uric acid levels and gouty arthritis.

5. It may precipitate uric acid renal stones in patients with acidic urine, dehydration, and with hyperuricemia.

6. It is generally ineffective at a creatinine clearance less than 50 cc/ min.

7. Those patients with peptic ulcer disease, known hypersensitivity to probenecid, a recent attack of gout, 24-hour urine for uric acid >600 mg., a history of renal stones of patients with renal failure with creatinine clearance less than 50 cc/min. will not be given probenecid. Patients with present or past problems of hyperuricemia would be excluded.

8. We would not include patients under 18 years old in this study, nor would pregnant patients be included.

9. It is possible that our patients could be taking other drugs which may interact with probenecid and rarely cause side effects.

Probenecid may decrease the renal excretion of the following drugs: aminosalycilic acid, penicillin, cephalosporins, dapsone, nalidixic acid, and methotrexate. Probenecid may inhibit the tubular secretion of the following drugs: Chlorapropamide, furosemide, indomethocin, and sulfinpyrazone. Rifampin may compete with probenecid for hepatic uptake which could lead to increased Rifampin levels. Patients on any of the above drugs could have higher serum levels of the drug as a result of interaction with probenecid. Except for patients on short courses (up to 2 weeks) of a penicillin or a cephalosporin; patients on the above drugs will be excluded from the study. Patients needing a penicillin or a cephalosporin for 2 weeks will be watched for side effects that might result from increased levels of these drugs. The medications of all patients will be closely reviewed at each clinic visit for possible drug-drug interactions.

F. Strategy for Data Analysis

1. Currently we do not have enough patients to form a large control group and to carry out detailed statistical analysis.

2. There is no extensive anecdotal literature on a particular treatment for calcinosis, therefore, clinical trials on large numbers of patients may not be warranted at this time.

3. Our plan is to perform a pilot study to see if probenecid in any way affects calcinosis. There is no reason to believe that calcinosis would improve spontaneously, and currently these patients are not receiving any other medication for calcinosis. For this reason, any improvement in calcinosis as seen by x-ray studies may be due to probenecid and may help to generate larger and statistically more

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meaningful studies. The serial blood and urine tests performed in this pilot group may tell us whether or not probenecid effects Ca++, $PO_4^{\equiv}$ metabolism and whether or not patients are actually taking the drug. These studies are done routinely by the Laboratory Medicine Department and the lab tests would not represent an unnecessary workload. X-ray studies are routinely taken every six months.

VI. Other Special Considerations and Supporting Data

A. There are no special arrangements with other institutions, companies, or manufacturers of scientific equipment.

B. Information collected will be subject to regulations of the Medical Department of the U.S. Navy. This work may lead to publication in a peer review journal. Lead authors will be the investigators. Data emanating from this study will be owned by the Department of the Navy.

C. Approval will be obtained from both Committees for Protection of Human Subjects at Naval Hospitals, San Diego, and Oakland.

VII. Informed Consent

Informed consent form is attached.

VIII. Qualifications of Investigators

Curriculum vitae for each investigator is attached.

IX. Budget

Only routine support funds are required.