

## Raynaud's Syndrome

## ABSTRACTS

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**Managing Raynaud's phenomenon: A practical approach**

Adee A.C. Bay Clinic, Hilo, HI United States

American Family Physician (United States) 1993, 47/4 (823-829)

Raynaud's phenomenon is characterized by vasospasm of the digits, most commonly the fingers, although the toes, ears, nose and even the tip of the tongue may be involved. The disorder is commonly precipitated by exposure to cold, although vasoconstrictive drugs and emotional distress may be triggers. Patients with Raynaud's phenomenon should avoid these triggers. Behavioral therapies, including stress management, relaxation training and biofeedback, are effective in some patients. When lifestyle changes fail to control symptoms, medications may be prescribed to correct various underlying pathophysiologic mechanisms. Medications that may be effective include calcium channel blockers, angiotensin converting enzyme inhibitors, alpha- adrenergic blockers, pentoxifylline, dipyridamole and low-dose acetylsalicylic acid.

### **Evening primrose oil (Efamol) in the treatment of Raynaud's phenomenon: a double blind study.**

Belch JJ; Shaw B; O'Dowd A; Saniabadi A; Leiberman P; Sturrock RD; Forbes CD

Thromb Haemost (Germany, West) Aug 30 1985, 54 (2) p490-4

Prostaglandin E1 (PGE1) and prostacyclin have been used in Raynaud's phenomenon (RP) but are unstable and require intravenous administration. An alternative approach is to stimulate the body's own PGE1 production via administration of the precursor essential fatty acid. We studied the effect of 12 capsules/day of evening primrose oil (EPO) on the manifestations of RP. 21 patients received a two week course of placebo, thereafter 11 received EPO for 8 weeks and 10 patients received placebo. As the weather worsened the placebo group experienced significantly more attacks than the EPO group. Visual analogue scales assessing the severity of attacks and coldness of hands improved in the EPO group. No changes were seen in either group in hand temperatures and cold challenge plethysmography. Blood tests showed some antiplatelet effects of the drug. In conclusion patients receiving EPO benefited symptomatically. This was not matched however by any change in objective assessment of blood flow, although changes in platelet behaviour and blood prostanoids were observed.

### **Raynaud's phenomenon in the emergency department**

Browne B.J.; Jotte R.S.; Rolnick M. Division of Emergency Medicine, Department of Surgery, Maryland University Medical Center, 22 S. Greene St., Baltimore, MD 21201-1595 United States

Journal of Emergency Medicine (United States) 1995, 13/3 (369-378)

Raynaud's phenomenon manifests as triphasic color changes of the digits, induced by exposure to low temperature or emotional stress. It is a relatively common disorder, estimated to affect 5% to 10% of the general population and 25% to 30% of otherwise healthy women. Although usually self-limiting, it can be severely painful and debilitating, and complicated by ulcerations and tissue necrosis. For the emergency physician treating a patient with an acute presentation of the phenomenon, the main challenges are to achieve adequate pain control, reverse vasospasm, and maintain viable tissue. Emergency treatment can also extend to patient education and arrangement of appropriate referrals and follow-up care.

### **Fish - oil fatty acid supplementation in mixed cryoglobulinemia: a preliminary report.**

Candela M; Cherubini G; Chelli F; Danieli G; Gabrielli A Institute of Clinical Medicine, University of Ancona, Italy.

Clin Exp Rheumatol (Italy) Sep-Oct 1994, 12 (5) p509-13

**OBJECTIVE:** Since fish oils seem to play a potential role in the treatment of inflammatory disorders by inhibiting arachidonic acid metabolism, the purpose of this study was to determine their therapeutic efficacy in mixed cryoglobulinemia (MC), an inflammatory condition caused by the deposition of immune complexes in vessel walls.

**METHODS:** In an 8-week double-blind randomized trial, ten MC patients received a daily dietary supplement of 3 gm of eicosapentaenoic acid (EPA) and 2 gm of docosahexenoic acid (DHA), while 10 other MC patients received placebo (olive oil). The severity of purpura, arthralgias, paresthesias, asthenia and Raynaud's phenomenon were monitored daily, and serological assays

were performed at the beginning of the study, at the end of the treatment period, and after 4 weeks of wash-out.

**RESULTS:** No significant differences were found between the two groups with regard to the clinical symptoms, although the percentage of patients who reported a clinical improvement was higher in the group treated with fish oils. As for the serological parameters, no variation was found in the placebo group, while in the group receiving fish oils a significant decrease in cryocrit and rheumatoid factor levels was observed, which in the case of rheumatoid factor persisted at the end of the wash-out period.

**CONCLUSIONS:** Under the experimental conditions employed in this study, we could not demonstrate a significant improvement in clinical symptoms in patients with mixed cryoglobulinemia treated with fish oils. However, since our results indicated some improvement in the serological parameters potentially involved in the pathogenesis of the disorder, further studies are warranted to establish the optimal dose and duration of fish oil supplementation in the treatment of MC.

### **Drug options for vasospastic disease**

Coffman J.D. Department of Medicine, Boston University School of Medicine, Boston, MA United States

Drug Therapy (United States) 1992, 22/10 (45-48+53-56)

Estimates of the prevalence of Raynaud's phenomenon range from 5% to 30% of the US population. Besides the primary disease, possible causes of the condition include connective tissue disease, carpal tunnel syndrome, arterial obstructions, hypothyroidism, adverse drug reactions, and use of vibrating tools. Although simple measures, such as keeping the hands, feet, and body warm, are effective in most patients, drug therapy may be necessary when vasospastic attacks interface with a patient's work or daily activities. Calcium channel blockers, sympatholytic agents, nitroglycerin, triiodothyronine, captopril, and prostaglandins have been used with varying degrees of success in symptomatic patients. Nifedipine is the current drug of choice.

### **Raynaud's phenomenon as the initial manifestation of hypothyroidism**

Coleman C.E.; Sessoms S.L.; Gowin K.M.; Boston R. Dr. S.L. Sessoms, 6550 Fannin Smith 1057, Houston, TX 77030 United States

Journal of Clinical Rheumatology (United States) 1998, 4/5 (270-273)

A 38-year-old man, who presented with Raynaud's phenomenon and no symptoms or signs of thyroid hormone deficiency, was found to have hypothyroidism. The Raynaud's phenomenon disappeared after 11/2 months of thyroid hormone replacement therapy. We review four case reports of Raynaud's phenomenon that disappeared after thyroid replacement therapy. We suggest that thyroid deficiency should be considered a possible cause of Raynaud's phenomenon.

### **Ginkgo biloba extract (EGb 761) and CNS functions: basic studies and clinical applications.**

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Curr Drug Targets 2000 Jul;1(1):25-58

The effects of EGb 761 on the CNS underlie one of its major therapeutic indications; i.e., individuals suffering from deteriorating cerebral mechanisms related to age-associated impairments of memory, attention and other cognitive functions. EGb 761 is currently used as symptomatic treatment for cerebral insufficiency that occurs during normal ageing or which may be due to degenerative dementia, vascular dementia or mixed forms of both, and for neurosensory disturbances. Depressive symptoms of patients with Alzheimer's disease (AD) and aged non-Alzheimer patients may also respond to treatment with EGb 761 since this extract has an "anti-stress" effect. Basic and clinical studies, conducted both in vitro and in vivo, support these beneficial neuroprotective effects of EGb 761. EGb 761 has several major actions; it enhances cognition, improves blood rheology and tissue metabolism, and opposes the detrimental effects of ischaemia. Several mechanisms of action are useful in explaining how EGb 761 benefits patients with AD and other age-related, neurodegenerative disorders. In animals, EGb 761 possesses antioxidant and free radical-scavenging activities, it reverses age-related losses in brain alpha 1-adrenergic, 5-HT1A and muscarinic receptors, protects against ischaemic neuronal death, preserves the function of the hippocampal mossy fiber system, increases hippocampal high-affinity choline uptake, inhibits the down-regulation of hippocampal glucocorticoid receptors, enhances neuronal plasticity, and counteracts the cognitive deficits that follow stress or traumatic brain injury. Identified chemical constituents of EGb 761 have been associated with certain actions. Both flavonoid and ginkgolide constituents are involved in the free radical-scavenging and antioxidant effects of EGb 761 which decrease tissue levels of reactive oxygen species (ROS) and inhibit membrane lipid peroxidation. Regarding EGb 761-induced regulation of cerebral glucose utilization, bilobalide increases the respiratory control ratio of mitochondria by protecting against uncoupling of oxidative phosphorylation, thereby increasing ATP levels, a result that is supported by the finding that bilobalide increases the expression of the mitochondrial DNA-encoded COX III subunit of cytochrome

oxidase. With regard to its "anti-stress" effect, EGb 761 acts via its ginkgolide constituents to decrease the expression of the peripheral benzodiazepine receptor (PBR) of the adrenal cortex.

### **Antiplatelet effect of pentoxifylline in human whole blood.**

de la Cruz JP, Romero MM, Sanchez P, Sanchez de la Cuesta F. Department of Pharmacology and Therapeutics, School of Medicine, University of Malaga, Spain.

Gen Pharmacol. 1993 May;24(3):605-9.

1. Pentoxifylline inhibits platelet aggregation in whole blood more than in platelet-rich plasma. 2. An inhibition of the erythrocyte uptake of adenosine contributes to the antiaggregatory effect of pentoxifylline.]

### **Fish - oil dietary supplementation in patients with Raynaud's phenomenon: a double-blind, controlled, prospective study.**

DiGiacomo RA; Kremer JM; Shah DM Division of Rheumatology, Albany Medical College, New York 12208.

Am J Med (United States) Feb 1989, 86 (2) p158-64

**PURPOSE:** The ingestion of omega - 3 fatty acids could benefit patients with Raynaud's phenomenon because, among other effects, these fatty acids induce a favorable vascular response to ischemia. The aim of our study was to investigate, in a double-blind, placebo-controlled manner, the effects of fish -oil fatty-acid dietary therapy in patients with rheumatic disease.

**PATIENTS AND METHODS:** Thirty-two patients with primary or secondary Raynaud's phenomenon were randomly assigned to olive-oil placebo or fish -oil groups. Patients ingested 12 fish -oil capsules daily containing a total of 3.96 g eicosapentaenoic acid and 2.64 g docosahexaenoic acid or 12 olive-oil capsules and were evaluated at baseline and after six, 12, and 17 weeks. All patients ingested olive oil between Weeks 12 to 17. Digital systolic blood pressures and blood flow were measured at room air and water baths of 40 degrees C, 25 degrees C, 15 degrees C, and 10 degrees C using strain gauge plethysmography. Onset of Raynaud's phenomenon was timed with a stop watch and defined as plethysmographic evidence of cessation of blood flow and blood pressure in the study finger.

**RESULTS:** In the fish -oil group, the median time interval before the onset of Raynaud's phenomenon increased from 31.3 +/- 1.3 minutes baseline to 46.5 +/- 2.1 minutes at six weeks ( $p = 0.04$ ). Patients with primary Raynaud's phenomenon ingesting fish oil had the greatest increase in the time interval before the onset of the condition. Five of 11 patients (45.5 percent) with primary Raynaud's phenomenon ingesting fish oil in whom the phenomenon was induced at baseline could not be induced to develop Raynaud's at the six- or 12-week visit compared with one of nine patients (11 percent) with primary Raynaud's ingesting olive oil ( $p = 0.05$ ). The mean digital systolic pressures were higher in the patients with primary Raynaud's phenomenon ingesting fish oil than in patients with primary Raynaud's ingesting olive oil in the 10 degrees C water bath (+32 mm Hg,  $p = 0.02$ ).

**CONCLUSION:** We conclude that the ingestion of fish oil improves tolerance to cold exposure and delays the onset of vasospasm in patients with primary, but not secondary, Raynaud's phenomenon. These improvements are associated with significantly increased digital systolic blood pressures in cold temperatures.

### **Drugs affecting plasma fibrinogen levels.**

di Minno G, Mancini M. Clinica Medica, Nuovo Policlinico, Napoli, Italy.

Cardiovasc Drugs Ther. 1992 Feb;6(1):25-7.

Current knowledge indicates that high plasma levels of fibrinogen help predict stroke and myocardial infarction. It is known that plasma fibrinogen is synthesized in the liver, that interleukin-6 (IL-6) affects this synthesis, and that, when exposed to appropriate stimuli, monocytes generate a variety of monokines, including IL-6. It is also known that prolonged administration of N-3 fatty acids, ticlopidine, fibrates, pentoxifylline, or alcohol lower plasma fibrinogen levels. The mechanism(s) involved in this effect are poorly understood. However, in view of the role of IL-6 and monocytes in the regulation of plasma fibrinogen levels, it is conceivable that the lowering effect of these drugs involves effects on some steps of the regulatory machinery. In addition to fibrinogen, IL-6 regulates the synthesis of other acute-phase proteins. This raises the question of whether high plasma fibrinogen levels do reflect the response of an acute-phase reactant to the severity of the atherosclerotic vascular damage taking place. Current evidence is inconclusive with respect to this possibility. On the other hand, the epidemiological data available indicate that measurements of plasma fibrinogen should be included in the cardiovascular risk-factor profile. In view of this, we believe that information emerging from population-based studies in which plasma fibrinogen is measured is important to identify appropriate directions to be followed to address

unsolved issues in the area.

### **Quantitative measurements of finger blood flow during behavioral treatments for Raynaud's disease.**

Freedman RR

Psychophysiology (United States) Jul 1989, 26 (4) p437-41

Quantitative measurements of finger blood flow have not been performed during temperature biofeedback or other treatments for Raynaud's disease. In the present investigation, finger blood flow was determined with venous occlusion plethysmography, in addition to measurements of finger temperature, heart rate, blood pressure, and skin conductance level. After a maximum vasodilation test, subjects received 10 sessions of finger temperature biofeedback or autogenic training. There were no group differences during the maximum vasodilation test. During training, temperature feedback subjects showed significant elevations in finger blood flow, finger temperature, and skin conductance level, whereas those who received autogenic training did not. These findings could not be explained by group differences in other cardiovascular measures and are consistent with previous studies suggesting the involvement of an active vasodilating mechanism in temperature feedback.

### **Nonneural beta-adrenergic vasodilating mechanism in temperature biofeedback.**

Freedman RR, Sabharwal SC, Ianni P, Desai N, Wenig P, Mayes M. Behavioral Medicine Laboratory, Lafayette Clinic, Detroit, MI 48207.

Psychosom Med 1988 Jul-Aug;50(4):394-401

Although finger temperature feedback has been used to produce digital vasodilation in normal persons and those with Raynaud's disease, the mechanism and site of this effect have not been studied. In the present investigation, feedback-induced vasodilation was attenuated by brachial artery infusions of propranolol in infused, but not contralateral, hands and was not affected by digital nerve blockade. Quantitative measurements of finger blood flow demonstrated that this vasodilation occurred in arteriovenous shunts in normal persons and in the finger capillary bed in those with Raynaud's disease. Raynaud's disease patients who received finger temperature feedback reported 80 fewer percent symptoms 1 and 2 years after treatment and retained the ability to increase finger temperature and capillary blood flow at these times. These effects were not shown by patients given autogenic training, a relaxation procedure.

### **[The effect of pentoxifylline and nicergoline on the systemic and cerebral hemodynamics and on the blood rheological properties in patients with an ischemic stroke and atherosclerotic lesions of the major cerebral arteries] [Article in Russian]**

Gara II.

Zh Nevropatol Psikiatr Im S S Korsakova. 1993;93(3):28-32.

Pentoxifylline versus nicergoline therapy has been studied in 56 patients with atherosclerosis of major cerebral arteries who had ischemic apoplexy. Pentoxifylline enhances circulation primarily in the stenotic vessels, while nicergoline in the intact cerebral arteries. The former is more potent in inducing antiaggregation inhibiting spontaneous platelet and red cell aggregation and reducing blood viscosity. The results of the study suggest better response in case of pentoxifylline treatment of patients with hypo- and eukinetic circulation, while in nicergoline treatment hyperkinetic hemodynamics patients benefit more in view of the drug cardiodepressive activity.

### **Effect of anti-platelet therapy (aspirin + pentoxiphylline) on plasma lipids in patients of ischaemic stroke.**

Gaur SP, Garg RK, Kar AM, Srimal RC. Department of Pharmacology and Clinical & Experimental Medicine Central Drug Research Institute, Lucknow.

Indian J Physiol Pharmacol. 1993 Apr;37(2):158-60.

Twenty-one patients of ischaemic stroke were put on prolonged administration of antiplatelet drugs (aspirin 320 mg once daily with pentoxiphylline 400 mg thrice daily). The serum lipids along with other biochemical parameters were estimated before starting the treatment and after completion of 2 months of therapy. No significant changes were observed in any of the biochemical parameters including lipid profile except in serum high density lipoprotein (HDL) which increased significantly ( $< 0.05$ ) after 2 months therapy. It is concluded that 2 months antiplatelet therapy has no adverse metabolic effect in patients of ischaemic stroke and the raised serum HDL may contribute to cerebral protective effect.

## **Symptoms of Raynaud's phenomenon in an inner-city African-American community: prevalence and self-reported cardiovascular comorbidity.**

Gelber AC, Wigley FM, Stallings RY, Bone LR, Barker AV, Baylor I, Harris CW, Hill MN, Zeger SL, Levine DM. Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA.

J Clin Epidemiol 1999 May;52(5):441-6

The objective of this study was to determine the prevalence of symptoms and the morbidity associated with Raynaud's phenomenon (RP) among African Americans. A total of 2196 randomly selected residents of an inner-city community, in Baltimore, completed a health-assessment survey. Symptoms of RP consisted of cold sensitivity plus cold-induced white or blue digital color change. One third (n = 703) reported cold sensitivity and 14% (n = 308) reported digital color change; 84 residents with symptoms of RP were identified, yielding an overall prevalence rate of 3.8% (95% confidence interval [CI] 3.0-4.6). RP was associated with poor or fair health status (odds ratio [OR] = 1.82, CI 1.18-2.81), heart disease (OR = 2.32, CI 1.39-3.87), and stroke (OR = 2.20, CI 1.17-4.15), after adjustment for age, gender, and physician-diagnosed arthritis. The prevalence of symptoms of RP in this African-American community is comparable to published reports from other populations. These community-based data suggest that identification of RP among African Americans should raise consideration of possible comorbidity, particularly cardiovascular disease.

## **Oxpentifylline in Parkinson's disease.**

Godwin-Austen RB, Twomey JA, Hanks G, Higgins J.

J Neurol Neurosurg Psychiatry. 1980 Apr;43(4):360-4.

The effects of oxpentifylline were assessed in a double-blind trial in 11 patients with Parkinson's disease already under treatment. No significant improvement was noted. Eight patients developed involuntary movements or a worsening of movements if already present. The significance of this unexpected finding is discussed.

## **On the significance of magnesium in extreme physical stress.**

Golf SW, Bender S, Gruttner J. Institute of Clinical Chemistry and Pathobiochemistry, University Medical School, Justus-Liebig-University, Giessen, Germany.

Cardiovasc Drugs Ther 1998 Sep;1234717-03-8:197-202

In a double-blind randomized study, 23 competitive triathletes competing in an event consisting of a 500-meter swim, a 20-km bicycle race, and a 5-km run were studied after 4-week supplementation with placebo or 17 mmol/d Mg orotate. The tests were carried out without a break. Blood was collected before and after the test, and between the different events for assaying energy stress and membrane metabolism. Swimming, cycling, and running times decreased in the Mg-orotate group compared with the controls. Serum glucose concentration increased 87% during the test in the control group and 118% in the Mg-orotate group, while serum insulin increased 39% in the controls and decreased 65% in the Mg-orotate group. Venous O<sub>2</sub> partial pressure increased 126% during the test in the controls and increased 208% in the Mg-orotate group. Venous CO<sub>2</sub> partial pressure after the bicycle race decreased 66% (significantly) in the Mg-orotate group compared with 74% in the controls. Blood proton concentration decreased to 90% in the Mg-orotate group (significantly) compared with 98% in the controls. Blood leukocyte count increased from 5.92/nL to 11.0/nL in the controls and from 5.81/nL to 9.10/nL in the Mg-orotate group, a significant difference. Serum cortisol was lower in the Mg-orotate group before and after the test compared with the controls. CK catalytic concentration after the test was elevated 140% in the controls compared with 122% Mg-orotate group. The stress-induced modifications of energy and hormone metabolism described in this study indicate altered glucose utilization after Mg-Orotate supplementation and a reduced stress response without affecting competitive potential.

## **Clinical diagnosis found in patients with Raynaud's phenomenon: a multicentre study.**

Grassi W; De Angelis R; Lapadula G; Leardini G; Scarpa R Clinica Reumatologica, Ospedale A. Murri, Jesi, Italy.

Rheumatol Int (Germany) 1998, 18 (1) p17-20

A multicentre observational study was conducted in order to detect the major clinical diagnosis found in 761 patients with Raynaud's phenomenon (RP) attending 50 Italian centres for rheumatology and internal medicine. Systemic sclerosis was the most frequent condition associated with secondary RP, occurring in 216 (28.4%) patients. The other most frequent clinical diagnoses included systemic lupus erythematosus (52 cases: 6.8%) and rheumatoid arthritis (38 cases: 5%). Other RP-related diseases

(hypertension, Sjogren's syndrome, mixed connective tissue disease, undifferentiated connective tissue disease, fibromyalgia, carpal tunnel syndrome, cryoglobulinemia, dermatomyositis, vasculitis, thoracic outlet syndrome, hypothyroidism, diabetes mellitus) occurred in less than 5% of cases. A total of 130 (48%) out of 268 patients with primary RP showed one or more clinical features indicating a fairly high risk of evolving into fully established systemic sclerosis. None of these patients fulfilled the ACR criteria for systemic sclerosis. This study shows that over 50% of patients with RP attending 50 Italian centres for rheumatology and internal medicine had a connective tissue disease. The large number of patients with primary RP and isolated clinical features of connective tissue disease indicates that more efforts should be focused on developing new criteria for the classification of RP.

### **Micronutrient antioxidant status in patients with primary Raynaud's phenomenon and systemic sclerosis.**

Herrick AL; Rieley F; Schofield D; Hollis S; Braganza JM; Jayson MI University of Manchester Rheumatic Diseases Centre, Hope Hospital, Salford, UK.

J Rheumatol (Canada) Aug 1994, 21 (8) p1477-83

**OBJECTIVE.** To investigate the possibility that micronutrient antioxidant status is an important factor in determining the severity of Raynaud's phenomenon (RP) and in differentiating between patients with primary Raynaud's phenomenon (PRP) and those in whom Raynaud's is secondary to systemic sclerosis (SSc).

**METHODS.** Four micronutrient antioxidants (selenium, vitamin E, beta-carotene and ascorbic acid) and 2 "markers" of free radical associated activity were assayed in peripheral blood from 10 patients with PRP, 9 with limited cutaneous SSc (ISSc), 9 with diffuse SSc (dSSc) and 15 healthy control subjects.

**RESULTS.** Plasma ascorbic acid was reduced in all 3 groups of patients: median level 10.6 mg/l in controls, 4.8 mg/l in PRP ( $p < 0.01$ ), 2.5 mg/l in ISSc ( $p < 0.01$ ) and 6.8 mg/l in dSSc ( $p < 0.05$ ). A reduction in serum selenium was especially found in dSSc (median 75 micrograms/l compared to 100 micrograms/l in controls,  $p < 0.05$ ). In keeping with these deficiencies, the serum concentration of 9, 11, linoleic acid was elevated in RP patients: median values for the molar ratio of the isomer to the parent fatty acid were 1.91% in controls, 3.70% in ISSc ( $p < 0.05$ ) and 3.85% in dSSc ( $p < 0.01$ ). Smoking patients showed lower levels of ascorbic acid and higher levels of the linoleic isomer than nonsmokers.

**CONCLUSION.** Deficiencies of ascorbic acid and selenium may predispose towards irreversible tissue injury in RP patients and cigarette smoke may be an independent risk factor. Micronutrient antioxidant supplements may be of therapeutic value.

### **Raynaud's phenomenon: State of the art 1998**

Ho M.; Belch J.J.F. J.J.F. Belch, University Department of Medicine, Ninewells Hosp. and Medical School, Dundee DD1 9SY United Kingdom

Scandinavian Journal of Rheumatology (Norway) 1998, 27/5 (319-322)

Raynaud's Phenomenon (RP) is a relatively common problem which may be troublesome and difficult to treat in a minority of patients. The state of the art in 1998 focusses on three key areas: the clinical spectrum of RP; its progression and prognosis; and its treatment. RP is a systemic disease, with a multifactorial aetiology and vasospasm affects not just the digits and skin but also major organs including the heart, lungs and kidneys. It is important to distinguish primary from secondary RP. RP may predate an associated connective tissue disease by many years and markers for this include severe RP symptoms with trophic skin changes, serological abnormalities and abnormal nailfold capillaries. Repeated attacks of vasospasm may cause ischaemic reperfusion injury to the endothelium, resulting in a vicious and self propagating cycle of cause and effect. Nifedipine remains the 'gold standard' of treatment but a number of new and promising drugs, eg relaxin, are currently under investigation. 'Vasodilator-plus' drugs, with the ability to also modulate some of the haemorrhological abnormalities in RP, are the drugs that are going to have a major clinical impact on the disease and hold promise for the future.

### **An experimentally controlled evaluation of the effect of inositol nicotinate upon the digital blood flow in patients with Raynaud's phenomenon.**

Holti G

J Int Med Res (England) 1979, 7 (6) p473-83

The vaso-active effects of inositol nicotinate (Hexopal) were investigated in thirty patients with primary and secondary Raynaud's phenomenon using several non-invasive experimental techniques under controlled conditions. The earlier formed impression that this drug requires a prolonged 'build-up' period was confirmed. Recording the time required to induce Raynaud's phenomenon as well as

assessments of total and nutrient digital blood flow showed significant beneficial therapeutic effects upon the skin's microcirculation by inositol nicotinate . This study suggests that the therapeutic effect of this drug is not merely due to vasodilation but that other mechanisms such as enhanced fibrinolysis and lowering of serum lipids may play a significant part in its overall effect. Smokers responded slower than non-smokers, but even elderly patients with longstanding vasospastic disease showed measurably improved digital circulation. Unlike some other drugs in this field inositol nicotinate was found to be effective orally and to be devoid of unwanted side-effects. However, in the majority of patients it failed to abolish their increased vascular spasm although it diminished it significantly in most. It appears to be a safe and well tolerated drug, which, together with other symptomatic measures, merits to be used in the management of vasospastic disease of the extremities even in the presence of partial obliteration of the microcirculation.

### **Sjogren's syndrome and the sicca syndrome: the role of prostaglandin E1 deficiency. Treatment with essential fatty acids and vitamin C.**

Horrobin DF; Campbell A

Med Hypotheses (England) Mar 1980, 6 (3) p225-32

Lack of adequate synthesis of prostaglandin (PG) E1 may be the key factor in Sjogren's syndrome. PGE1 is important for lacrimal and salivary gland secretion and for T lymphocyte function: a deficiency could therefore account for the main features of Sjogren's syndrome and the sicca syndrome. PGE1 could also account for many of the other features often associated with these syndromes. These include the Raynaud's phenomenon, the abnormalities of renal function and the precipitation of the syndrome by vitamin C deficiency. Vitamin C is important in PGE1 biosynthesis. PGE1 treatment has been shown to correct the immunological abnormalities in the NZB/W mouse, the animal model of Sjogren's syndrome. An attempt to treat humans with Sjogren's syndrome by raising endogenous PGE1 production by administration of essential fatty acid PGE1 precursors, of pyridoxine and of vitamin C was successful in raising the rates of tear and saliva production.

### **Biofeedback, autogenic training, and progressive relaxation in the treatment of Raynaud's disease: a comparative study.**

Keefe FJ; Surwit RS; Pilon RN

J Appl Behav Anal (United States) Spring 1980, 13 (1) p3-11

Twenty-one female patients suffering from diagnosed idiopathic Raynaud's Disease were trained to raise digital skin temperature using either autogenic training , progressive muscle relaxation, or a combination of autogenic training and skin temperature feedback. Patients were instructed in the treatment procedures in three one-hour group sessions spaced one week apart. All patients were instructed to practice what they had learned twice a day at home. Patients kept records of the frequency of vasospastic attacks occurring over a four-week baseline period, and during the first four weeks and the ninth week of training. In addition, patients underwent four laboratory cold stress tests during which they were instructed to maintain digital temperature as the ambient temperature was slowly dropped from 26 degrees to 17 degrees C. Cold stress tests were given during week 1 of baseline and during weeks 1, 3, and 5 of training. No significant differences between the three behavioral treatment procedures were obtained. In addition, the ability of patients to maintain digital temperature during the cold stress challenge showed significant improvement from the first to the last tests. Symptomatic improvement was maintained by all patients nine weeks after the start of training. The implications of these findings for the behavioral treatment of Raynaud 's Disease are discussed.

### **[Hemorheologic effects of ginkgo biloba extract EGb 761. Dose-dependent effect of EGb 761 on microcirculation and viscoelasticity of blood]. [Article in German]**

Koltringer P, Langsteger W, Klima G, Reisecker F, Eber O. Abteilung fur Neurologie und Psychiatrie, Krankenhaus der Barmherzigen Bruder Graz-Eggenberg.

Fortschr Med 1993 Apr 10;111(10):170-172

Method: In a randomized open clinical trial involving 42 patients with pathological visco-elasticity values, the effect of a single intravenous injection of 50, 100, 150 or 200 mg of the Ginkgo biloba extract EGb 761, commercially available as Tebonin p.i. on the microcirculation of the skin (Doppler flowmetry) and the visco-elasticity of whole blood was investigated. Results: A dose-dependent significant increase in the microcirculation was found. In the case of visco-elasticity, this dose-dependence was less marked. The present study thus confirms the positive effect of EGb 761 on the microcirculation and whole-blood visco-elasticity in patients with pathological visco-elasticity values, already found in earlier studies, and shows it to be dependent on the dose employed.

### **Remission of Raynaud's phenomenon after L-thyroxine therapy in a patient with hypothyroidism.**

J Endocrinol Invest (Italy) Jan 1992, 15 (1) p49-51

A 50-year-old man is described who had a 15-year history of Raynaud's phenomenon with severe and frequent vasospastic attacks in his fingers and toes during the past years. Exacerbation of his digital symptoms, which started about 4 years ago, was accompanied by signs of thyroid deficiency, such as tiredness, memory impairment, decreased libido, constipation, dryness of skin and bradycardia. Hormonal evaluation revealed primary hypothyroidism and the patient began substitution therapy with L-thyroxine. After 2 months of treatment not only did he become euthyroid but the digital symptoms also disappeared. The patient may thus represent one of the very few cases whose thyroid replacement therapy proved to be highly effective in treating both hypothyroidism and Raynaud's phenomenon.

### **Platelet resistance to prostacyclin. Enhancement of the antiaggregatory effect of prostacyclin by pentoxifylline.**

Manrique RV, Manrique V.

Angiology. 1987 Feb;38(2 Pt 1):101-8.

With regard to existence of high prostacyclin (PGI<sub>2</sub>) levels during atheromatosis and thrombus formation, resistance of platelets to prostacyclin and its analogues seems to play an important pathophysiologic key role for the clarifying of vasoocclusive phenomena. Platelet resistance to prostacyclin was studied in vitro and ex vivo in 160 atherosclerotic patients (assessed by objective diagnostic criteria) with and without thrombotic complications and in 50 controls. Prostacyclin resistance phenomena were more pronounced and frequent in patients with occlusive complications, the difference from controls being statistically significant. However, there was no significant difference between the controls and the nonthrombotic patient sample. The intraplatelet cAMP levels might be the metabolic basis of the PGI<sub>2</sub> resistance phenomenon, because in the patient group, platelet cAMP levels were decreased by 50% after Ca<sup>2+</sup> stimulation. Compared to controls beta-thromboglobulin and thromboxane B<sub>2</sub> plasma levels were significantly increased (30 +/- 9 to 87 +/- 26 ng/ml and 9 +/- 5 to 54 +/- 21 pg/ml, respectively), confirming the hyperreactivity state of resistant platelets. From the therapeutic point of view, patients with resistant platelets require PGI<sub>2</sub> doses that cause, however, increased side effects. We were able to demonstrate in vivo that IV pretreatment with pentoxifylline--a known stimulator of cAMP formation in platelets-- followed by a simultaneous and continuous IV infusion of PGI<sub>2</sub> + pentoxifylline, permitted us to reduce significantly the mean PGI<sub>2</sub> doses needed for triggering an antiplatelet effect, without inducing side effects. In ex vivo studies, PGI<sub>2</sub> resistant platelets of atherosclerotic patients pretreated with pentoxifylline showed normalized stimulation response, and platelet cAMP levels increased from 7.8 +/- 2.7 to 15.2 +/- 1.9 pmol/10(8) platelets.(ABSTRACT TRUNCATED AT 250 WORDS)

### **Comparative double-blind trial of dl-alpha-tocopheryl nicotinate on vibration disease.**

Matoba T; Kusumoto H; Mizuki Y; Yamada K

Tohoku J Exp Med (Japan) Sep 1977, 123 (1) p67-75

Sixty inpatients with vibration disease were examined on the effect of dl-alpha-tocopheryl nicotinate by comparative double-blind study. The observed period was 6 weeks and the dose was 6 capsules a day (600 mg as dl-alpha-tocopheryl nicotinate, Juvela Nicotinate, referred to as EN). The physical exercise therapy was applied to all patients throughout the test period. EN group became better with a significant difference from P (placebo) group in the subjective symptoms, the clinical examinations and the collective improving rate (p less than 0.01, 0.05, 0.01), respectively. The improvement of the subjective symptoms of both groups was higher 6 weeks than 3 weeks after administration. Most items in EN group became better significantly (p less than 0.05) as compared with those in P group. The examinations of the peripheral functions in EN group showed a significant improvement 6 weeks after administration in comparison with those in P group. Blood chemistry, blood cell counts and serum electrolytes changed within normal range. Thus, this preparation would be a curative agent for patients with vibration disease.

### **Treatment of the Raynaud's phenomenon with piracetam.**

Moriau M; Lavenne-Pardonge E; Crasborn L; von Frenckell R; Col-Debeys C Department of Internal Medicine, University of Louvain, UCL, Brussels Belgium.

Arzneimittelforschung (Germany) May 1993, 43 (5) p526-35

Piracetam (Nootropil, CAS 7491-74-9) has been investigated in the treatment of primary and secondary Raynaud 's phenomenon in three sequential and complementary studies. The first study in 20 patients with primary Raynaud 's phenomenon, utilising clinical and ultrasound examination, capillaroscopy and laboratory tests established a daily dose of 8 g as most effective. The second

study in 58 patients (47 primary, 11 secondary) confirmed the therapeutic efficacy of piracetam in both primary and secondary Raynaud's phenomenon. The third study, of crossover design, in 30 patients with severe Raynaud's syndrome, examined various agents given singly or in combination. The results not only confirmed the efficacy of piracetam but in addition allowed comparison of the efficacy of the principal therapeutic agents or regimens used in the treatment of Raynaud's syndrome and the formulation of a list of these therapies in decreasing order of efficacy, thus: piracetam 4 g/d + buflomedil 600 mg/d; piracetam 8 g/d; buflomedil 600 mg/d; piracetam 4 g/d + acetylsalicylic acid 100 mg/d; pentoxifylline 1200 mg/d; calcium antagonists; ketanserin 120 mg/d. The particular efficacy of 8 g piracetam daily in 3 divided doses at 8-hourly intervals can be attributed to its unique dual mode of action; inhibition of platelet function by inhibition of thromboxane A<sub>2</sub> synthetase or antagonism of thromboxane A<sub>2</sub> and increased formation of prostaglandin I<sub>2</sub>, together with a rheological effect involving reduction in blood and plasma viscosity through an increase in cell membrane deformability and a reduction of 30-40% in the plasma concentrations of fibrinogen and von Willebrand's factor. In addition, the administration of piracetam appears to be devoided of adverse effects.

### **The effect of inositol nicotinate (Hexopal) in patients with Raynaud's phenomenon. A placebo-controlled study**

Murphy R. Waterloo Health Centre, Blyth, Northcumberland United Kingdom

Clinical Trials Journal (United Kingdom) 1985, 22/6 (521-529)

A double-blind placebo-controlled study of the effect of inositol nicotinate (Hexopal) in the treatment of Raynaud's phenomenon is described. Sixty-five patients, 20 males 45 females, aged 18-75 years, weighing 40-100 kg were enrolled by 45 General Practitioners in East Anglia, Scotland and North Midlands. They were given either Hexopal or placebo 4 x 500 mg tablets twice daily for three months. The two groups were well matched for pre-treatment characteristics and well balanced for environmental temperature during the trial. After six weeks'treatment 14 out of 29 patients in each group had improved but at the end of the study 21 in the Hexopal group (78% of those remaining) had improved whilst the number in the placebo group remained at 14 (56% of those remaining). A statistically significant improvement in symptoms and reduction in frequency of Raynaud's attack was seen only in the Hexopal group. Compared with placebo, symptoms were significantly better with Hexopal after three months of treatment. This study, conducted as far as possible under natural conditions in the cold season, produced further confirmation that Hexopal not only reduced the severity of Raynaud's symptoms but also the frequency of Raynaud's attacks.

### **Quantitative thermographic assessment of inositol nicotinate therapy in Raynaud's phenomena.**

Ring EF; Bacon PA

J Int Med Res (England) 1977, 5 (4) p217-22, Journal Code: E62

The basal temperature of the hands has been measured by quantitative thermography in a group of normal controls and rheumatoid patients exhibiting Raynaud's phenomenon. The thermographic index for both the dorsum of the hand and the fingers was significantly lower in the patients with Raynaud's. Oral treatment with inositol nicotinate (Hexopal) was followed by an initial rise in the thermographic index in both areas. After the initial increase the temperature fell again but then rose after two months treatment. At nine months two subjects on continuous therapy had higher indices than the four who had discontinued therapy. It is suggested that long-term treatment with nicotinate acid derivatives may produce improvement in the peripheral circulation by a different mechanism than the transient effect detected by short-term studies.

### **Thermal feedback in Raynaud's phenomenon secondary to systemic lupus erythematosus: long-term remission of target symptoms.**

Sappington JT, Fiorito EM.

Biofeedback Self Regul 1985 Dec;10(4):335-41

Thermal feedback shows promise when applied to Raynaud's phenomenon secondary to systemic lupus erythematosus (SLE). A female subject was followed over an 8-year period that included initial training, 1-year follow-up, and 8-year follow-up. Peripheral circulation was initially very poor, as evidenced by low basal fingertip temperatures and trophic lesions at the fingernails. An intensive 5-week training regimen in thermal self-regulation yielded evidence of hand warming, followed by an increase in basal finger temperature. Reported vasospasms were markedly reduced and the lesions healed in the ensuing weeks. As of the 1-year follow-up, the skill was intact. Symptoms remained in substantial remission throughout the 8-year period during which the subject practiced somatic relaxation and hand warming without electronic feedback. Objective temperature measurement at the 8-year juncture yielded results similar to the initial acquisition, gradual manifestation of control over the first 4 days. The subject also reported diminution of vascular headache, another symptom of SLE. While much of the biofeedback literature is focused on stress-related disease, research of this kind affirms the value of self-regulatory technique in illnesses whose causes are primarily physical.

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Neurologia. 2001 Jan;16(1):39-42.

Pentoxifylline is a synthetic derivative of xantine which stimulates adenosine receptors, inhibit phosphodiesterase and increases cyclic monophosphate adenosine. It is also considered a dopaminergic D1 receptor agonist. Worsening of patients with Parkinson's disease when taking this product has been reported. On the other hand, it is considered that adenosine A2A receptors antagonists have antiparkinsonian properties. Four cases of patients with a mean age of 77 years who developed a rigid akinetic syndrome following therapy with a mean dose of 1100 mg/day of pentoxifylline over a mean period of 32 days are presented. Two of these patients presented clinical characteristics of drug-induced parkinsonism and the other two showed Parkinson's disease. The possibility of pentoxifylline causing an imbalance between D1 and D2 receptor stimulation and producing pharmacologic parkinsonism, or rather, the possibility of pentoxifylline unmasking subclinical Parkinson's disease are discussed.

### **Raynaud's phenomenon in hypothyroidism.**

Shagan BP; Friedman SA

Angiology (United States) Jan 1976, 27 (1) p19-25

Two patients with Raynaud's phenomenon were found to be hypothyroid and their symptoms disappeared with thyroid replacement therapy. Vascular reactivity studies in one patient demonstrated decreased vasomotor tone after therapy. Raynaud's phenomenon may be an expression of altered autonomic function in hypothyroidism .

### **Hypothyroidism, Raynaud's phenomenon, and acute myocardial infarction in a young woman.**

Sipila R; Viitasalo K; Heikkila J Clin Cardiol (United States) Jun 1983, 6 (6) p304-6

We describe an acute inferior myocardial infarction in a 29-year-old woman with normal coronary arteries. She has suffered from Raynaud's phenomenon in the fingers for several years. Manifest thyroid deficiency was discovered during hospitalization. A functional-type link between hypothyroidism and myocardial infarction via vasospasm manifested as Raynaud's phenomenon is proposed as one possible etiology for the syndrome of myocardial infarction in young women.

# RAYNAUD'S SYNDROME

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## **Raynaud's phenomenon as the initial manifestation of hypothyroidism**

Coleman C.E.; Sessoms S.L.; Gowin K.M.; Boston R.  
Dr. S.L. Sessoms, 6550 Fannin Smith 1057, Houston, TX 77030 United States  
Journal of Clinical Rheumatology (United States) 1998, 4/5 (270-273)

A 38-year-old man, who presented with Raynaud 's phenomenon and no symptoms or signs of thyroid hormone deficiency, was found to have hypothyroidism . The Raynaud 's phenomenon disappeared after 11/2 months of thyroid hormone replacement therapy. We review four case reports of Raynaud 's phenomenon that disappeared after thyroid replacement therapy. We suggest that thyroid deficiency should be considered a possible cause of Raynaud 's phenomenon.

## **Drug options for vasospastic disease**

Coffman J.D.  
Department of Medicine, Boston University School of Medicine, Boston, MA United States  
Drug Therapy (United States) 1992, 22/10 (45-48+53-56)

Estimates of the prevalence of Raynaud's phenomenon range from 5% to 30% of the US population. Besides the primary disease, possible causes of the condition include connective tissue disease, carpal tunnel syndrome, arterial obstructions, hypothyroidism, adverse drug reactions, and use of vibrating tools. Although simple measures, such as keeping the hands, feet, and body warm, are effective in most patients, drug therapy may be necessary when vasospastic attacks interface with a patient's work or daily activities. Calcium channel blockers, sympatholytic agents, nitroglycerin, triiodothyronine, captopril, and prostaglandins have been used with varying degrees of success in symptomatic patients. Nifedipine is the current drug of choice.

## **Effect of magnesium sulfate infusion on circulating levels of noradrenaline and neuropeptide-Y-like immunoreactivity in patients with primary Raynaud's phenomenon**

Leppert J.; Myrdal U.; Hedner T.; Edvinsson L.; Tracz Z.; Ringqvist I.  
Department of Research, University of Uppsala, Central Hospital, S-721 89 Vasteras Sweden  
Angiology (United States) 1994, 45/7 (637-645)

The effect of a short-term magnesium sulfate (MgSO<sub>4</sub>) infusion on venous plasma concentration of noradrenaline (NA) and neuropeptide-Y-like immunoreactivity (NPY-LI) was investigated in 12 women with primary Raynaud's phenomenon (PRP) and in 12 healthy matched controls. The Raynaud's patients did not demonstrate any significant changes in mean basal plasma NA concentration (0.29 ± 0.15 vs 0.37 ± 0.09 ng/mL, ns) after MgSO<sub>4</sub> infusion. However, in the controls there was more than twice the amount of circulating noradrenaline (cNA) (0.21 ± 0.14 vs 0.54 ± 0.22 ng/mL, P < 0.001) after MgSO<sub>4</sub> infusion, compared with the preinfusion value. Measurements during the cold pressor test prior to the MgSO<sub>4</sub> infusion showed a significant increase of cNA in both the PRP group and the control group (from 0.29 ± 0.15 to 0.33 ± 0.16 ng/mL, P < 0.05, and from 0.21 ± 0.14 to 0.29 ± 0.16 ng/mL, P < 0.005, respectively). After MgSO<sub>4</sub> infusion the levels of cNA during the cold pressor test increased significantly only in the PRP group (from 0.37 ± 0.09 to 0.41 ± 0.11 ng/mL, P < 0.05). Circulating NPY-LI concentrations increased significantly during MgSO<sub>4</sub> infusion in the Raynaud's patients as well as in the controls from 105 ± 21 to 127 ± 23 pmol/L, P < 0.05, and from 107 ± 17 to 132 ± 27 pmol/L, P < 0.01, respectively. There were no detectable changes during the cold pressor tests in either group. In healthy women short-term MgSO<sub>4</sub> infusion induced a sympathetic response, shown by the increased concentration of cNA and NPY-LI, while in PRP patients there was only an increase in NPY-LI. The discrepancy between PRP patients and healthy controls supports the view of a so-called 'local fault' in the sympathetic nerve terminal of arterial/arteriolar walls in Raynaud's patients.

## **Thromboxane metabolite excretion in patients with hand-arm vibration syndrome.**

Nowak J; Barregard L; Benthin G; Granung G; Wennmalm A  
Department of Clinical Physiology, Huddinge University Hospital, Karolinska Institute, Stockholm, Sweden  
Clin Physiol (England) Jul 1996, 16 (4) p361-7

As chronic exposure to hand-held vibrating tools may cause endothelial injury, a subsequent sustained platelet activation with the increased release of vasoconstricting thromboxane A<sub>2</sub> (TxA<sub>2</sub>) could be of pathophysiological importance in vibration-induced Raynaud's phenomenon. Therefore, the aim of this study was to elucidate whether or not hand-arm vibration syndrome is accompanied by increased endogenous TxA<sub>2</sub> biosynthesis. The study involved 64 men, aged 23-61 years, stratified according to the exposure to vibrating tools, the presence of Raynaud's phenomenon, and smoking habit. Forty of them were car mechanics and 24 were age-matched healthy volunteers who served as controls. The assessment of platelet TxA<sub>2</sub> formation in vivo was performed by quantification of the urinary excretion of its major metabolite, 2,3-dinor-thromboxane B<sub>2</sub> (2,3-dinor-TxB<sub>2</sub>), employing gas chromatography-mass spectrometry. The average urinary excretion rate of 2,3-dinor-TxB<sub>2</sub> in patients with Raynaud's phenomenon was 296 ± 42 pg/mg creatinine and did not differ significantly from the corresponding values in controls (328 ± 62 pg/mg creatinine) or individuals exposed to vibrating tools, but without any signs of vasospastic disease (232 ± 29 pg/mg creatinine). The only statistically significant difference was found between smokers and non-smokers (P < 0.001), a finding confirming the existence of chronic platelet dysfunction in cigarette smokers. The present data indicate that chronic exposure to vibrating tools, with or without Raynaud's phenomenon, is not associated with an enhanced platelet function as monitored by the urinary excretion of 2,3-dinor-TxB<sub>2</sub>. Hence, a possible vibration-induced vascular injury does not seem to provide a stimulus sufficient to induce a persistent platelet activation.

## **Raynaud's phenomenon: State of the art 1998**

Ho M.; Belch J.J.F.

Raynaud's Phenomenon (RP) is a relatively common problem which may be troublesome and difficult to treat in a minority of patients. The state of the art in 1998 focusses on three key areas: the clinical spectrum of RP; its progression and prognosis; and its treatment. RP is a systemic disease, with a multifactorial aetiology and vasospasm affects not just the digits and skin but also major organs including the heart, lungs and kidneys. It is important to distinguish primary from secondary RP. RP may predate an associated connective tissue disease by many years and markers for this include severe RP symptoms with trophic skin changes, serological abnormalities and abnormal nailfold capillaries. Repeated attacks of vasospasm may cause ischaemic reperfusion injury to the endothelium, resulting in a vicious and self propagating cycle of cause and effect. Nifedipine remains the 'gold standard' of treatment but a number of new and promising drugs, eg relaxin, are currently under investigation. 'Vasodilator-plus' drugs, with the ability to also modulate some of the haemorrhological abnormalities in RP, are the drugs that are going to have a major clinical impact on the disease and hold promise for the future.

### **Plasma catecholamines during behavioral treatments for Raynaud's disease.**

Freedman RR; Keegan D; Migaly P; Galloway MP; Mayes M  
Lafayette Clinic, Detroit, MI 48207.  
Psychosom Med (United States) Jul-Aug 1991, 53 (4) p433-9

We have previously demonstrated that the vasospastic attacks of Raynaud's disease can be induced despite blockade of efferent digital nerves and that feedback-induced vasodilation is mediated through a non-neural, beta-adrenergic mechanism. Here, we sought to determine the role of sympathetic activity, as measured by plasma epinephrine and norepinephrine, during finger temperature feedback and autogenic training. Thirty-one female patients with idiopathic Raynaud's disease were randomly assigned to receive finger temperature feedback or autogenic training over 28 days. Half of each group began and finished training during the follicular phase of the menstrual cycle, the other half during the luteal phase. During training, significant temperature elevations were shown by feedback patients but not by autogenic patients. There were no significant effects for norepinephrine and epinephrine for either group. Cycle phase did not interact with training effects or with catecholamines. These findings do not support the role of decreased sympathetic activation in behavioral treatments for Raynaud's disease.

### **Quantitative measurements of finger blood flow during behavioral treatments for Raynaud's disease.**

Freedman RR  
Psychophysiology (United States) Jul 1989, 26 (4) p437-41

Quantitative measurements of finger blood flow have not been performed during temperature biofeedback or other treatments for Raynaud's disease. In the present investigation, finger blood flow was determined with venous occlusion plethysmography, in addition to measurements of finger temperature, heart rate, blood pressure, and skin conductance level. After a maximum vasodilation test, subjects received 10 sessions of finger temperature biofeedback or autogenic training. There were no group differences during the maximum vasodilation test. During training, temperature feedback subjects showed significant elevations in finger blood flow, finger temperature, and skin conductance level, whereas those who received autogenic training did not. These findings could not be explained by group differences in other cardiovascular measures and are consistent with previous studies suggesting the involvement of an active vasodilating mechanism in temperature feedback.

### **The behavioral treatment of Raynaud's disease: a review.**

Rose GD; Carlson JG  
Department of Psychology, University of Hawaii, Honolulu 96822.  
Biofeedback Self Regul (United States) Dec 1987, 12 (4) p257-72

Raynaud's disease is a peripheral vascular system disorder characterized by episodes of vasoconstriction in the hands and feet resulting in a lowering of skin temperature and pain. Recent studies are reviewed that focus on the behavioral treatment of Raynaud's disease--in particular, biofeedback and autogenic training. Methodological problems and other difficulties include the measurement of skin temperature, schedules of reinforcement/feedback, and characteristics of the experimenter and subject.

Studies in this area indicate some promise for certain behavioral interventions, especially finger temperature biofeedback under cold stress conditions. On the other hand, further research is needed to clarify the mechanisms, especially that of vasodilation, and the applications of temperature biofeedback, as well as the role of attitudinal, interpersonal, and cognitive factors. (43 Refs.)

## **Bringing the feet in from the cold: thermal biofeedback training of foot-warming in Raynaud's syndrome.**

Crockett D; Bilsker D  
Biofeedback Self Regul (United States) Dec 1984, 9 (4) p431-8

The biofeedback-assisted treatment of a case of Raynaud's syndrome was examined in order to determine the relationship between learning of the hand-warming response and the subsequent ability to produce foot-warming responses. It was found that fluctuations in dermal hand and foot temperatures were not significantly related, either within or across treatment sessions. The obtained hand-warming response was of high magnitude and rapidly learned, while the foot-warming response was more modest and took substantially more trials to learn. These results indicate that an easy generalization of the hand-warming response cannot be assumed.

## **Behavioral treatment of Raynaud's phenomenon in scleroderma.**

Freedman RR; Ianni P; Wenig P  
J Behav Med (United States) Dec 1984, 7 (4) p343-53

Twenty-four patients with Raynaud's phenomenon and scleroderma were randomly assigned to receive finger temperature biofeedback, frontalis EMG biofeedback, or autogenic training. Only those receiving temperature feedback showed significant increases in finger temperature during training and during a posttraining test of voluntary control, effects not attributable to general relaxation. However, no group demonstrated significant clinical improvement, assessed by symptom reports and by ambulatory monitoring of finger temperature. The need for careful classification of patients with Raynaud's disease and Raynaud's phenomenon in scleroderma is emphasized.

## **Biofeedback, autogenic training, and progressive relaxation in the treatment of Raynaud's disease: a comparative study.**

Keefe FJ; Surwit RS; Pilon RN  
J Appl Behav Anal (United States) Spring 1980, 13 (1) p3-11

Twenty-one female patients suffering from diagnosed idiopathic Raynaud's Disease were trained to raise digital skin temperature using either autogenic training, progressive muscle relaxation, or a combination of autogenic training and skin temperature feedback. Patients were instructed in the treatment procedures in three one-hour group sessions spaced one week apart. All patients were instructed to practice what they had learned twice a day at home. Patients kept records of the frequency of vasospastic attacks occurring over a four-week baseline period, and during the first four weeks and the ninth week of training. In addition, patients underwent four laboratory cold stress tests during which they were instructed to maintain digital temperature as the ambient temperature was slowly dropped from 26 degrees to 17 degrees C. Cold stress tests were given during week 1 of baseline and during weeks 1, 3, and 5 of training. No significant differences between the three behavioral treatment procedures were obtained. In addition, the ability of patients to maintain digital temperature during the cold stress challenge showed significant improvement from the first to the last tests. Symptomatic improvement was maintained by all patients nine weeks after the start of training. The implications of these findings for the behavioral treatment of Raynaud's Disease are discussed.

## **Behavioral approaches to Raynaud's disease.**

Surwit RS  
Psychother Psychosom (Switzerland) 1981, 36 (3-4) p224-45

No abstract.

## **A 1-year follow-up of Raynaud's patients treated with behavioral therapy techniques.**

Keefe FJ; Surwit RS; Pilon RN

J Behav Med (United States) Dec 1979, 2 (4) p385-91

The purpose of this study was to assess to what degree learned control of digital temperature and vasospastic attacks can be retained by Raynaud 's patients over a full year period. Subjects were 19 patients suffering from diagnosed idiopathic Raynaud 's disease who had undergone behavioral training. These patients had been trained to increase digital temperature using either autogenic training , biofeedback , or a combination of autogenic training and temperature biofeedback . Results indicated that the mean number of vasospastic attacks per day occurring 1 year after training was approximately equal to the number occurring at the end of the initial training (1.2-1.3 per day). Patient satisfaction with the treatment program was above average (3.5 on a 5-point scale). The patients' ability to maintain digital temperature during the cold stress challenge was impaired, however. At 1-year follow-up, digital temperature readings taken in the laboratory were identical to baseline levels.

## **Behavioral treatment of Raynaud's disease.**

Surwit RS; Pilon RN; Fenton CH

J Behav Med (United States) Sep 1978, 1 (3) p323-35

In order to assess the efficacy of a behavioral intervention in the treatment of idiopathic Raynaud's disease, 30 female patients were trained to control their digital skin temperature using autogenic training or a combination of autogenic training and skin temperature feedback either in the laboratory or at home. All trained subjects demonstrated a significant ability to maintain digital skin temperature in the presence of a cold stress challenge and reported significant reductions in both frequency and intensity of vasospastic attacks. The addition of skin temperature feedback to autogenic training did not provide additional clinical benefit.

## **Long-term effectiveness of behavioral treatments for Raynaud's disease**

Freedman R.R.

Lafayette Clinic, Wayne State University, Detroit, MI 48207 United States

Behavior Therapy (United States) 1987, 18/4 (387-399)

Raynaud 's disease is characterized by episodic digital vasospasms of unknown etiology. Although surgical and pharmacologic treatments have been problematic, behavioral procedures have shown considerable efficacy. Temperature biofeedback reduces reported symptom frequency and enables patients to voluntarily increase finger temperature and capillary blood flow for 1 year after treatment. Symptomatic improvement persists for up to 3 years. This procedure is mediated by a nonneural beta-adrenergic vasodilating mechanism rather than through physiological relaxation. Relaxation-based procedures, such as autogenic training , produce smaller symptom reductions at one-year follow-up with no retention of physiological effects. The effects of classically conditioned vasodilation are retained for 1 year in normal persons and may be of value in the treatment of Raynaud 's disease.

## **Biofeedback training in clinical cardiovascular disease**

Surwit R.S.

Dept. Med. Psychol., Duke Univ. Med. Cent., Durham, N.C. United States

Primary Cardiology (United States) 1980, 6/9 (34-48)

Biofeedback mechanisms have been shown to be effective in treating mild hypertension. Various forms include binary feedback training to lower blood pressure and heart rate, analogue feedback to control forearm and frontalis electromyographic activity, and meditation-relaxation procedures. The simple technique of having the patient take his own blood pressure and consciously attempt to lower it by whatever mechanism he can is quite effective. Thermal feedback training to control migraine headaches and Raynaud 's disease has been successful. Autogenic training to control skin temperature is also an effective instrument.

## **[Esophageal motor abnormalities, gastroesophageal reflux and duodenogastric reflux in patients with Raynaud's disease]**

Pucciani F; Bechi P; Pantalone D; Panconesi R; Paparozzi C; Pagliai P; Cortesini C  
Clin Ter (Italy) Dec 31 1989, 131 (6) p373-80

Twenty-four patients with Raynaud 's phenomenon, without ARA criteria for classification, were examined, after clinical history, by means of esophageal manometry, combined gastric and esophageal pH-monitoring, endoscopy. The results showed in these patients a high incidence of esophageal motor abnormalities (66.6%), of gastroesophageal reflux (50%), and of duodenogastric reflux (45.8%).

## **[Clinical studies on various therapy for the intractable trauma of toes and fingers in cases of diabetes mellitus and peripheral ischemic diseases]**

Kuyama T; Umemura H; Sudo T; Kawamura M; Shobu R; Tsubakimoto R; Nishimoro A  
Second Department of Surgery, School of Medicine, Kinki University, Osaka, Japan.  
Nippon Geka Gakkai Zasshi (Japan) May 1988, 89 (5) p763-70

In cases of ischemic extremities and diabetes mellitus, the trauma on finger and toe is very intractable. For such injuries amputation of extremity is indicated very often because of severe necrosis. The number of such cases has been increasing recently because many cases of these patients have arteriosclerotic arterial occlusion and diabetes mellitus, and these are correlated with the changes of aging. The number of cases of Buerger's disease has been also increasing and it is another etiology of intractable trauma in ischemic extremity. The repeated hyperbaric oxygenation, sympathetic block, warfarin therapy and insulin bath with bubbling of hyperbaric oxygen , were applied to has been of such necrosis. By these procedures, the rate of amputation of extremity decreasing. It was concluded that the surgical reconstruction of artery for ischemic extremity has never any meaning as the therapy of such intractable injuries, if blood flow in the peripheral tissue is not kept physiologically, before vascular reconstruction. In order to increase peripheral tissue circulation, the hyperbaric oxygenation, sympathetic block and warfarin therapy wer performed in many cases and these methods were very effective for intractable injuries with severe necrosis.

## **'Phenomenon of hyperbaric accumulation of venous partial pressure of oxygen' concerning the hyperbaric therapy and lumbosacral sympathetic ganglionectomy Linf 2 and Linf 3 for healing of incurable wounding in patients with periphery circulatory disturbances**

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II Dept. Surg., Kinki Univ. Sch. Med., Osaka Japan  
Acta Medica Kinki University (Japan) 1976, Vol. 1/- (1-16)

The authors reported the results of the hyperbaric therapy for patients with the disease which may have a genetic origin in part, namely certain forms of cancer and L.E.Raynaud 's syndrome, and furthermore, thromboangiitis obliterans which have a unclear origin and in addition Raynaud 's syndrome, chronic stage of arteritis luetica and ulcus cruris. The clinical results, finding, interpretations and implications are discussed. The phenomena of hyperbaric accumulation of venous partial pressure of oxygen are described and the authors supposed that wound healing of ischemic ulcers caused by successive hyperbaric oxygenation were due to subepithelial and in granulations of ulcers revascularity of capillaries. The above facts were assumed on the basis of the clinical results of thermocamera, optical pulse wave calculation and plasma ultra-centrifugation lipoprotein fraction, relating with decrease in sympathetic irritation.

## **Micronutrient antioxidant status in patients with primary Raynaud's phenomenon and systemic sclerosis.**

Herrick AL; Rieley F; Schofield D; Hollis S; Braganza JM; Jayson MI

**OBJECTIVE.** To investigate the possibility that micronutrient antioxidant status is an important factor in determining the severity of Raynaud 's phenomenon (RP) and in differentiating between patients with primary Raynaud 's phenomenon (PRP) and those in whom Raynaud 's is secondary to systemic sclerosis (SSc).

**METHODS.** Four micronutrient antioxidants (selenium, vitamin E , beta-carotene and ascorbic acid) and 2 "markers" of free radical associated activity were assayed in peripheral blood from 10 patients with PRP, 9 with limited cutaneous SSc (ISSc), 9 with diffuse SSc (dSSc) and 15 healthy control subjects.

**RESULTS.** Plasma ascorbic acid was reduced in all 3 groups of patients: median level 10.6 mg/l in controls, 4.8 mg/l in PRP ( $p < 0.01$ ), 2.5 mg/l in ISSc ( $p < 0.01$ ) and 6.8 mg/l in dSSc ( $p < 0.05$ ). A reduction in serum selenium was especially found in dSSc (median 75 micrograms/l compared to 100 micrograms/l in controls,  $p < 0.05$ ). In keeping with these deficiencies, the serum concentration of 9, 11, linoleic acid was elevated in RP patients: median values for the molar ratio of the isomer to the parent fatty acid were 1.91% in controls, 3.70% in ISSc ( $p < 0.05$ ) and 3.85% in dSSc ( $p < 0.01$ ). Smoking patients showed lower levels of ascorbic acid and higher levels of the linoleic isomer than nonsmokers.

**CONCLUSION.** Deficiencies of ascorbic acid and selenium may predispose towards irreversible tissue injury in RP patients and cigarette smoke may be an independent risk factor. Micronutrient antioxidant supplements may be of therapeutic value.

## **[Thermographic assessment of Raynaud's phenomenon in childhood mixed connective tissue disease]**

Yokota S; Kuriyama T; Takahashi Y; Mori M; Shike H; Ibe M; Mitsuda T; Aihara Y  
Department of Pediatrics, Yokohama City University School of Medicine.  
Ryumachi (Japan) Dec 1994, 34 (6) p955-60

To assess Raynaud 's phenomenon objectively, thermographic estimation of hands and fingers was performed before and after the disease- and Raynaud 's phenomenon-directed therapy in 3 children with mixed connective tissue disease. All the cases were positive in Raynaud 's phenomenon, and the surface temperature of their hands and fingers were decreased even before cold challenge. After the cold provocation test at 4 degrees C for 10 sec., the temperature of all or some of the fingers were rapidly decreased, and the recovery of surface temperature of these fingers were markedly delayed. Even after methylprednisolone pulse therapy the pattern of the finger temperature were essentially unchanged, suggesting that steroids are not effective in the treatment of Raynaud's phenomenon. The long-term administration of vitamin - E , oral prostaglandin E1, and/or serotonin-receptor inhibitor were also proved to be not beneficial in improving Raynaud 's phenomenon. Thus, thermography is useful in diagnosing Raynaud 's phenomenon objectively, in determining the efficacy of anti-Raynaud drugs, and in estimating long-term course of the phenomenon.

## **Is vitamin E involved in the autoimmune mechanism?**

Ayres S Jr; Mihan R  
Cutis (United States) Mar 1978, 21 (3) p321-5

Autoimmune diseases are characterized by an alteration of the body's defense mechanism, designed for protection against infections and toxic injuries, which for unknown reasons attacks and destroys normal tissue. Some evidence strongly suggests that such diseases are the result of hydrolytic enzymes that escape from lysosomes whose membranes have been damaged by lipid peroxidation or other causes and that combine with and denature normal tissue proteins--in effect converting them into foreign proteins--to which the body then reacts by producing antibodies. During the past ten years, in a private dermatologic practice, we have conducted clinical investigations on the possible therapeutic value of vitamin E in the management of a number of disabling skin diseases of unknown etiology as well as several muscular disorders. Among the diseases that were successfully controlled were a number in the autoimmune category, including scleroderma, discoid lupus erythematosus, porphyria cutanea tarda, several types of vasculitis, and polymyositis. Since vitamin E is a physiologic stabilizer of cellular and lysosomal membranes, and since some autoimmune diseases respond to vitamin E , we suggest that a relative deficiency of vitamin E damages lysosomal membranes, thus initiating the autoimmune process.

## **Comparative double-blind trial of dl-alpha-tocopheryl nicotinate on vibration disease.**

Matoba T; Kusumoto H; Mizuki Y; Yamada K  
Tohoku J Exp Med (Japan) Sep 1977, 123 (1) p67-75

Sixty inpatients with vibration disease were examined on the effect of dl-alpha-tocopheryl nicotinate by comparative double-blind study. The observed period was 6 weeks and the dose was 6 capsules a day (600 mg as dl-alpha-tocopheryl nicotinate, Juvela Nicotinate, referred to as EN). The physical exercise therapy was applied to all patients throughout the test period. EN group became better with a significant difference from P (placebo) group in the subjective symptoms, the clinical examinations and the collective improving rate ( $p$  less than 0.01, 0.05, 0.01), respectively. The improvement of the subjective symptoms of both groups was higher 6 weeks than 3 weeks after administration. Most items in EN group became better significantly ( $p$  less than 0.05) as compared with those in P group. The examinations of the peripheral functions in EN group showed a significant improvement 6 weeks after administration in comparison with those in P group. Blood chemistry, blood cell counts and serum electrolytes changed within normal range. Thus, this preparation would be a curative agent for patients with vibration disease.

## **[The effect of dimethyl sulfoxide on the thromboelastographic indices and the microcirculation in patients with rheumatic diseases]**

Murav'ev IuV; Loskutova TT; Anikina NV; Shcherbakov AB; Sokolov VB  
Ter Arkh (USSR) 1989, 61 (12) p106-9

Using a blind method for assessing the results, a study was made of the effect of dimethylsulfoxide (DMSO) on fibrin formation and microcirculation in 42 patients with rheumatic diseases (rheumatoid arthritis, systemic scleroderma, Raynaud 's syndrome). It has been shown that the therapeutic effect of DMSO in rheumatic diseases is determined to a definite degree by its normalizing action on fibrin formation and microcirculation.

## **Pathophysiology of capillary circulation: Raynaud's disease.**

Arnot RS; Boroda C; Peacock JH  
Angiology (United States) Jan 1978, 29 (1) p48-52

Despite the frequency of Raynaud 's disease in cold climates, the etiology of the condition remains uncertain. This report reviews the literature since Raynaud 's original description and Lewis and Pickering's addition to the concept, and several recent observations which add to our understanding of the disease are discussed. We investigated the effect of posture and a vasodilator drug on the digital capillary circulation; digital blood flow increases as the body moves from a recumbent, through a sitting, to an upright position. Bradilan, a vasodilator drug, increases the circulation in the recumbent and sitting positions, but has no effect in standing patients, despite symptomatic relief.

## **Vasodilator drugs in peripheral vascular disease**

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New England Journal of Medicine (United States) 1979, 300/13 (713-717)

In vasospastic diseases, vasodilator drugs that act upon the sympathetic nervous system may have a beneficial effect in many patients by increasing cutaneous capillary blood flow. These agents may decrease persistent vasospasm or the number and intensity of attacks in Raynaud 's phenomenon but usually do not produce complete relief. Full benefit is often prevented by unpleasant and sometimes severe side effects that limit dosage. Reserpine or guanethidine is the drug of choice; tolazoline long-acting tablets are added when further relief is needed. Papaverine, niacin, isoxsuprine and cyclandelate are representative of vasodilator drugs that directly relax vascular smooth muscle. When administered by mouth, these drugs are not potent peripheral vasodilators, and it may be concluded that they are not of value in the treatment of peripheral vascular diseases. Review of the clinical studies of vasodilator drugs in obstructive vascular disease reveals little substantive evidence to support their use. They are not effective in the treatment of either intermittent claudication or ischemic symptoms or signs at rest. They fail to increase blood flow in most patients with ischemic limbs, even when administered locally by the intra-arterial route. No drug has been shown to

increase muscle blood flow during exercise when patients with intermittent claudication experience symptoms.

## **Treatment of the Raynaud's phenomenon with piracetam.**

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Arzneimittelforschung (Germany) May 1993, 43 (5) p526-35

Piracetam (Nootropil, CAS 7491-74-9) has been investigated in the treatment of primary and secondary Raynaud 's phenomenon in three sequential and complementary studies. The first study in 20 patients with primary Raynaud 's phenomenon, utilising clinical and ultrasound examination, capillaroscopy and laboratory tests established a daily dose of 8 g as most effective. The second study in 58 patients (47 primary, 11 secondary) confirmed the therapeutic efficacy of piracetam in both primary and secondary Raynaud 's phenomenon. The third study, of crossover design, in 30 patients with severe Raynaud 's syndrome, examined various agents given singly or in combination. The results not only confirmed the efficacy of piracetam but in addition allowed comparison of the efficacy of the principal therapeutic agents or regimens used in the treatment of Raynaud 's syndrome and the formulation of a list of these therapies in decreasing order of efficacy, thus: piracetam 4 g/d + buflomedil 600 mg/d; piracetam 8 g/d; buflomedil 600 mg/d; piracetam 4 g/d + acetylsalicylic acid 100 mg/d; pentoxifylline 1200 mg/d; calcium antagonists; ketanserin 120 mg/d. The particular efficacy of 8 g piracetam daily in 3 divided doses at 8-hourly intervals can be attributed to its unique dual mode of action; inhibition of platelet function by inhibition of thromboxane A2 synthetase or antagonism of thromboxane A2 and increased formation of prostaglandin I<sub>2</sub>, together with a rheological effect involving reduction in blood and plasma viscosity through an increase in cell membrane deformability and a reduction of 30-40% in the plasma concentrations of fibrinogen and von Willebrand's factor. In addition, the administration of piracetam appears to be devoided of adverse effects.

## **Comprehensive management of Raynaud's syndrome**

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Clinics in Plastic Surgery (United States) 1997, 24/1 (133-160)

Raynaud 's syndrome stands as a landmark to our ignorance of the mechanisms involved in the interrelationship of the central nervous system and peripheral circulatory physiology. Proper management for these unfortunate patients demands an integrated comprehensive effort of the pharmacologic, physical medical, and surgical disciplines.

## **Raynaud's phenomenon in the emergency department**

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Journal of Emergency Medicine (United States) 1995, 13/3 (369-378)

Raynaud 's phenomenon manifests as triphasic color changes of the digits, induced by exposure to low temperature or emotional stress. It is a relatively common disorder, estimated to affect 5% to 10% of the general population and 25% to 30% of otherwise healthy women. Although usually self- limiting, it can be severely painful and debilitating, and complicated by ulcerations and tissue necrosis. For the emergency physician treating a patient with an acute presentation of the phenomenon, the main challenges are to achieve adequate pain control, reverse vasospasm, and maintain viable tissue. Emergency treatment can also extend to patient education and arrangement of appropriate referrals and follow-up care.

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