

# Temperature-associated vascular disorders: Raynaud's phenomenon and erythromelalgia.

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## INTRODUCTION

*We are too much accustomed to attribute to a single cause that which is the product of several, and the majority of our controversies come from that. Baron Justus von Leibig (1803-73)*

Superficially, Raynaud's phenomenon, a disease associated with cold, and erythromelalgia, a warmth related disorder, could be considered the antithesis of each other. However, both these microcirculatory disorders, first described in the second half of the nineteenth century, have many features in common and, indeed, may share the same etiology, that is microvascular ischemia. The complicated structure that is the microcirculation can produce a variety of responses to a single noxious stimulus with sensations of cold and heat at opposite ends of the spectrum. In this chapter Raynaud's phenomenon and erythromelalgia -are compared and contrasted so that the correct diagnosis of 'these conditions and appropriate remedy can be selected by the clinician.

## Raynaud's Phenomenon

Maurice Raynaud first defined the syndrome which bears his name 133 years ago.<sup>1</sup> He described episodic digital ischemia provoked by cold and emotion. It is classically manifest by pallor of the affected part followed by cyanosis and rubor. Vasospasm in the digital vessels leads to the pallor (Fig. 22.1). The subsequent static venous blood leads to the development of cyanosis. The rubor is caused by hyperemia after the return of blood flow. Raynaud's phenomenon (RP) can be a benign condition but, if severe, can cause digital ulceration and gangrene. It is nine times more common in women than in men and has an overall prevalence in the population of approximately 10%, although it may affect as many as 20-30% of women in the younger age groups.<sup>2</sup> There is also a familial predisposition which is more marked if the age of onset is less than 30 years.<sup>3</sup> Until recently little was known about the true etiology and the extent of the disorder. This lack of knowledge has led to difficulties in the treatment and prediction of prognosis in RP. Several aspects relating to these points must be addressed to enable the clinician to provide good quality management of the RP patient.

Raynaud's original definition itself now requires significant modification, for example, the full triphasic color change is not essential for the diagnosis of RP as a history of cold-induced digital blanching with subsequent reactive hyperaemia can still reflect significant vasospasm. Furthermore, stimuli other than cold and emotion can provoke an attack, for example, chemicals including those in tobacco smoke,<sup>4</sup> hormones<sup>5</sup> and trauma. The recent advances which have been made in the understanding of the extent of RP, its etiology and progression, have all contributed to the better management of the patient with vasospasm.

## THE SYSTEMIC NATURE OF VASOSPASM

Raynaud's phenomenon is recognized clinically by the characteristic color changes in the fingers and toes. Similar findings are also observed in the earlobes and the tip of the nose. Recently 'systemic' vasospasm has been reported. Raynaud's phenomenon has been associated with migraine headaches and cerebral artery spasm.<sup>6</sup> Vasospasm in the lungs has been documented following a reduction in the lung diffusion capacity after the induction of digital vasospasm by a cold challenge.<sup>7</sup> Coronary artery spasm<sup>8</sup> may also be secondary to vasospasm in these patients, where myocardial perfusion

measurements in subjects undergoing a cold pressor test showed that the majority of severely affected RP patients had a reversible cold-induced perfusion defect. Raynaud's phenomenon of the intramural vessels of the heart has been suggested as a cause of the myocardial contraction band necrosis seen in RP associated with connective tissue disorders (CTDs). Furthermore, it has been estimated that over three quarters of the patients with RP and the CTD systemic sclerosis (SSc) have symptoms relating to their oesophagus.<sup>9</sup> In about 50% physical abnormalities such as stricture and achalasia are present but in the rest, and in other patients with RP and esophageal symptoms, no abnormality can be detected by barium swallow, endoscope, manometry or pH testing. Recently, esophageal vasospasm has been detected, a cold challenge to the esophagus producing a delay in the rewarming time in patients with RP.<sup>10</sup> A thickened sclerosed esophagus might also have contributed to these findings however, as it may be expected to rewarm more slowly than healthy vascularized tissue, although a thickened esophagus could not explain the abnormalities seen in Raynaud's disease (RD) where normal tissue would be expected.

With this evidence of vasospasm in the heart, lung and esophagus it is interesting to speculate that abnormalities of the vasculature may exist throughout the entire patient. These abnormalities may contribute to the wide spectrum of symptoms seen in RP such as preclampsia, infertility, hypertension and impotence, and must be considered by the clinician concerned with the management of RP (Fig. 22.2).

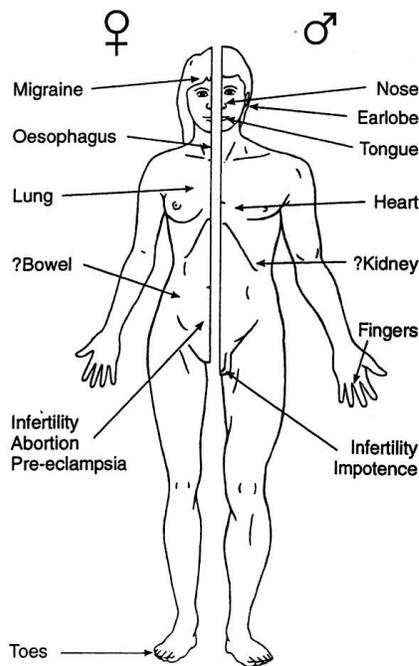


Fig. 22.2 The systemic nature of vasospasm.

## **CLASSIFICATION OF RAYNAUD'S PHENOMENON**

One of the main problems for the clinician involved in the management of RP has been the inconsistent terminology used to describe Raynaud's attacks. Raynaud's phenomenon is the general term used to describe cold related digital-vasospasm. It is subdivided according to the presence or absence of an associated disorder: Raynaud's syndrome (RS), if there is, and primary Raynaud's disease (RD), if there is not. This European classification is not globally accepted, however. In Australia and in the United States of America phenomenon and syndrome tend to be used interchangeably making assessment of the literature difficult. A further complication has been identified from long-term studies which have shown that RP may be the precursor of systemic illness by over 20 years.<sup>11</sup> Whilst the majority of patients who present to general practitioners have primary RD, recently developed sensitive laboratory procedures have shown that over 50% of the patients referred to hospital have an associated systemic disease, i.e. RS.<sup>12</sup> The conditions associated with RS are listed in Table 22.1. The best recognized of these being the CTDs and RS of occupational origin.

Raynaud's syndrome is found in the majority of patients with SSc and mixed connective tissue disease (MCTD) and also in patients with systemic lupus erythematosus, Sjogren's syndrome and polymyositis and dermatomyositis. Raynaud's syndrome occurs in rheumatoid arthritis and hyperviscosity syndromes in a percentage similar to that seen in the normal population (10%); however, the symptoms tend to be more severe.

Workers exposed to polyvinylchloride (PVC) can develop RP of occupational origin and vasospasm can occur in ammunition workers outside their place of work when the vasodilatory effects of the nitrates are removed. Vibration white finger disease (VWF) is the most common form of occupational RS.<sup>13</sup> As its name suggests, VWF occurs in workers exposed to vibrating machines such as chainsaws, pneumatic grinders and buffs. It is estimated that about half of all workers using vibrating equipment can develop RS although resolution of the symptoms may occur in 25% of cases if a job change is effected early in the course of the disease, i.e. before Grade 2 on the Taylor Pelmear Scale of classification.<sup>14</sup> Clinicians previously thought that hands only were affected in this form of RP. However, VWF has recently been described as affecting both fingers and toes.<sup>15</sup>

The development of occupational RP can also be associated with the long-term exposure to cold in the absence of vibration and is said to occur in 14% of men working outdoors. Furthermore, about 50% of the workers who frequently rewarm their fingers after filleting frozen fish develop RP.<sup>16</sup> The greater frequency of rewarming produces larger differences in temperature and thus more tissue damage and this probably contributes to the increased instance of RP seen in this latter group of workers.

Many, other conditions are associated with RS. The challenge in the management of this condition is not in making the diagnoses of vasospasm but rather in differentiating between primary Raynaud's disease and secondary Raynaud's syndrome and, possibly more important, detecting early those who may progress to the development of such an underlying condition.

## **THE DIAGNOSIS OF RAYNAUD'S PHENOMENON**

A well-structured plan of investigation is important for the good management of these patients. As they present to a variety of hospital specialists such as vascular surgeons, rheumatologists and dermatologists, investigations may be polarized towards the particular interest of the doctor concerned. Thus, although the rheumatologist may be expert at diagnosing associated early CTD she or he may miss an embolic cause from a subclavian artery stenosis or aneurysm. The opposite is of course true for the vascular surgeon. The adoption of a management protocol which outlines sensible investigations of RP by all workers in the field no matter what their core specialty would greatly benefit the patient with RP.

## **Table 22.1 Conditions associated with Raynaud's phenomenon**

### Immunological

Systemic sclerosis (90%)  
Mixed connective tissue disease (85%)  
Systemic lupus erythematosus (10-44%)  
Sjogren's syndrome (33%)  
Dermatomyositis/polymyositis (20%)  
Rheumatoid arthritis (10-15%)  
Cryoglobulinaemia (10%)  
(%: Percentage of patients with disease who have RP.)

### Obstructive

Atherosclerosis (especially thromboangiitis obliterans)  
Thoracic outlet syndrome (e.g. cervical rib) Embolus

### Occupational

Vibration white finger disease  
Vinylchloride disease  
Frozen food packers  
Ammunition workers (outside work)

### Other

Malignancy  
Endocrine (e.g. hypothyroidism)  
Reflex sympathetic dystrophy  
Arteriovenous fistula  
Hepatitis B  
Uraemia

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In the majority of cases the diagnosis of RP can be made from the clinical history. Blanching is necessary to make the diagnosis and those patients who do not exhibit blanching but merely report cyanosis after exposure to cold have acrocyanosis. Although closely related to RP the site of the spasm is usually in the postcapillary venules. Thus, a history of digital blanching on exposure to cold plus or minus cyanosis or rubor in the absence of clinical evidence of obstructive vascular disease allows the diagnosis of RP to be made. It is only rarely that objective measures of blood flow are needed, e.g. when the patient is unable to give a clear history, or in the presence of occlusive vascular disease when the contribution of vasospasm to the clinical problem needs to be determined. Significant occlusive vascular disease above a brachial artery is most easily detected in the clinic by measuring the blood pressure in both arms. If the systolic pressure of one arm is significantly lower than the other (iÜ 15 mmHg difference) then there may be occlusive disease in that limb. If both appear low then formal blood flow measures should be carried out.

There are many different techniques which can be used to measure blood flow to the digits, however, satisfactory standards of measurement have not yet been adequately established due to their variation in healthy individuals, especially after a cold challenge. In clinical practice, measurement of digital systolic blood pressure following local cooling of the hand in cool water at a temperature of approximately 15iãC is widely used due to its simplicity. A drop in the pressure of more than 30 mmHg is usually significant.<sup>17</sup> This technique, however, will give a significant number of false negatives unless the following five precautions are observed:

1. The patient must be warm and vasodilated prior to the first pressure recordings. Superficially this

appears obvious but many patients who had cold hands at the start of their tests have been told that they did not have RP when no further pressure drop was detected after cold challenge. Obviously if vasoconstriction is already present only a small fall can occur after the cold challenge. The starting digital pressures must be as near brachial pressure as can be achieved. The best way to obtain this is by leaving the patient to acclimatize in the laboratory for a period of 30 minutes. If in doubt the rubber gloved hand can be rewarmed in water at a temperature of about 34°C.

2. Poor flow prior to the start of the test can also occur at the time of ovulation in women.<sup>5</sup> Assessment should be avoided mid cycle in premenopausal women.

3. Excessive vasodilation can also lead to a failure to detect a pressure drop. The most common source of error here is to see the patient at the clinic, start treatment, for example, with a calcium channel antagonist, and complete a card for later vascular assessment. Some patients respond so well to treatment that a significant drop in pressure cannot be obtained whilst on this treatment. All vasoactive medication should be stopped 24 h prior to testing, should such testing be considered necessary.

4. Additionally, if the patient comes in from a warm environment the body itself is warm and this protects the patient from developing vasospasm if digital cooling is used in isolation. Body cooling is one way of avoiding this problem. Unfortunately, this facility is not available everywhere but one should avoid testing on hot days.

5. Occasionally, the patient will present at the laboratory with hot burning hands, a Raynaud's attack having occurred during travel to the hospital and the patient then being in the reactive hyperaemic phase. Tests carried out at this time will also fail to produce a significant pressure drop as the cold challenge cannot overcome the chemically induced vasodilatation. Ideally, patients should not have had a vasospastic attack on the day of the test. In practice, this can be difficult to achieve and allowing 2-3 h to elapse between events may be sufficient.

The digital systolic blood pressure measurement: can be made using strain gauge plethysmography. In this method a finger cup with a small tubular outlet serves as the plethysmograph and encloses the terminal phalanx of the finger. This is connected to a pressure transducer to measure changes in the fingertip volume on a recorder. If proximal digital venous occlusion is applied the fingertip swells and the size to which it swells is proportional to the arterial inflow and the accumulation of blood in the fingertip is measured. The initial slope of the curve is assumed to represent arterial inflow. If the occlusion cuff pressure is raised to the point that pulsatility disappears digital systolic blood pressure can be measured. The disadvantages of the test are that considerable skill on the part of the operator is required, its measurement is discontinuous so that it cannot assess changes in flow, and in finger with fibrosed subcutaneous tissue as in the CTDs there is little vascular space to fill and blood flow or even pulsatility can be difficult to measure. Conversely, the technique is also inadequate for measuring high blood flow as the finger fills so quickly that the slope of the curve is difficult to quantify. Photoplethysmograph can also be used here and with the advent of more sophisticated and sensitive Doppler ultrasound equipment some workers now find it possible to measure the pressure at which the return of flow occurs by this method. No matter which technique is employed, the measurement of digital systolic blood pressure after a moderate cold challenge is the most widely employed method of assessment.

Radioisotope clearance methods where the patient is given an injection of a radioactive preparation over the area of measurement can also be used. The emitted radiation is measured by a detector focused on the injected spot. The radioactive tracer will be washed out by blood flow leading to an exponential decline of the radioactivity intensity which can be transformed into an estimate of blood perfusion. A varying injection depth and tissue damage caused by the injection are, however, potential sources of error. Additionally, the method is costly and it cannot be adequately used with a cold challenge unless a different digit is used and the procedure is of necessity invasive.<sup>17</sup>

Thermography uses skin temperature as an indication of finger blood flow. However, skin temperature

is not only dependent on blood flow but also receives a contribution from venous and arterial blood. Furthermore, the equipment is expensive and although noninvasive it is unreliable in unskilled hands. Additionally, it requires a temperature-controlled environment for optimal results.

Laser Doppler flowmetry has become popular for evaluating skin microcirculation.<sup>18</sup> The nature of the signal detected is related almost exclusively to the velocity and number of moving red blood cells. Measurement occurs directly and continuously with a short response time and it is a non-invasive technique. This makes it ideally suited for measuring changes in microcirculatory flow. The same precautions apply to this technique as for the digital systolic blood pressure estimation however, and furthermore the results can be difficult to interpret as the depth of penetration of the laser light means that the results will include some contribution from the arteriovenous anastomotic blood flow. As with thermography a temperature-controlled environment is required.

Each of the above techniques, apart from the first require sophisticated equipment and although they can be usefully employed in RP there are numerous drawbacks. Unless one is involved in clinical trials where accurate assessment of flow is required, measurement of the digital systolic blood pressures before and after cold challenge is usually sufficient.

## **ETIOLOGY**

Once the diagnosis of RP is confirmed a search for its etiology is then required. As RP is a common condition such a program should be simple, relatively cheap, sensitive and non-invasive. A detailed history is essential. Those with an obvious associated disorder will be easily detected but difficulties arise in diagnosing early CTD or predicting those likely to progress to CTD. Gifford and Hines<sup>18</sup> carried out one of their earlier studies into disease progression. In a study of 6229 RP patients over the age of 28 years progression to CTD occurred in 24%. Another early study<sup>20</sup> suggested a figure of 50%. Both these studies, however, were published prior to 1950 and since then there has been an increasing awareness that RS may be much more common than previously thought. At present, the frequency with which secondary conditions are recognized varies widely with reported studies and may depend in part on the thoroughness with which a search for an associated disorder is undertaken, on the development of the RP at the time seen, and on clinician referral patterns. This latter aspect is clearly illustrated by Edwards and Porter.<sup>21</sup> In 1976 the authors reported an incidence of RS of 81% in their population of 100 RP patients. By 1988 the study population had grown to 615 patients but the percentage of those with RS had fallen to 46. The authors commented that in early years of their studies the patients were only referred if severely symptomatic. As the authors' interest in RP became more widely recognized, more patients with milder symptoms were referred.

The early detection of CTD in a patient with RP can be difficult but recently more clearly defined pointers have been described which have strong links with disease progression and are important when managing the patient with RP. There are three areas which can prove useful: (1) clinical features; (2) microscopic nailfold examination; and (3) laboratory tests.

### **Clinical features**

The occurrence of certain clinical features may suggest a higher likelihood of disease progression (Table 22'.2). The American Rheumatism Association (ARA) criteria for the various CTDs have a high specificity but low sensitivity for the disease.<sup>22</sup> Thus patients who present with isolated features of CTD will not fulfill the ARA criteria; nevertheless these RP patients are more likely to develop a CTD than those without such symptoms.<sup>12</sup> Of these the most sensitive is digital ulceration which in the absence of trauma or some other unusual occurrence is strongly linked to later CTD development. Sclerodactyly and pitting scars over the finger pulp are also associated with later CTD development. Thus any features of CTD occurring in association with RP should alert the clinician.

The age of onset of RP may also be important. Raynaud's phenomenon is a frequent finding in young women in their teens and twenties and most have primary RD.<sup>2</sup> Those presenting for the first time in their third and fourth decades are at risk of developing RS.<sup>23</sup> In patients with RP onset at age 60 years or above 80% will have an associated disorder, though in this older age group the majority of cases are secondary to atherosclerosis.<sup>24</sup> Conversely, RP occurring in very young children, though rare, is usually due to an underlying CTD.<sup>25</sup> It is also of interest that those patients who do develop the CTD SSc are much more likely to develop limited SSc (calcinosis, Raynaud's, oesophagitis, sclerodactyly, telangiectasia, CREST) if the history of the preceding RP spans many years. Those presenting with SSc within a year of onset of RP tend to have diffuse SSc (previously called progressive systemic sclerosis).<sup>26</sup> Other suspicious symptoms which should perhaps alert the clinician are the occurrence of chilblains in adults, the occurrence of severe attacks persisting throughout the summer months and an asymmetrical color change with a few digits involved initially. These also suggest RS as opposed to simple RD. Questions relating to the patient's occupation or cold exposure will often, particularly in men, allow a diagnosis of VWF to be made but it is important to remember that various 'female-associated' appliances can have similar effects on the microvasculature, these include machines such as floor polishers and industrial sewing machines. Drug history is equally important and it should be noted that even the cardioselective  $\beta$ -blockers produce a degree of peripheral vasoconstriction (Table 22.3).

### **Table 22.2 Features suggestive of progression to Raynaud's syndrome**

#### Clinical

Young children  
Older age of onset  
Recurrence of chilblains as adult  
Vasospasm all year round  
Asymmetrical attacks  
Digital ulceration or any isolated feature of CTD

#### Laboratory

Raised erythrocyte sedimentation rate  
Detection of antibodies  
Elevated von Willebrand factor antigen

#### Nailfold microscopy

Abnormal vessels

A full physical examination is of course essential, not only to assess the above but also to gauge the presence of obstructive vascular disease and search for signs of associated autoimmune conditions such as thyroid disease and vitiligo. Particular attention should be paid to the microscopic examination of the nail folds.

### **Table 22.3 Drugs which may cause Raynaud's phenomenon**

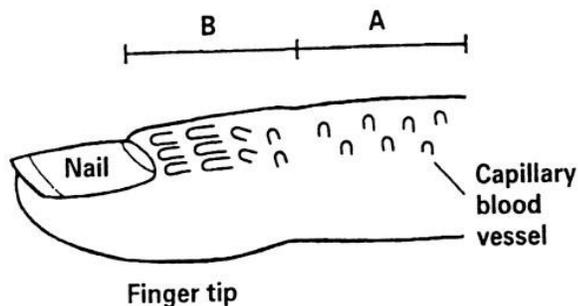
Ergotamines and other migraine therapies  
 $\beta$ -Blockers  
Cytotoxic drugs  
Cyclosporin  
Bromocriptine  
Sulphasalazine

### Microscopy of the nailfold vessels

Direct observation of the capillaries in human skin dates back to the early 1900s. Recent refinements have permitted photographic recordings of the rows of horizontal capillary loops at the nailfold just above the cuticle<sup>27</sup> but less sophisticated apparatus allows clinician to examine the nailfold vessels as part of her or his routine clinical workup. Using a simple ophthalmoscope at the highest power the nailfold can be visualized and abnormal vessels detected. Normally no vessels can be seen but patients with RP likely to progress to a CTD have abnormally dilated nailfold capillary loops (Fig. 22.3). Although detection of such vessels as one of the most sensitive markers for disease progression it should be noted that abnormal vessels can appear in other microangiopathic states such, diabetes mellitus and after trauma. It has been suggested, however, that when abnormal nailfold capillaries microscopy and positive serum antibody estimations are combined they can detect more than 90% of patients destined to have SSc.<sup>28</sup>

### Laboratory tests

Laboratory tests should include routine blood biochemistry including thyroid hormone levels as hypothyroidism is associated with RP. A full blood count should be carried out. A normochromic, normo- or microcytic anaemia of a chronic disorder can be found in RS, or an iron deficiency anaemia in a young woman which augments the symptoms of primary RD. A macrocytosis may reflect an associated autoimmune disorder. The erythrocyte sedimentation rate (ESR) or plasma viscosity are usually normal in RD but they may be elevated in RS. It should be noted however that there may be some impairment of the acute-phase response in SSC<sup>29</sup> resulting in a normal ESR or plasma viscosity. Urinalysis will help detect early renal disease in CTD or diabetes and a chest X-ray will determine whether a bony cervical rib is present or basal lung fibrosis which may be seen early in CTD. Care should be taken to remember that a fibrous cervical rib can still produce significant vascular occlusion and should be considered when the Raynaud's is associated with motor and sensory impairment.



- A – Vessels perpendicular, NOT visible on ophthalmoscopy
- B – Vessels becoming parallel. Visible if enlarged

**Fig. 22.3** Schematic representation of abnormal nailfold vessels.

Improvements in the techniques of antinuclear antibody determination have substantially increased the usefulness of this approach in RP. Whilst a mildly affected patient presenting to the general practitioner does not require testing, those patients severe enough to require consideration of a hospital referral should have them carried out. The core tests for RP of suspected immunopathological origin would be rheumatoid factor titre for detection of early rheumatoid arthritis, antinuclear antibody for systemic lupus erythematosus (anti-DNA antibodies are usually carried out in most laboratories automatically if the antinuclear antibody is positive), anticentromere antibody for limited SSc and antitopoisomerase antibody (formally scleroderma 70 antibody) for diffuse SSc.<sup>30</sup> For these latter two tests some laboratories may

simply screen for extractable nuclear antigens only, proceeding to no other assays if this produces a negative result. Whilst none of the above are entirely specific or indeed fully sensitive they provide a good framework for the early diagnosis of the rheumatic disorders. The presence of these antibodies early on in the RP suggests that later progression to RS will occur.<sup>31</sup>

Another test that may be of some use is to measure the endothelial product von Willebrand factor antigen (previously Factor VIII related antigen). Von Willebrand factor antigen is released in large quantities by damaged endothelium and therefore tends to be elevated in RS but normal in RD.<sup>32</sup> It may also have a predictive value in the evolution or regression of disease<sup>33</sup> although this still requires further evaluation in larger studies.

Both cryoglobulinaemia and cryofibrinogenaemia, where cold-precipitated proteins are detected, are very rare disorders. Although both allow the precipitation of large molecules in the cool digital circulation and thus can cause RP they should not be tested for during the initial screen unless there is a high index of clinical suspicion. These disorders occur only infrequently and the tests require special sample preparation at the time of blood letting. They should be considered in a patient with severe RP where all other tests have proven negative or where other clinical symptoms suggest the diagnosis.

Thus it can be seen that whilst the diagnosis of vasospasm itself should not be difficult, the investigations for an associated disorder are more complex. However, the importance of early detection of an underlying disorder cannot be underestimated. The diagnosis of a CTD has implications for future screening and follow-up in hospital outpatient clinics. The diagnosis of an occupational disorder may have important financial consequences for the patient in terms of compensation awards and progression of the disorder may be prevented by a change in occupation. Further lifestyle changes directed by the careful evaluation of an RP patient can also provide a significant benefit, e.g. the withdrawal of some anti-migraine drugs or  $\beta$ -blockers and their substitution with a vasodilating  $\beta$ -blocker or other alternative treatment.

Once the patient has been assessed as outlined, the majority of hospital-referred patients require some form of drug treatment. In order to direct such treatment, however, it is important to understand some of the etiological considerations of RP. There is no care for RP and understanding of the mechanisms required for amelioration of the symptoms can only be successfully devised if all the various components contributing to decreased blood flow are separated and evaluated.

## **PATHOPHYSIOLOGY OF VASCULAR SPASM**

There are three factors which should be considered as having etiological importance in RP: (1) neurogenic mechanisms, (2) blood and blood vessel wall interactions and (3) abnormalities of the inflammatory and immune responses.

### Neurogenic mechanisms

Maurice Raynaud believed that hyperreactivity of the sympathetic nervous system caused an increase in vasoconstrictor responses to cold,<sup>1</sup> whereas Lewis<sup>34</sup> hypothesized a 'local fault' in which precapillary resistance vessels were hypersensitive to local cooling. Most work has focused on the peripheral sympathetic nervous system. The alpha-adrenergic receptor sensitivity and/ or density is increased in RP.<sup>35</sup> Other studies have shown the pathophysiological role for the  $\beta$ -presynaptic receptors with an increase in the responsiveness in the nerve endings in the RS peripheral vessels.<sup>36</sup>

The role of the central sympathetic system is, however, less clear. Local vibration of one hand induces vasoconstriction of the other which is abolished by proximal nerve blockade. This suggests the existence of a central sympathetic vasoconstrictive mechanism.<sup>37</sup> In support of this concept is the fact that central sympathetic vasoconstriction induced by body cooling may produce vasospasm in the absence of local digital cooling. Other work does not support this concept however. Infusions of  $\alpha$  and  $\beta$ -adrenergic agonists in RD patients do not show any abnormalities in the responses to reflex cooling or indirect heating.<sup>38</sup> Thus, although abnormalities of the nervous system may exist in RP they are, at present, not clearly defined. Early work suggesting an autonomic dysfunction in RS<sup>39</sup> could not be substantiated by later work.<sup>40</sup>

An intriguing finding is one relating to a potential dysfunction of a calcitonin gene-related peptidedependent neurovascular axis. Calcitonin gene-related peptide (CGRP), a potent vasodilator, has been evaluated in a pilot study and results suggest that the quantity of CGRP-containing neurons

detected in the digital skin of RP patients may be decreased when compared with normal subjects.<sup>41</sup>

### **Blood and blood vessel wall interactions**

The above-described abnormalities of blood vessel tone cannot however explain all the features of RP. Flow in the microcirculation is critically dependent on the integrity of the endothelium and the various properties of the liquid and cellular elements of blood.

The endothelium is a functioning organ releasing important chemicals one of which is prostacyclin (PGI<sub>2</sub>). Prostacyclin is a potent antiplatelet agent and vasodilator and although it may be elevated in the early stages of vascular disease,<sup>42</sup> in the later stages PGI<sub>2</sub> stimulating factor may be decreased,<sup>43</sup> facilitating platelet aggregation and vasoconstriction. As discussed above, von Willebrand factor is released from the damaged endothelium and its release can have prothrombotic effects by its participation both in the coagulation cascade and in platelet aggregation. Endothelin, another endothelial product, causes vasoconstriction and elevated baselinulasma levels of endothelin have been reported in RP which are further increased by cold challenge. Other manifestations of endothelial dysfunction have also been detected in RP, such as a net defect in the lysis of fibrin modulated via a decreased tissue plasminogen activator level and an increased plasminogen activator inhibitor.

The cellular elements of blood may also be abnormal in RP. The platelet is more aggregable, releasing increased amounts of the vasoconstrictor and platelet aggregant thromboxane A<sub>2</sub> (TXA<sub>2</sub>) and other plateletreleased products.<sup>47</sup> The red blood cell (RBC) appears less deformable in RP generally and a cold temperature in association with the acidosis present in cold ulcerated fingers will also increase RBC stiffness.<sup>48</sup> Rigid red cells can thus occlude the microcirculation and these may augment a vasospastic attack. An important role has also been claimed for the white blood cells (WBC) in maintaining flow in the small vessels.<sup>49</sup> Polymorphonuclear leucocyte activation with increased release of prothrombotic free radicals and increased cell aggregation have been reported in RP and these may also contribute to the decreased flow seen in this disorder.<sup>50</sup>

It should be noted that RD patients do not show these blood and endothelial abnormalities whilst the majority of RS patients do. Interestingly, this is true for both CTD-associated RS and that associated with VWF.<sup>51</sup> While this suggests that these changes are likely to be a consequence of the RP rather than a cause, they may augment the symptoms of vasospasm and their attenuation is a potentially important feature in the drug management of RP.

### **Inflammation and immunity**

More conventionally the WBC has been considered to be important as the producer and modifier of the inflammatory and immune responses. The endothelium is also involved in these processes by the production of its vasoactive agents, growth factors and growth inhibitors. Disordered immune/inflammatory responses occurring in the majority of severe cases of RS via their association with the CTDs<sup>52</sup> but also in VWF which has no clear immune/inflammatory basis.<sup>50</sup> Tumour necrosis factor and lymphotoxin, phagocytes/macrophages and T-cell derived proteins, along with immune complex deposition in the vessel wall are likely to be involved in the vascular damage seen in RS.<sup>53</sup>

## **MANAGEMENT OF RAYNAUD'S PHENOMENON**

### **Sympathectomy**

Upper limb sympathectomy gives a high relapse rate and an especially poor response in RS.<sup>54</sup> It is therefore no longer indicated for RP in the upper limb. It should be noted however that the more selective laparoscopic thoracic sympathectomy operation has not yet been assessed in RP although it is likely that it will fail in the same way. The same may not be so for the more localized digital sympathectomy where early work has produced encouraging results.<sup>55</sup> Long-term follow-up assessments are however essential in view of the subsequent failure of conventional sympathectomy in the upper limb. In contrast sympathectomy still has an important role in the treatment of RP affecting the feet, This discrepancy is not understood. Sympathectomy in the lower limbs can produce rewarding results. In the upper limb the surgeon may still contribute by removal of infected nails which allows healing of severe

long term ulceration. In SSc the tightness of the skin over the fingertips also contributes to the decreased blood flow and this can clearly be seen by asking the patient to extend the fingers and observing the development of blanching. Operations to remove part of the terminal phalanx and so relieve pressure may also be useful. Occasionally the ischemia becomes so severe that amputation is necessary but this is required increasingly infrequently.

### **Plasma exchange**

The beneficial effect of plasma exchange may result from the alteration of platelet, WBC and RBC behavior.<sup>56</sup> Blood viscosity is lowered and immune complexes are removed.<sup>57</sup> However, this form of treatment produces only limited success, is time consuming and expensive. It is not a cure and requires repetition at a later date. Consequently, plasma exchange is reserved for patients with severe intractable ulceration and at the present time the prostaglandins are replacing this treatment in this situation.

### **Supportive measures**

Much can be done for patients with mild disease without recourse to drugs. Stopping smoking can be beneficial as the effects of smoking a single cigarette are profound and long lasting producing a considerable decrease in finger blood flow. It is likely that moderate passive smoking will have similar effects and patients should be advised of this possibility.<sup>5</sup> A change in occupation and the withdrawal of drugs known to be associated with RP can also be useful. Although the contraceptive pill has been linked anecdotally to the development of RP this has never been conclusively proven in epidemiological studies. It is current practice to stop the contraceptive pill only if there is a clear link with the development of the disease. Likewise, RP is not a contraindication for hormone replacement therapy (HRT), as HRT may protect women against the development of vascular disease in general.<sup>58</sup> Treatment using self-training biofeedback techniques has sometimes been successful but requires well motivated patients. It has been suggested that biofeedback induced vasodilation is mediated through a non-neural, beta-adrenergic mechanism. However, measurement of plasma adrenaline and noradrenaline during finger temperature feedback and autogenic training failed to support the hypothesis of a role of decreased sympathetic activation and behavioural treatments for Raynaud's phenomenon. The etiology of the benefit derived from such a treatment is still not fully understood therefore.<sup>60</sup>

Many patients are apprehensive about their disease, reassurance is often required and information regarding both their disease and in the UK the self-help group, the Raynaud's and Scleroderma Association (Alsager, Cheshire), is often gratefully received. This group provides information booklets about various disorders associated with RP which can be requested by both doctor and patient. In the same way, the Arthritis and Rheumatism Council provides some useful patient booklets on CTD, however, they do not have one aimed specifically at RP.

It is also important to advise patients on protecting themselves from the cold. Achieving this without becoming a hermit is difficult but practical solutions to the problem do exist. Again, the Raynaud's and Scleroderma Association have an informative guidance booklet on how to keep warm. Electrically heated gloves and socks are the perfect solution for some patients. A rechargeable battery fixed on a belt provides up to 3 hours of warmth and the wires can be concealed beneath the clothing to give a normal appearance. Infrequently irritation of ulcers by the added heat has been noted. Chemical hand warmers obtained from local chemists and sports shops (or cheaply from the above association) provide a satisfactory alternative source of heat. These come in both disposable and reusable forms. The reusable hand warmers are 'primed' by boiling or by heating in a microwave oven. They are then carried in the pocket until needed when they can be activated by finger pressure over a designated spot. 'Comfort shoes' obtained from surgical appliance departments can be useful. The padded soles keep the feet warm and relieve the pressure on the toes which can result in vasospasm. Pressure is well recognized by the patients as causing vasospasm and they generally learn to avoid such tasks as carrying hand-held plastic shopping bags. It is less well recognized however that properly designed padded footwear can relieve pressure over the digital arteries and spread the pressure more evenly throughout the foot thus attenuating the vasospastic symptoms.

Good wound care of ulcers should also be undertaken. Any ulcer that is moist should be swabbed and the swab sent for culture. A major pitfall in the management of digital ulceration in severe RP is the

failure of the clinician to detect infection. When the blood flow to the digit is severely impaired ischemic and infective pain may be confused and the conventional inflammatory response may not occur; this is further augmented in the SSc patient where the acute phase response is known to be attenuated.<sup>29</sup> Significant infection can be present even in the absence of warmth, erythema and pus formation. It may be that one should consider a trial of antibiotics in all cases prior to considering amputation of the digit. The organisms detected are usually staphylococci but infection by less common organisms can occur so culture should always be carried out.

## **DRUG TREATMENT OF RAYNAUD'S PHENOMENON**

The drugs most commonly used in the treatment of RP are shown in Table 22.4. A treatment protocol is outlined in Fig. 22.5.

### **Calcium channel blockers**

Many studies have been carried out investigating the use of calcium channel antagonists in RP and nifedipine has now become the gold standard of Raynaud's treatment.<sup>61</sup> Its mechanism of action in RP is predominantly through vasodilation but it also has antiplatelet<sup>62</sup> and possibly other anti-thrombotic effects. Its use however is limited by the vasodilatory side-effects to which the RP patient appears very susceptible which include dizziness, palpitations, headache, flushing and ankle swelling. To attenuate these side-effects the patient should use the Retard® preparation, commencing at 10 mg twice a day, increasing to three times a day and then after 2 weeks to 20 mg twice a day, increasing to three times a day if required. The side effects usually disappear with continued treatment, so unless they are intolerable the patient should persevere for 7-10 days before discontinuing the therapy. It has not however been passed for use in pregnancy and the patient must be advised to avoid pregnancy when this drug is prescribed. If side-effects require discontinuation, two options are possible. The first is to use nifedipine capsules (not the Retard® tablets) as a rescue medication during a severe spasm attack, the tablet being crushed by the teeth and placed below the tongue. Thus the drug is not taken frequently enough to produce constant side-effects. The second option is to use another calcium channel antagonist with less vasodilatory effects. Both diltiazem<sup>64</sup> and isradipine<sup>65</sup> may be useful. It is not yet clear whether another calcium channel blocker, nicardipine, is useful in RP as two early pilot studies showed conflicting results<sup>66, 67</sup> and a later controlled multicentre double-blind study, although showing a decrease in the number of vasospastic attacks, could show no change in the severity of the spasm or in the cold-induced reactive hyperaemia test.<sup>6</sup> Verapamil has been found to be ineffective.

### **Table 22.4 Drugs and dosages commonly used in Raynaud's phenomenon**

#### **Drug: Dosage**

**Inositol nicotinate:** 500 mg three times a day increasing to inositol nicotinate forte 750 mg twice a day

**Naftidrofuryl:** 100mg three times a day increasing to 200 mg three times a day

**Thymoxamine:** 40 mg four times a day increasing to 80 mg four times a day. Discontinue after 2 weeks if no response

**Oxpentifylline:** 400mg three times a day increasing to 800 mg three times a day if no response

**Nifedipine Retard:** 10 mg twice a day increasing to three times then 20 mg twice a day increasing to three times

**Prostacyclin:** Start infusion at 1 ng/kg/min increase by 1 ng/kg/min every hour to approximately 5 ng/kg/min or side-effects. 6-8 hr. duration of infusion given 3-5 times over 3-5 days

**Epogam®:** 12 caps/day for 3- month trial

**Maxepa®:** 10 caps/day for 3-month trial

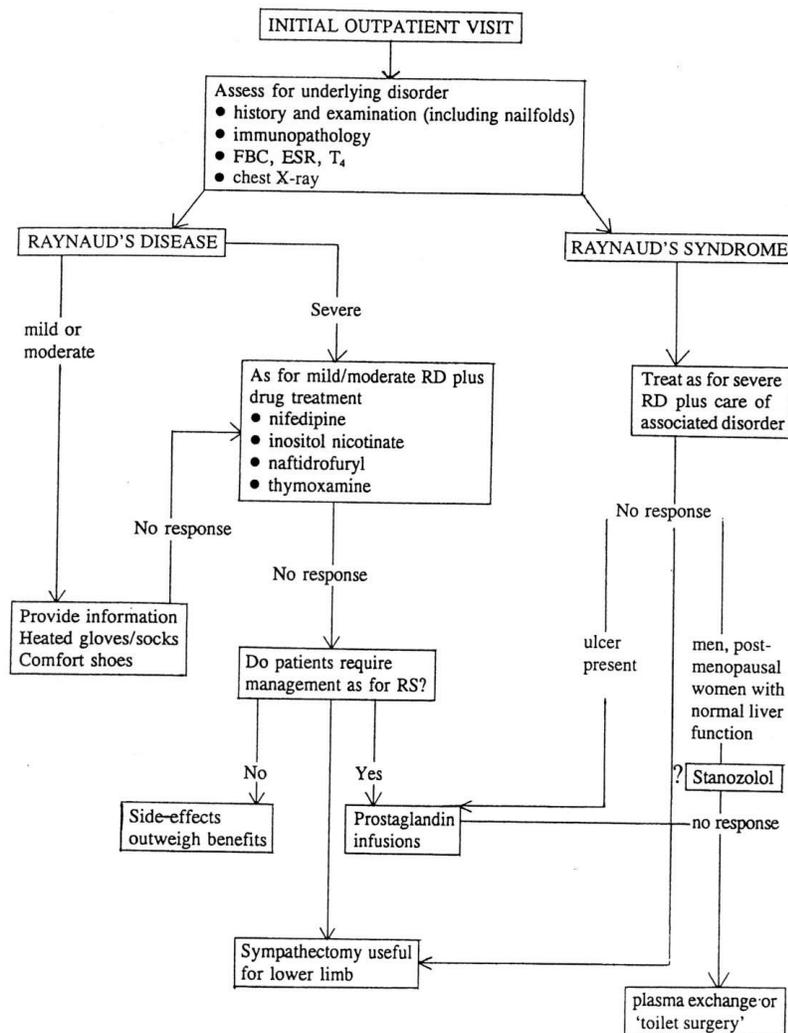


Fig. 22.5 Treatment flowchart.

### Other vasodilators

The use of other vasodilators in RP remains controversial as most studies have been uncontrolled. Four compounds do, however, merit consideration. Inositol nicotinate<sup>69</sup> has produced encouraging results in mild to moderate RP. The drug may take up to 3 months to produce an effect and should therefore be given for at least this period of time. Similarly, the use of naftidrofuryl<sup>70</sup> may produce benefit over the same time period as oxpentifylline.<sup>71</sup> Although these drugs are known vasodilators their action in RP may be through other mechanisms. It is interesting that full benefit may not always become apparent until after 2-3 months of treatment. These potential mechanisms may include modification of some of the rheological abnormalities mentioned earlier. Thymoxamine the selective  $\alpha_1$ -blocker<sup>72</sup> may also be tried initially for a period of 2 weeks. A trial of these treatments given in sufficient dosages for a sufficient period of time may be worthwhile. It is unusual, however, for the more severely affected patient to benefit from these treatments and the majority of patients who do benefit will have been treated by such drugs at general practitioner level and will not, thus, form part of the hospital population of RP. Thus in

such a population simple vasodilators are often ineffective with the limiting factor being the development of side-effects at high dosage.

## Prostaglandins

Prostaglandins (PGs) are the metabolic products of essential fatty acids (EFAs) and their discovery has opened up new therapeutic approaches to RP. Prostaglandin E, and PGI<sub>2</sub> both have potent vasodilatory and antiplatelet properties, whereas TXA<sub>2</sub> has opposite actions.<sup>12</sup> It is possible to manipulate the balance of these chemicals in favour of antithrombotic and vasodilatory effects. Prostaglandin E, treatment has to be given intravenously (i.v.) through a central line with an incremental dosage regime up to a maximum of 7.5 ng/kg/min.<sup>73</sup> Although 10 ng/kg/min was used in earlier studies, vasodilatory side-effects such as headache, flushing and hypotension persuaded later workers to lower the dosage. Most studies suggest a benefit from a 72-h i.v. infusion of PGE<sub>1</sub><sup>74</sup> in RS; however, it is probably unhelpful in RD.<sup>75</sup> The use of PGE<sub>1</sub> as adjunctive therapy to aid wound healing following surgery has some support also.<sup>76</sup>

Prostacyclin also requires i.v. administration but this can be through a peripheral vein.<sup>77</sup> A careful watch over the drip site should still be kept to avoid the pronounced inflammatory response seen after infusion into the tissues. The regimen for PGI<sub>2</sub> treatment differs in that it is best given using a 6-8h, 3-5 dose intermittent regime over 3-5 days. Further infusion can be given thereafter on a daily basis at weekly intervals if ulceration is severe. The dose is also incremental, increasing from 1 ng/kg/min to a maximum of between 5 and 7.5 ng/kg/min. The dosage should be titrated to side-effects which are also vasodilatory. In general women have more severe side-effects than men.<sup>78</sup> The intermittent regimen described above appears to prevent tachyphylaxis of the platelet and rebound platelet aggregation after discontinuing the drip.<sup>79</sup> Blood pressure and pulse should be measured during the time of increasing dose.

The beneficial effects of these PG infusions may outlast the infusion time. In most studies the 6-week assessment continued to show a clinical and objective improvement in the RP symptoms. In our experience the effect can persist from 1 week to 6 months, when repetition of the infusion is required. The antiplatelet effects of PGI<sub>2</sub> do not persist past the termination of the infusion by more than 2-3 h.<sup>80</sup> Similarly, the clinical effects of vasodilation such as headache and flushing pass off quickly after the end of the infusion.<sup>81</sup> At the time of the first reporting of this prolonged benefit, it was common to read of an unexplained 'cytoprotective' effect. This term has been poorly defined but it has been used by many authors to explain the long-term beneficial effects of the vasodilatory prostaglandins. Sinzinger *et al*<sup>82</sup> went some way to providing an explanation in their study of labeled platelets in patients with arterial atherosclerosis. Prior to treatment the labeled platelets became adherent to atherosclerotic plaques. Prostacyclin decreased the platelet adhesion and this was maintained long after the infusion had been terminated. It is possible therefore, to speculate that the PGs may facilitate endothelial repair thereby breaking the vicious cycle of endothelial cell damage and altered blood flow. Alternatively, in the majority of patients studies of RS secondary to SSc or other rheumatological conditions abnormalities of WBC behavior occur in these conditions as part of the inflammatory process. Prostacyclin attenuates WBC activity and such an alteration in neutrophil and lymphocyte function might well be important in the provision of this therapeutic response seen with the prostaglandins.<sup>82</sup>

As yet neither PGE<sub>1</sub> or PGI<sub>2</sub> are licensed in the UK as treatments for RP, nor is iloprost, a PGI<sub>2</sub> analogue, which may also be beneficial in RP.<sup>84</sup> Whereas both E<sub>1</sub> and I<sub>1</sub> are unstable, iloprost is not and this makes it easier to handle despite requiring i.v. administration. Double-blind, placebo-controlled studies of iloprost<sup>85, 86</sup> showed a significant decrease in duration and severity of vasospastic attacks over the study period of 6 weeks. In these and other studies, the dose of 2 ng/kg/min given over 8 h appeared effective but vasodilatory side effects did occur. A subsequent study<sup>86</sup> compared the above regimen with 0.5 ng/kg/min and found both regimens to be equally effective in decreasing the frequency, duration and severity of vasospastic attacks. Ulcer healing occurred to a similar degree in both treatment groups. As expected a low dose was associated with fewer side-effects and was better tolerated by the patients. Another study, which is of clinical relevance, was carried out by Rademaker *et al*<sup>87</sup> where iloprost was compared with nifedipine treatment. Both treatments effectively reduced attacks and it was suggested that nifedipine was less effective in healing digital ulcers and additionally produced more side effects. Despite its efficacy as a treatment and its equipotency

with nifedipine, iloprost still remains a second choice treatment because of its mode of administration and the fact that it is not yet registered for use in RP.

### **Manipulation of the arachidonic acid pathway**

Other approaches to manipulating the body's own production of vasodilatory prostaglandins are also being evaluated. Evening primrose oil is rich in  $\gamma$ -linoleic acid (GLA) which is metabolized to dihomo- $\gamma$ -linolenic acid (DGLA) and fish oil is rich in eicosapentanoic acid (EPA) and docosahexanoic acid (DHA). Dihomo- $\gamma$ -linolenic acid, EPA and DHA are precursors of vasodilatory prostaglandins, and dietary supplementation with these EFAs may stimulate endogenous production of such PGs. Only a few studies have investigated such treatments however 88, 89 and both need to be given in a full dose for at least 3 months before being deemed ineffective, that is Epogam® 12 capsules a day and Maxepa® 10 capsules a day. Disappointingly, only a mild response has been detected and as with PGs, RP is not a licensed indication for their use. The other alternative for the patient is to purchase the compounds from a health food store but this proves to be very expensive.

Inhibition of the cyclo-oxygenase enzyme by non-steroidal anti-inflammatory agents (NSAIs) produces a significant antiplatelet effect. However, a study of acetylsalicylic acid together with dipyridamole in patients with RP failed to show any benefit.<sup>90</sup> As aspirin inhibits the cyclo-oxygenase enzyme it can prevent not only the production of TXA<sub>2</sub> but also PGI<sub>2</sub>, although some thrombotic situations have been improved by NSAIs, such a treatment has not proven effective in RP.<sup>91</sup>

Specific inhibition of the enzyme thromboxane synthetase results in a decrease in TXA<sub>2</sub> formation and should promote vasodilatation and platelet disaggregation. Nevertheless, studies of such compounds were disappointing.<sup>91, 92</sup> Recent developments of a combination of thromboxane synthetase inhibition and thromboxane receptor site blockade may be more promising.<sup>93</sup>

### **Fibrinolytic agents and others affecting blood rheology**

Parenteral administration of low molecular weight dextran or ancrod, a defibrinating agent, have been reported to alleviate RP. However, the need to monitor blood coagulation and the development of antibodies to ancrod limits their application. Likewise, oxerutin, an agent affecting red cell aggregation has been shown to be useful in one small study. However, no convincing studies have been carried out recently using any of the above three agents.

Stanozalol is an anabolic steroid that increases fibrinolysis and the results obtained with this compound are possibly more persuasive.<sup>94</sup> The drug is given in a dose of 5 mg. twice a day and the beneficial effects can take up to 3 months to become apparent. Side-effects can be severe however, and include an elevation of liver enzymes, virilisation and dyspepsia. This unlicensed agent is now rarely employed and then only in postmenopausal women or males who have normal liver function tests.

### **Drugs for the future**

Although the i.v. administered PGs may be useful, their i.v. administration makes them less than satisfactory. This is particularly so for PGE<sub>1</sub>. The major problem with PGE<sub>1</sub> is that it is an inflammatory mediator and this produces the five cardinal signs of inflammation round the site of peripheral venous access.<sup>95</sup> This necessitates its infusion through a central line which is an invasive procedure involving the risk of pneumothorax,<sup>96</sup> a complication best avoided in patients at risk of developing pulmonary fibrosis in association with SSc. Of interest, therefore, is a novel approach to this problem in which PGE<sub>1</sub>, has been incorporated into lipid microspheres and given as a bolus i.v. dose through a peripheral vein daily for 4 weeks. In this multi-center, double-blind, placebo-controlled study<sup>97</sup> no objective measures of blood flow could be carried out. However, in the 135 patients with CTD-associated RS ulcer healing appeared significantly better after lipo-PGE<sub>1</sub>, treatment.

Studies of the orally active PGI<sub>2</sub> analogue cicaprost proved disappointing<sup>98</sup> although a recent pilot study of oral iloprost was perhaps more encouraging<sup>99</sup> as were the results obtained from the study of oral limaprost.<sup>100</sup> Delivery of prostaglandins through

the skin has also been studied<sup>101</sup> and these proved popular with the RS patient as well as providing both subjective and objective improvement in the disorder.

In addition to the development of orally or transdermally active prostaglandins, interest has been shown in ketanserin. Plasma serotonin has been shown to be increased in RS, possibly reflecting increased platelet aggregation and it may be contributing to the vasoconstriction. Ketanserin, a serotonin antagonist with mild alpha-adrenergic antagonistic effects, may be useful in RP. This was demonstrated in a large multi-center study of 222 patients with both RD and RS.<sup>102</sup> Unfortunately, due to the multi-center nature of the study, objective tests of blood flow could not be measured. However, symptomatic benefit occurred which suggested that ketanserin may be a drug for the future.

Patients with RD may have a hypersensitivity to the potent, endogenous vasodilator CGRP. A pilot study of CGRP infused into patients with RD caused an increase in hand/skin blood flow throughout the duration of the infusion which persisted for 3 days after termination of the infusion.<sup>103</sup> This and other vaso-active compounds are under scrutiny as potential treatments for RP. The better evaluation and understanding of the pathophysiology of RP has led to a better selection of treatments for study with significant advances in the management of RP continuing to be made.

## **CONCLUSION**

Raynaud's phenomenon is a common condition and until recently its management was difficult. However, with a careful clinical history and examination and with selection of specific blood tests it is now possible to correctly diagnose RP and to assess the likelihood of progression to an associated disorder. Although a cure is not available, many patients with RP can achieve a satisfactory amelioration of their symptoms using a combination of non-drug aids and drug therapy. Nevertheless, it should be remembered that the final prognosis of RS is determined by that of the underlying disorder which must first be detected, monitored and treated independent from the vasospastic symptoms.

Erythromelalgia

## **INTRODUCTION**

'My feet are killing me' is a phrase often employed after a particularly arduous ward round, but for the erythromelalgic patient such a phrase has a more sinister meaning. Erythromelalgia (EM) is a disease characterized by increased temperature and redness of the skin particularly of the lower limbs associated with intense burning pain. These symptoms can be precipitated by exercise, dependency and exposure to heat and partial relief may be obtained by elevation of the affected part or by cooling. The disorder can be debilitating and distressing.

The first reported case was documented by Graves<sup>104</sup> in 1834 and the syndrome itself described by Mitchell<sup>105</sup> in 1874. It was named by Mitchell as erythromelalgia based on the three Greek words, erythros, melos and algos which translated mean 'red,' 'extremities' and 'pain.' In 1938 Smith and Allen<sup>106</sup> proposed that the syndrome be named 'erythermalgia' thus incorporating the Greek therm, meaning 'heat', as they believed that an increase in skin temperature was an integral part of the syndrome. However, although 'erythromelalgia' does not include the description of an elevation in skin temperature, 'erythermalgia' does not refer to the involvement of the limbs which is so typical of this disease. 'Erythermomelalgia'<sup>107</sup> incorporates all four features but use of this unwieldy label has not been widespread and in common with most other authors we use the term EM.

## **CLINICAL MANIFESTATIONS OF ERYTHROMELALGIA**

An EM attack is heralded by a pricking or itching sensation which develops into burning pain of a severe and distressing nature. The attacks are associated with erythema, warmth and, on occasions, swelling of the affected part. The attacks last for a variable length of time ranging from minutes to days and can be provoked by exercise, warmth and a dependent posture of the limbs.

Erythromelalgia is much more common in the legs than in the arms. The clinical syndrome presents when the skin temperature is increased into the critical range of between 32 and 36°C.<sup>108</sup> Thus attacks occur when patients are near heating appliances, put their limbs under the bed covers at night or into warm water, when they cover the affected part with, for example, shoes or gloves, or when they are walking. Conversely, relief can be obtained by lowering the temperature of the skin. Thus, patients frequently expose their extremities or immerse them in cool or ice water. It is well recognized that extreme measures are sometimes undertaken by the EM patient in their search for symptomatic relief. These include sleeping with their feet out of a window, in the fridge, walking barefoot in the snow and filling Wellington boots with ice (personal communications and others).<sup>109</sup>

### **PRIMARY AND SECONDARY ERYTHROMELALGIA**

Like RP, EM can take either a primary or secondary form. In the same way, in primary EM there is no associated disorder whereas in contrast in secondary EM there is an association with a variety of disorders, particularly those in which there is an increase in the platelet count, for example, thrombocythemia<sup>110</sup> and in hyperviscosity syndromes, for example, polycythaemia rubra vera.<sup>111</sup> Interestingly, some of the diseases which are more conventionally associated with RS are also associated with EM. These include diseases in which there is microvascular ischemia<sup>111-114</sup> particularly when the ischemia is part of an inflammatory vascular disease such as occurs in diabetes,<sup>115</sup> systemic lupus erythematosus (SLE)<sup>112</sup> and other vasculitides (Table 22.5). As the etiology, pathology and, therefore, treatment of both primary and secondary EM are quite different an attempt should always be made to differentiate between the two forms. Although this is not always easy some specific clinical and laboratory features may be helpful (Table 22.6).

#### **Table 22.5 Disorders associated with erythromelalgia**

##### Thrombocytosis

Thrombocythemia

Polycythemia

##### Microvascular ischemia

Hypertension

Diabetes

Rheumatoid arthritis

Systemic lupus erythematosus

Syphilis

##### Hyperviscosity Leukemias

particularly chronic myeloid leukemia

##### Mechanism uncertain

Gout

Familial nephritis

In 1932 Brown defined his five criteria for the diagnosis of primary EM. These were as follows:

1. Attacks of bilateral or symmetrical burning pain in the hands and feet.
2. During attacks the affected parts are flushed and congested and exhibit increased local heat.

3. The attacks are initiated or aggravated by standing, exercise or exposure to heat.
4. Relief is obtained by elevation or exposure to cold.
5. The condition is refractory to treatment.

Using these five criteria as a clinical guide separation of primary and secondary EM can often be made. Both the arms and legs tend to be affected in primary EM whereas in secondary EM the attacks tend to be unilateral or otherwise asymmetrical, predominantly affecting only the legs. In our experience, supported by work from other groups,<sup>106</sup> the secondary form of EM is more amenable to treatment. These features agree with the original criteria defined by Brown. Some additional, though rather subtle, differentiating features are also recognized. One of these is the age of the patient, with a younger age group affected by the primary form. The average age of onset of secondary EM is usually well over 40 years." A family history tends to suggest a primary form of EM. This is usually absent in those in which there is an associated disorder. Whilst the sex distribution is equal in the secondary form primary EM occurs more frequently in the male sex.

Although the etiology may differ, trophic changes occur in both types of EM. In primary EM the sensation of warmth is so distressing that often excessive cooling is employed such as immersion in iced water and cold injury may result. In secondary EM decreased tissue nutrition and trophic changes occur secondary to ischemia. Interestingly, the mechanisms by which cooling produces clinical relief may also differ in the two groups. Cold will induce anesthesia in both forms but additionally in primary EM it produces vasoconstriction and in secondary EM a decreased oxygen requirement of the affected tissue.

**Table 22.6 Features of primary and secondary erythromelalgia**

	Primary	Secondary
Site of symptoms	Often arm and legs	Usually lower limbs
Symmetrical/bilateral	Yes	No
Age	Young	Older
Sex	Male	Both
Family history	Yes	No
Laboratory tests	Usually normal	Can be abnormal e.g. ESR, immunopathology
Trophic changes	Yes from self-induced cooling	Yes from underlying ischemia

### **PREVALENCE AND INCIDENCE**

Secondary EM is far more common than primary EM although the exact ratio is unknown. As the symptoms of EM can predate the development of the associated disease by over 12-16 years<sup>110, 111</sup> a number of patients initially documented as primary EM may in fact have an early secondary form of the disorder. Indeed, some workers believe so strongly that the vast majority of primary EM patients will progress to the secondary form of the disease that they recommend continuous follow-up and blood tests.<sup>117</sup> As has occurred with Raynaud's disease the primary EM population is likely to decrease further as more sophisticated laboratory tests become available. Our own EM investigation unit is a tertiary referral center in which we see cases where a previous hospital consultant has failed to determine the cause of the EM. Using a 6-h diagnostic program (two 3-h sessions) we find an associated disease or underlying cause for the symptoms in approximately 65% of patients. Thus, as we understand more about the mechanisms of blood flow so the primary EM population diminishes.

Not only is it difficult to calculate the incidence of both primary and secondary EM but it is also impossible to document the true incidence of each associated disease and secondary EM. There are two reasons for this: (1) the literature is inaccurate and (2) different clinician referral patterns exist. An increased temperature of the affected part is one of the major criteria of the diagnosis of EM. It cannot be diagnosed just on the basis of a sensation of heat. Even in 1972 a review of the literature<sup>109</sup> showed that only approximately half the published reports dealt with true EM. The others related to erythralgia (red, pain) and most probably have their origins in obstructive peripheral vascular disease. Clinician referral patterns produce a marked bias also. For example, Michiels and his colleagues in the Netherlands have published widely on EM. Myeloproliferative disease is the underlying cause in the vast majority of their patients usually as a thrombocythemia. Such has been the frequency of this relationship they suggest that "EM is a separate microvascular disorder that appears to be an expression of underlying thrombocythemia." In contrast only 21 out of 51 (41%) of patients presenting to the Mayo Clinic have secondary EM<sup>111</sup> and our own experience with 112 patients reveals only six with a Myeloproliferative disease. It is unlikely that the incidence of associated disorders varies so widely with geography and we remain convinced that the above merely reflects referral patterns. Support for this comes from our own hematologists who have a number of patients with EM and myeloproliferative disorders which they manage satisfactorily without referral to our group. The same difficulty exists in deciding on the prevalence of associated disorders in RS and the true incidence of EM and its associated conditions will only be determined by population studies.

## **PATHOPHYSIOLOGY**

In primary EM where there is no associated disorder it is probably correct to say that there is excessive vasodilatation and increased blood flow in the absence of ischemia. It is of interest that primary EM and primary RD often coexist.<sup>118</sup> As the primary form of Raynaud's is thought to be primarily an instability in vascular tone<sup>119</sup> it is possible to speculate that this may also be so for primary EM. As with primary RD, primary EM is linked with migraine<sup>120</sup> and possibly with pre-eclampsia in pregnancy,<sup>121</sup> though large epidemiological studies have not been possible in this disorder so far.

Although the pathology of primary EM is not fully understood it might be supposed that a general instability of vascular tone might cause distress by increased blood pressure in the minute skin vessels during an attack. Interestingly, although such increased blood flow may initiate the symptoms it does not maintain them as shown by the fact that the distress is not alleviated by occluding the blood vessels using a proximal blood pressure cuff.<sup>111</sup> A defective PG metabolism has also been postulated by Jorgensen and Sondergaard.<sup>122</sup> Abnormal bullous reactions appeared in EM patients following intradermal injections of PGs. A normal reaction in the skin was found to other inflammatory mediators however such as bradykinin, histamine and serotonin. Prostaglandins in general are highly vaso-active in the human skin. When injected dermally the PGs of the E series produce prolonged inflammation. Prostaglandins are also known to cause hyperalgesia and modulate pain sensation.<sup>123</sup> However, although an increased sensitivity to PGs could explain the symptoms of EM it does not explain what triggers the attack or why the patients can experience symptom free intervals. Uno and Parker<sup>124</sup> demonstrated decreased numbers of nerve terminals in the sweat glands and periarterial plexi in EM patients and postulated a "congenital sympathectomy" as a basis for the disease. However, this was only a single case study.

It has been suggested that the development of EM may be related to virus infections of the upper respiratory tract.<sup>125</sup> One report from China documents an outbreak of EM in five schools in one city where 12% of the pupils developed EM. A history of pharyngitis was given by 91 % of the students and 61% had symptoms of an upper respiratory tract infection just before the EM developed. A pox virus was later isolated but as human infection with pox virus is uncommon today the relevance of the above findings is uncertain. The current research into neuropeptides and their effects may, however, be relevant to EM. Calcitonin gene-related peptide is a marker for a class of sensory ganglion neurons in the superficial spinal and medullary dorsal horn.<sup>126</sup> Peripheral terminals with CGRP-like immunoreactivity are found in

tissues in which sensory stimuli are usually painful. This suggests a role for CGRP in nociceptor processing. Calcitonin gene-related peptide is also an important vasodilator and a report of a patient with the features of EM showed increased staining for CGRP in the spinal cord at the point corresponding to the distribution of the perceived burning pain.<sup>127</sup> As approximately 56% of our primary EM patients date their symptoms from a time of injury to the back the above hypothesis is attractive. It should be remembered, however, that back injury is common and further studies are required to investigate the frequency of back injury in these patients and this CGRP hypothesis.

From the nature of the symptoms in primary EM it seems logical that the underlying cause must be some mechanism whereby blood flow is intermittently increased. Interestingly, however, the mechanism of this increased flow could be ischemic. It has been suggested that when there is a surge in the blood pressure within the microcirculation the pre-capillary arterioles constrict thus protecting the vulnerable capillaries.<sup>128</sup> This increased tone diverts blood into the deep dermal and sub-dermal arteriovenous shunts. Blood flow may therefore be deficient distally although the subject will have the sensation of a bounding circulation, and this ischemia may further stimulate blood flow.

An ischemic basis for secondary EM is more firmly established. Our work suggests that it can take two forms. The first where blood flow is increased inappropriately through the arteriovenous (AN) anastomoses and the second form as a result of reactive hyperemia such as seen following a Raynaud's attack. Regulatory mechanisms that rely largely on variations in cutaneous blood flow maintain core body temperature within a narrow range. The cutaneous circulatory system is well suited for its role in thermal regulation. One way in which it does this is through the AN anastomoses which are abundant in acral areas (Fig. 22.7). In warm or hot environments such as between 32 and 36°C the A/V anastomoses open and heat exchange takes place with the external environment. In cool environments the nutritional flow is maintained whilst the A/V anastomosis is closed to conserve heat. In 'ischemic' secondary EM an obstruction to nutritional flow might occur. This could be through various mechanisms such as increased platelet aggregation,<sup>110</sup> endothelial cell swelling or hyperviscosity of the blood.<sup>111</sup> Respiration of the cells would continue anaerobically. This combined with tissue damage secondary to the ischemia would cause release of inflammatory chemicals which can cause both pain and vasodilatation of the A/V anastomosis. The end result is a continuous surge of blood through the A/V shunt into the venous side of the circulation which completely bypasses the narrowed or occluded nutritional vessels. Poor flow in the nutritional vessels if prolonged would result in the ischemia-related trophic changes sometimes seen with secondary EM. The patient, however, would still be subject to EM attacks as the increased flow in the A/V anastomosis would be manifest clinically as erythema and an objective increase in temperature of the affected area. Objective measures used to assess EM support this hypothesis where an increase in Doppler detected flow and hot thermograms are found but low transcutaneous tissue oxygen levels reflect poor microcirculatory flow.<sup>110</sup>

We have already noted the association of EM with RP<sup>118</sup> and a number of EM patients may have a reactive hyperemic basis for their symptoms. A significant number of EM-like patients in whom cold-induced vasoconstriction can be objectively demonstrated show no symptoms during the vasospasm but suffer markedly from burning and warm extremities during the return of flow, that is during the so-called reactive hyperemic phase. The ischemic stimulus in these cases is vasospasm rather than the blood platelet or other cellular elements described earlier and obviously treatment must reflect the underlying ischemic etiology. In our experience, the elderly lady presenting with EM usually falls into this - vasoconstrictive category.

### **MAKING THE DIAGNOSIS OF ERYTHROMELALGIA**

Erythema and a burning pain may be seen in obstructive vascular disease, particularly thromboangiitis obliterans.<sup>109</sup> The presence of cooler extremities however differentiates obstructive vascular disease from EM. Fabry's disease in children can present with episodes of burning pain in the palms of the hands and the feet.<sup>129</sup> These symptoms may predate the cutaneous angiokeratomas so classical in this disorder, however it can be easily diagnosed by demonstrating deficient  $\alpha$ -galactosidase A activity in the blood.

Bacterial cellulitis and other local infections should also be considered when making a differential diagnosis of a warm painful leg. In reality, however, confusion between local infection and EM is not a problem.

There are, however, a number of disorders that can closely mimic EM, in particular the post-traumatic reflex dystrophies. These include the shoulder hand syndrome, reflex sympathetic dystrophy and causalgia.<sup>130</sup> Hyperalgesia and a burning pain are features of these conditions although skin color and temperature may vary. The extremity is, usually cold and painful which makes a differential diagnosis easier; however it can be warm and erythematous. Nevertheless, virtually all cases of post-traumatic reflex dystrophy are associated with trauma, e.g. physical trauma in the case of reflex sympathetic dystrophy and myocardial infarction or cerebrovascular accident in the case of shoulder hand syndrome.

Once a diagnosis of EM has been made on clinical grounds it is important to differentiate between primary and secondary EM (Table 22.6). The history may itself provide pointers to the associated disorder, e.g. photosensitivity in SLE, polyuria and polydipsia in diabetes. Similarly, a detailed clinical examination may be helpful with particular attention being paid to the peripheral circulation, peripheral nervous supply and blood pressure (Table 22.7).

#### **Table 22.7 .Investigation of erythromelalgia**

- History and detailed clinical examination
- Full blood count including platelets and white cell differential.
- Plasma viscosity/ESR
- Blood sugar
- Immunopathology - ANA, RA latex
- Vascular assessments, e.g. Doppler pressures, thermography, issue pO<sub>2</sub> monitoring, laser Doppler flowmetry

A full blood count including a platelet count may point to some myeloproliferative disorder and a bone marrow aspirate may be required. Both plasma viscosity and ESR tend to be normal in primary EM but may be elevated in the secondary form of the disorder. More detailed laboratory tests may also be helpful such as an elevation in blood sugar which may point to diabetes or a positive antinuclear antibody test in SLE. A rheumatoid factor estimation should also be part of the immunopathology screen and we have seen three EM patients with elevated titres of anticardiolipin antibody (antiphospholipid syndrome).

Some form of detailed vascular investigation is invariably required. Although the equipment within the various laboratories tends to differ, 'non-invasive' vascular tests can be useful. The requirement is to be able to measure both the macro- and microcirculation with some device which differentiates microcirculatory nutritional flow and flow through the AN anastomosis, e.g. thermography will show the increase in heat although a transcutaneous tissue oxygen monitor will show decreased tissue pO<sub>2</sub>.<sup>110</sup> Assessments should be carried out in both a warm and cool environment and the effect of posture will give some insight into autonomic nervous control, for example, failure of vasoconstriction on standing would occur in some diabetics with EM. As cold sensitivity is such a feature of the older EM sufferer a

measure of circulation before and after cold exposure is essential.

## **THERAPY FOR ERYTHROMELALGIA**

The management of each EM patient depends on the respective etiology of that particular patient's burning pain. Poorly defined patient groups have led to widespread controversies in the literature. Obviously, if microvascular ischemia contributes to EM vasodilators may be of use. However, their use in a vasodilatory EM is contraindicated and may worsen the situation.<sup>131</sup> Conversely, vasoconstrictive  $\alpha$ -blockade may worsen ischemic EM but help vasodilatory EM.<sup>132</sup> Those workers who studied predominantly EM secondary to thrombocythemia<sup>117</sup> can actually use a response to aspirin as a diagnostic test,<sup>110</sup> whereas other forms of EM referred to elsewhere received no benefit from such a treatment.<sup>133</sup> We divide our treatment strategies for EM into four broad groups: aspirin and other NSAIs, vasoconstrictor therapy, vasodilator therapy and symptomatic treatment.

### **Non-steroidal anti-inflammatory agents**

Aspirin can provide relief even in low dose form (75 mg) for 2-4 days in some patients particularly those with a myeloproliferative disease and especially thrombocythemia,<sup>110</sup> and also in those with some form of microvascular obstruction, e.g. diabetes.<sup>115</sup> The mechanism whereby benefit is obtained is not entirely clear. Although the duration of benefit might suggest an antiplatelet effect, other antiplatelet drugs do not control the symptoms of EM. The antipyretic effects of aspirin are not long lived enough to be the cause of the above benefit. Inhibition of cyclo-oxygenase and thus decreased prostaglandin synthesis may be relevant'.. as may aspirin's free radical scavenging properties.<sup>114</sup> Reperfusion-generated free radicals are thought to contribute to the reactive hyperemic response in microvascular thrombosis.<sup>135</sup>

### **Vasoconstrictors**

In our experience, vasodilatory EM is the least common form of the disorder and although vasoconstrictors can be effective in this form it is not a therapy that should be embarked on without objective evidence of vasodilatation.  $\alpha$ -Blockade is anecdotally the most promising form of such treatment for EM and reports of its success are documented in the literature.<sup>112, 133</sup> Unfortunately, if inappropriately prescribed, the EM can worsen. If their use is considered appropriate, however, the. unselective beta-blockers have the most potent peripheral vasoconstricting effects.

Ephedrine has been used in the past, though in the doses required to relieve the EM symptoms via vasoconstriction side-effects can be troublesome.<sup>136</sup>

### **Vasodilators**

Vasodilator therapy may benefit patients with EM secondary to poor microcirculatory flow. The difficulty is to avoid overshoot of the vasodilator response as high dose potent vasodilators can aggravate hyperemic EM. Naftidrofuryl has produced satisfactory responses in a number of our patients. It is not a strong vasodilator and part of its mechanism of action may be to decrease tissue oxygen requirements and serotonin antagonism.<sup>137</sup> Nifedipine may also be used in the Retard® formulation, but its potent vasodilatory effects can, by themselves, cause EM<sup>131</sup> so care must be taken with patient selection and a warning given that the symptoms may initially though temporarily appear to worsen on such therapy. Some authors report success with the serotonin antagonist methysergide,<sup>114, 117, 139</sup> and with nitroprusside.<sup>140</sup> Others have not found these to be helpful although patient selection has not been clearly defined in these studies.<sup>141</sup> We<sup>142</sup> and others<sup>143</sup> have used prostacyclin and prostacyclin analogues but as i.v. administration is required this should be reserved for very severely affected patients. Lower limb sympathectomy should, in theory, improve microvascular ischemia but it will worsen or indeed cause vasodilatory EM. Reports of both favorable and unfavorable responses are to be found in the published literature<sup>147, 145</sup> and it should be stressed that when considering this form of treatment for EM a

temporary sympathectomy using a local anesthetic should first be tried.

Interestingly, it has been suggested that vasodilatation can be used as a treatment even in cases where there is a documented increase in blood flow.<sup>114</sup> It is thought that the steal phenomenon seen in patients receiving vasodilators for obstructive peripheral vascular disease is the mechanism whereby benefit is obtained. The widespread systemic vasodilatation steals blood away from the affected area.<sup>146</sup> Such a phenomenon may also explain an apparent lack of benefit in some ischemic EM patients where the microvascular obstruction is severe. As response to vasodilator therapy is unpredictable, patients should be warned about the possible aggravation of symptoms. However, these should be temporary and should disappear on cessation of the vasodilator.

### **Symptomatic treatment**

Our best results have been achieved by combining the above with measures to relieve symptoms of EM. Patients should be instructed to avoid extremes of temperature, e.g. direct heat such as from an electric fire should be avoided and the patient should be advised against cooling below 20°C as ice immersion can cause tissue damage and less severe cooling will provoke a reactive hyperemic response and the very symptoms of EM that one wishes to avoid. "Comfort shoes" to relieve pressure over the soles of the feet can help and are available on prescription. Usually we employ one of the drugs used in the management of chronic pain.<sup>141</sup> Both carbamazepine and amitriptyline in particular have proven very valuable by controlling the burning sensation/pain. On occasions, transcutaneous electrical nerve stimulation (TENS) has provided benefit.

No one treatment is superior to another and the choice of medication must be made after careful consideration of clinical and laboratory findings. In general, combinations have proven more useful than a single drug. It should also be noted that the treatment of the associated disorder can induce remission of the EM symptoms, e.g. venesection and chemotherapy in polycythemia rubra vera and prednisolone in SLE.

### **CONCLUSION**

Erythromelalgia is a distressing, debilitating disorder. The physician should attempt to detect the underlying or associated pathology otherwise treatment will be haphazard and even detrimental. The natural impulse of the patient to cool a burning area should be controlled. Literature reports are biased by referral patterns and advice given should only be employed after careful clinical and laboratory assessment of each individual patient.

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*(The rest of the list of references was not made available to TEA for this re-printing of the article.)*