

# A way to understand erythromelalgia.

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A painful syndrome characterized by pain, heat and redness of the extremities has received at least two different names: erythromelalgia and erythermalgia. The term 'erythromelalgia', which is derived from the 3 Greek words erythros (red), melon (extremities) and algos (pain) was first proposed by Mitchell in 1878 [15] to indicate red, painful extremities. Mitchell was not entirely certain about whether the increased temperature of the skin should be included as a part of the syndrome or not. In 1938, Smith and Allen [18] proposed a term than in their opinion, was more descriptive, namely 'erythermalgia' from the 3 Greek words erythrotes (redness), thermé (heat) and algos (pain). However, neither term completely describes the disorder, The former does not include the increased temperature of the skin, and the latter does not include reference to the involvement of the limbs, which is one of the typical features of the disease. A completely descriptive term might be 'erythermomelalgia'. but for convenience the first term proposed can be maintained.

The clinical picture is characterized by the following symptoms in the affected parts; red discoloration and increased temperature of the skin, deep and superficial burning pain, and in many cases edema. The symptoms simultaneously involve the distal parts of the lower limbs and less frequently, of the upper limbs as well. The attacks of erythromelalgia are induced by increased temperature, either in the environment or locally, and by prolonged dependence of the affected parts. Thus, attacks occur when the patients put the limbs under the covers or near heaters or into warm water, when they wear shoes or gloves, or walk. The duration of the attacks varies from a few minutes to hours. Pain relief is obtained by lowering the temperature of the skin or by changing the position of the limbs. For this reason, the patients use cold packs or throw off the covers, or elevate the limbs. The onset of the disorder is usually gradual. The symptoms may remain mild for years or may become so severe that they lead to complete disability. The disorder may begin in any decade of life, and is slightly more prevalent in males.

Smith and Allen distinguished a primary form from a form secondary to hypertension, polycythemia vera, organic neurologic or vascular diseases, After the first observation of Smith and Allen, many authors reported erythromelalgia in a great many diseases, which

included many forms of arthritis, diabetes, thrombocythemia, and even frostbite and allergic diseases [2,5,13,17,18]. The poor definition of erythromelalgia, it seems, led to some fundamental misunderstandings. Many authors define as 'erythromelalgia' all the cases of burning pain and redness of the limbs, as Mitchell did, without considering one of the typical and perhaps most important characteristics, which is the increase in temperature of the skin during the attacks. This leads to confusion of erythromelalgia with painful rubor, because the latter does not include any increase in skin temperature. In addition, there is confusion with the underlying concept of 'erythralgia', a term proposed by Lewis [14]. Catchpole, for instance, considered 'erythromelalgia' and 'erythralgia' to be synonymous, quoting Lewis incorrectly [6]. Therefore, in order to clarify this very important concept in human pathophysiology, particularly with regard to the alterations of the skin, it is necessary to define 'erythralgia' from the observations of Lewis and subsequently of others [1,8,12,20].

'Erythralgia' is an altered condition of the skin characterized by redness, increased temperature, spontaneous or induced burning pain, hyperalgesia in the area of the lesion and in the surroundings. It may be experimentally induced by physical agents (ultraviolet rays, faradic current, scratching, cold or hot stimuli etc.) or by chemicals (chloroform, mustard oil, histamine, cantaridine etc.). From the site of the injury, the lesion extends to the so called 'area of stable erythema'. This area is surrounded by an area of reflex erythema (i.e. not directly due to the lesion but to then activation of neuronal reflexes). The symptoms are increased by the dependent position and are relieved by raising the limb. One of the most interesting, of Lewis' observations is that in the hyperalgesic area, in the absence of spontaneous pain, the threshold of induced pain is lower than in the normal skin, One of the best methods to assess this effect is to apply a radiant heat stimulus. Radiant heat induces burning pain in normal skin when the temperature reaches 43°C: in the erythralgic area this 'critical temperature' is lowered. varying with the degree of damage and the surface area of injury, up to as little as 32°C in very severe lesions. Lewis called this condition, the 'susceptible state of the skin'. Obviously this susceptible state may be found in many disorders such as urticaria. frostbite, burns. erythema from sun rays, and in many diseases of the macro- and micro-vessels. Therefore, the erythralgic state may be considered a type of inflammation of the skin.

Lewis did not consider 'erythromelalgia' to be a particular and distinctive disorder but included it in the erythralgic conditions of the skin. He first proposed that a vasoactive agent.

TABLE 1: ERYTHRALGIC STATES		
From external agents	Secondary to diseases	Idiopathic
from ultraviolet rays from sun rays from chemicals burns frostbite Etc.	allergic reactions infectious diseases gout and other arthritides myeloproliferative disorders (polycythemia sera, thrombocythemia etc.) venous insufficiency. etc.	erythromelalgia

was involved in the pathogenesis of the erythralgic states [14], The release of histamine, serotonin and the production of kinins was later demonstrated. [6,12). Recently, a role

has been attributed to prostaglandins in the pathogenesis of erythromelalgia. The prostaglandins of the E-series are vasoactive substances, which, when injected intradermally, induce prolonged erythema and pain. Jorgensen and Sondergard have shown that in two cases of erythromelalgia there were: (1) increased amounts of prostaglandin E, in the cutaneous perfusate and (2) increased synthesis of prostaglandins from endogenous precursors and from labeled arachidonic acid in cutaneous biopsy specimens [11]. The causative factors of these erythromelalgias are unknown. Erythromelalgia like other erythralgic states worsens in the dependent position of the limbs, probably because the increased venous pressure slows down the removal of the local alofenic and vasoactive metabolites. In polycythemia vera and thrombocythemia, the microthrombi release vasoactive substances and decrease the velocity of the flow within the microvessels, preventing the removal of these substances. Table I summarizes a classification of the erythralgic states based on these points.

In our Pain Clinic in Florence we have observed 3 cases of erythromelalgia of the lower limbs out of 5000 patients examined during the past 10 years (2 females, 1 male.) In these patients a light thermal stimulus, such as the heating of the limbs under the blankets during the night, induced the symptoms. In the intervals between attacks, the historeactivity of the skin tested with carbon dioxide snow did not differ from that observed in healthy, subjects. In these patients, low doses of aspirin (500-1000 mg daily) had no effect on the symptoms and it was not possible to confirm the classic observation of Smith and Allen that a single dose of 650 mg of aspirin may produce a marked relief persisting for as long as several days [18]. On the contrary, excellent results with complete disappearance of the symptoms were obtained with 10 daily sympathetic blocks with local anesthetics (Carbocaine 1%) alternating the left and right sympathetic chain at L2 - L4 levels. One year later in one case, and three years later in another, the symptoms did not reappear. The last patient also is actually under control.

The use of reversible sympathetic blocks for the treatment of erythromelalgia as far as we know has never been described before. Some authors [4,19] reported good clinical results with sympathectomy or with neurolytic irreversible blocks of the lumbar sympathetic ganglia. Such good results were not obtained by others [7,18] In many clinical conditions, such as causalgia and other algodystrophies, in which the sympathetic nervous system is directly involved in the pathogenic mechanism, sympathectomy does not always induce improvement and in many cases the symptoms worsen some days after surgery. This is probably due to the development of denervation hypersensitivity of peripheral receptors to circulating catecholamines. For this reason it seemed reasonable to us to try reversible sympathetic blocks. The long-lasting good clinical results we obtained made other therapeutic procedures unnecessary. For the treatment of erythromelalgia many drugs such as aspirin [18], beta-blocking agents [3], nitroprusside [16], methysergide [6] etc. were proposed. Unfortunately because of the rarity of the disease controlled clinical trials are not feasible. However, our clinical results indirectly support the idea that the disturbances found in erythromelalgia are under sympathetic control and that the interruption of the vicious circuits (periphery-central nervous system-periphery) can induce a steady improvement. Also from the clinical point of view some similarities exist among erythromelalgia and causalgic states such as seeking for relief by wet

applications, edema and osteoporosis. Galletti et al have shown that hyperalgesia and other signs and symptoms of erythralgia in the skin are reduced after sympathetic blocks [9,10].

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