Erythromelalgia – A condition caused by microvascular arteriovenous shunting.

By Knut Kvernebo, M.D.

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Chapter 1 - Introduction

Erythromelalgia (EM) is a rare disorder characterized by red, warm and painful extremities. In what superficially appears to be the antithesis of Raynaud's disease, victims of EM seek relief by cooling of the affected extremity. Over the years terms such as erythermalgia [1], and erythralgia [2] have also been used for the condition. Graves [3] reported the first case of a patient with burning, red and warm extremities in 1834, but as late as 1933 the existence of the condition was questioned [2]. In today's standard textbooks [5-7], the clinical entity of EM is accepted. and in the Medline system, 84 reports with key word EM, appeared in the. years 1966-1988. Little is known, however, about the pathogenetic mechanisms of the disorder, and no therapeutic regime has proven effective in curing the disease. Symptomatic relief is achieved in all cases by cooling of the affected extremity, most often in cold water.

A doctor consulting a textbook about EM will for example find the following quotation: "The cause of the primary disease is unknown. The exact basis for the spontaneous vasodilatation with the rise in temperature and the burning sensation is not known. Consistent value of one drug has not been found" [7]. Another textbook states that: "True EM is as rare as it is mysterious" [8].

When a female patient suffering severely from EM was referred to our department in 1983, the author recognized the clinical picture of EM, but studies of the literature available did not give any information as to how to help this poor lady. Working in a department with a clinical laboratory well equipped for examinations of arterial and venous extremity blood flow and skin microvascular perfusion. offered both the challenge and the opportunity to investigate the pathophysiology of her peripheral blood circulation. The results, which showed severely disturbed hemodynamics. were presented in both national and international fora [9-13], and a number of patients suffering from EM were referred to the author. A more. thorough understanding of pathophysiological and thereby pathogenetic mechanisms was obtained, and this knowledge gave a basis for therapeutic trials.

Aim of the study

The main aim of this report is to present a hypothesis of the pathogenetic mechanisms of the condition, based on a review of the literature, and the results of clinical, epidemiological, histopathological and pathophysiological studies of 40 patients with EM.
During the progress of the study the clinical classification systems of EM given in the literature did not seem satisfactory. A new clinical system for grouping patients is therefore proposed.

When a pathogenetic understanding was obtained, it was logical to treat patients according to this knowledge, and the results of a therapeutic trial are given in a separate chapter.

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Chapter 2 - History and definition

History

Graves [1] reported the first case of a patient with burning, red and warm extremities in

1834, and in 1878 Mitchell [2] described the symptoms precisely and suggested the term erythromelalgia (erythro, red + melos, limb + algos, pain). During the ensuing 55 years, reports of this entity appeared so sporadically that, in 1933, Lewis [3] considered that the term lacked a precise definition and should therefore be abandoned.

Definition

Today most authors use the term erythromelalgia, and seem to agree on the following definition [5]: *Erythromelalgia is a rare disorder of unknown etiology characterized by intense burning extremity pain associated with erythema and increased skin temperature. Warmth intensifies the discomfort while cold provides relief.*

Smith and Allen [4] proposed to divide the patients into primary (idiopathic) and secondary (related to nervous. peripheral vascular or other diseases) EM.

The clinical entity of EM is not questioned by leading textbooks [6-8]. In the literature, however, no objective laboratory criteria for the use of the diagnosis has to the author's knowledge been described. and little has been understood of pathogenetic mechanisms.

Own experiences

The definition of EM given above is in the authors opinion adequate, and in the present material, 40 patients are included on the basis of these clinical criteria. The intensity of involvement and the time span of the symptoms varied considerably in these patients, and the classification systems previously proposed in the literature are according to the author, not optimal. A new clinical classification system and a clinical severity score index is therefore proposed in the chapter describing clinical manifestations.

Laboratory criteria for the diagnosis of EM have to the author's knowledge not previously been described. In the chapter dealing with pathophysiology, a proposal of hemodynamic criteria for the diagnosis of EM is given. Many patients have a fluctuation of symptoms and pathology of the hemodynamic and rathology of the hemodynamcs may be absent in periods when no symptoms are present. Some patients are therefore included in the present material on the basis of a classical medical history, in spite of normal clinical and hemodynamic findings at the time of examination.

References

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Chapter 3 - Clinical manifestations and epidemiology

Findings in the literature

EM has been described and discussed by a number of observers. In reading these descriptions, however, one cannot help being struck by the confusion of diagnostic criteria. This confusion no doubt has its origin in the fact that a combination of redness and pain is a frequent concomitant of many different diseases of the peripheral circulation.

The most striking features of erythromelalgic patients are red burning extremities which are also unduly hot. A9 any authors claim that the disturbance is triggered off by a warm environment, which causes intense and sudden vasodilatation in affected skin. In some patients symptoms are chronic, while in others symptoms appear in attacks. Analgesics have limited effect. Relief is achieved by cooling the affected extremities, for example by walking barefoot on cold floors or even in snow, by applying cold objects to the skin or by immersion in a bucket of cold water.

In 1938 Smith and Allen [1] recognized two distinct groups of involved patients: the primary or idiopathic form and the secondary form which is associated with a primary disease.

In a review of 51 cases seen at the Mayo Clinic during the years 1951 to 1960, the largest material of EM published so far. Babb et al. [2] used this classification. They included patients on the basis of the description of burning pain, even if skin temperature was not shown to be elevated or there was an absence of red skin color. A summary of the findings is presented in Table I.

Thirty of the 51 cases were classified as primary disease. The distress tended to occur intermittently and attacks were related to situations that either promoted increased heat or caused prolonged dependence of the affected part. The attacks were associated with walking, standing, sleeping under covers, wearing shoes or gloves, or placing the extremity near heaters. Several patients had noticed an increase either in the number of attacks or in their intensity, or both, during the summer. The duration of the attacks varied from minutes to hours, the most common duration was two to three hours. Two thirds had noticed increased heat and redness in the affected extremity during the attacks.

Pain intensity was described as moderate to severe in most patients. In three patients it

was severe enough to require elevation and cooling of the feet almost continuously. Most patients had sought relief by lowering the skin temperature by various means such as immersion in clod water, walking in snow, on wet sand, on cold floors, by sleeping with the affected part outside the covers or with the feet elevated. Distribution was symmetrical in 28 out of 30 cases. Most often only the lower extremities were involved. Half of the patients had affection of only the soles of the feet. In some, the toes and fingers were affected while in others, the entire hand or foot was involved. In two patients, symptoms extended from the feet to the knees.

Twenty-one of the 51 cases were classified as suffering from secondary disease. All patients in this group were > 40 years. The character of distress and the factors that increased the symptoms were, in general, similar to the ones described for the patients with the primary type. EM was most frequently associated with one of the myeloproliferative disorders, particularly polycythemia vera. A noticeable feature in these patients was that EM was the initial complaint and preceded the full-blown myeloproliferative disorder by years. Other associated disorders were hypertension, venous insufficiency, diabetes mellitus. systemic lupus erythematosus and rheumatoid arthritis.

Common to most patients reported in literature are burning and red extremities. Case reports, however, show that the diagnosis of EM is applied to patients who have striking differences in their disease. The spectrum of clinical expressions ranges from chronic familial EM with debut of symptoms before the age of 10 years [3, 4, 5], to cases of acute massive disease [6]. The term primary EM in the classification of Smith and Allen therefore includes a heterogenous group of subjects.

Lazareth et al. [7] has recently described three major and four minor clinical criteria for the diagnosis of EM, Table 11. They propose to demand all three major and at least two of the minor criteria for the diagnosis. From the author's experience, not all patients who no doubt should be included (for example cases with erythromelalgic syndrome, see below), experience typical attacks, and a response of symptoms to acetylsalicylic acid is seldom seen.

Own experiences

This monograph is based on the author's experiences after examination of 39 patients with EM during the years 1983 to 1989, and from a retrospective examination of the records of one patient. The criteria for inclusion were:

Table I: Findings in the material of Babb et al. [2].

	Primary EM	Secondary EM
Age at onset	any age	> 40 years
Sex	Female/Male = 1/2	Female/Male =1/1
Distribution	Symmetric	Asymmetric
Sites of involvement	Lower extremities	Lower and/or upper extremities
Associated disorder	No	Yes
Treatment response	Poor	Variable

History of burning extremity pain associated with erythema and increased skin temperature, and relief from cooling of affected areas.

It is important to realize that a history of burning pain is not sufficient for inclusion. Many patients whose complaint is burning pain of the extremities suffer from other

disorders like venous and arterial insufficiency, osteoarthrosis and polyneuropathy. In some of these cases, it is possible that a primary disorder can be in an initial phase and can be difficult to diagnose. In the present material it was therefore decided to demand the finding of erythema and increased skin temperature during periods with symptoms, and relief from cooling, before the diagnosis of EM was applied.

Table II: Diagnostic criteria according to Lazareth et al. [7].

Major criteria	Paroxysmal attacks Burning pain Redness in affected skin
Minor criteria	Typical precipitating factors (heat exposure, effort) Typical relieving factors (cold, rest) Elevated skin temperature in affected skin Response of symptoms to acetylsalicylic acid

Clinical symptoms and findings

In addition to burning pain, erythema, elevated temperature and relief from cooling, common features for most subjects were a worsening of symptoms by physical activity, by warming affected extremities and by prolonged dependency of the affected part. Many patients also experienced a deterioration of symptoms after intake of alcohol. Elevation of the affected extremities gave some relief in several patients. The heterogenicity of the patients was, however, large and is illustrated by the following case reports.

Case Reports

Case example 1 *(the case reports have been deliberately distorted).*

LHJ, female, born 1 I Nov. 1954. Her family chart is presented in the etiology chapter. Her mother's sister was known to have warm feet and in periods suffer from burning pain. The aunt was known to have the peculiar habit of cooling her feet in cold water in summertime or by walking barefoot in snow during the winter. A female cousin. the daughter of another of LHJ's maternal aunts also had symptoms compatible with EM. From the age of 25 this cousin had periods of warm burning feet, associated with redness and elevated temperature. In the vascular laboratory we did not find any pathology in peripheral hemodynamics, but on the basis of the medical history the cousin was classified as suffering from chronic primary erythromelalgic phenomenon (EPPC) with severity category 2 (see later in this chapter).

LHJ has two daughters, of whom one was born in 1970 and the other in 1975. The elder is healthy, but the younger complains of periods of warm feet, and wants to borrow her mother's bucket of cold water from time to time. She has been examined in our vascular laboratory, but we were not able to demonstrate pathological findings. She has not been included in our material.

LHJ is married. has never had any paid job, and is on social welfare. She has not had any severe illness apart from EM.

History of EM

As a small girl, she was always a little clumsy, she was a slow runner and easily got

tired when playing. From the age of 5-6 she complained periodically of warm burning feet, and cooled her feet by walking barefoot on cold floors and outdoors. From the age of 13 she started cooling her feet in a bucket of cold water, and up to now this has been her main way of obtaining relief.

As the years passed, she consulted several doctors. general practitioners, a dermatologist, a psychiatrist and a neurologist, without succeeding in getting the correct diagnosis. She tried a wide range of drugs, from analgesics to cardiovascular and psychoactive drugs, all with limited or no effect. Repeated consultations with a psychiatrist did not alter her symptoms. She also tried various types of paramedical regimes like homoeopathic drugs and acupuncture without effect.

From the age of 23 years, her feet were pink in color, and in 1982 she started getting small ulcers in the affected skin. At this point she was actively cooling her feet up to 10-12 hours a day, and had the bucket of cold water with her 24 hours a day. In 1983 she was admitted to the Dept. of Dermatology at The National Hospital in Oslo, Norway with infected wounds in the affected skin. She was diagnosed as suffering from EM; the wounds were treated locally and healed. She was transferred to the Dept. of Orthopedics and was evaluated for bilateral crural amputation. The patient refused this procedure, and was transferred to our hospital for further evaluation.

When she was first examined by the author, she was 29 years old. At this point she had intense erythema from the mid leg and distally, and used the bucket of cold water up to 12 hours a day. Soaking was performed intermittently for periods of 15 to 30 minutes during the day. At night the bucket was placed on a chair at the side of the bed. She slept with her feet outside the covers, and when the burning became severely painful, she woke up and soaked her feet in the bucket. To avoid humidifying of the skin, she developed the habit of first putting her legs and feet into a plastic bag. and then dipping them into the water.

Clinical findings

LHJ was a little overweight. but in good general condition. She did not use any regular medication. and had only little effect of analgesics when we first saw her in 1983.

The rectal temperature was between 33.3 and 35.5°C on repeated measurements. She complained of freezing easily and wanted to have a room temperature of 27-30°C. Blood pressure was 150/90 mmH2 and pulse rate was 88. Apart from EM related signs no pathology was found.

Local status of the upper limbs was without pathology. The lower limbs were intensely red from the mid leg and distally. From the knee and distally the limbs had a non pitting edema.

Standard biochemical blood tests were within the normal range. No autoantibody was demonstrated, and immunological tests for rheumatoid arthritis was negative.

Immunelectrophoresis showed normal titers for IgG, IgA, IgM and complement C3 and C4. C3d was slightly elevated.

Her disease was classified as Erythromelalgic syndrome (see bleow), severity group 5 (see below). Peripheral hemodynamics showed ultrasound Doppler velocity profile group 3 (see chapter 7), Laser Doppler flowmetry group 3 (see chapter 7) and severity reduced transcutaneous oxygen tension, (see chapter 7). Further information on this patient is given later in this presentation (chapter 5 etiology; chapter 6, histopathology; chapter 7, pathophysiology; chapter 9, treatment.)

Case example 2

Female. born in 1977. She was the youngest of three siblings. In her family there was no history of EM - like disease. She did not have any serious disease up to the present problem.

On the evening of August 1st. 1985, she complained of burning pain symmetrically in the fingertips, but slept during the night. Next morning; the situation was worse with attacks of pain, in the fingers and in the lateral foot and 5th toe bilaterally. The family doctor was called and she was admitted to the Dept. of Pediatrics in the county hospital.

The pain increased in severity and attacks appeared more frequently. During attacks she started cooling her hands and feet in cold water. The department claimed the problems were of a psychogenic nature. This statement upset the parents who refused to accept it and discharged the girl from the hospital, bringing her home after three days. After further two days she was admitted to another local hospital where treatment with analgesics including morphine were given without effect. At this stage the symptoms were very severe with almost continuous pain and a need for cooling also during the night. and after a few days the girl was transferred to the Dept. of Pediatrics. The National Hospital in Oslo. Norway where she stayed from 11.8. to 17.9. 1985.

The diagnosis of EM was confirmed. and during this stay she was examined with a wide range of biochemical blood tests, urine examinations. cerebral CT scan. spinal puncture and sternal bone marrow puncture. The only pathology was increased complement activation (C3 93 AU/ml, reference value < 45 AU/ml, and Tcc 31.0 AU/ml, reference value < 6.6 AU/ml).

The girl was severely ill, and treatment with antihistamins, acetylsaliylic acid, different analgesics including narcotic analgesics, tricyclic anti-depressant drug, major and minor tranquillizers and penicillin was tried. In addition parenteral nutrition and psychotherapy were given. For some days the pain was so debilitating that the patient received continuous epidural and bilateral plexus anesthesia with bupivacain hydrochloride (Marcain®).

This patient was transferred to the author's department 17.9 1985, approximately six weeks after the initial symptoms. During this period she had had a weight reduction from

25 to 19 kg. The affected skin was humid and swollen because of the extensive use of cold water for cooling. The body temperature was 37.5°C, and she had tachycardia with a frequency of 120-140 at rest. Her organ status did not reveal any other pathology.

Her disease was classified as acute primary erythromelalgic phenomenon (EPPA) (see below), severity group 6 (see below). Peripheral hemodynamics showed ultrasound Doppler velocity profile group 3 (chapter 7) and laser Doppler flowmetry group 3 (chapter 7). Information on etiology is given in chapter 5 and on treatment in chapter 9.

Case Example 3

Female, born in 1969, the youngest of four children. There was no history of EM in her family. She had previously been healthy, but had like her father and sister a mild degree of Raynaud's phenomenon in the forgers, and a profuse auxiliary sweat secretion.

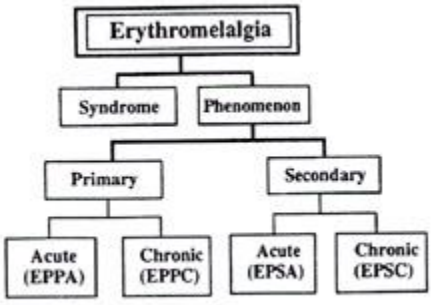

Fig. 1: Clinical classification of EM

In November 1985 she had a mild upper airway infection which was not treated. In the beginning of December, at the age of 16 years, she was participating in a training camp for cross country skiers. One evening she experienced aching pain in her toes, symmetrically in both feet. A tendency to erythema and edema was also observed. After some hours the fingers on both hands were also affected. The following 48 hours she slept during the night, and did not take any analgesics, but she was unable to participate in test cross country ski test races. After two days there was a worsening of symptoms, and the aching transformed into burning pain. She could not sleep, and realized that cooling her hands and feet in cold water gave relief, which analgesics did not. She was admitted to the local hospital and then transferred to the Department of Internal Medicine, at The National Hospital, Oslo, Norway where the diagnosis EM was confirmed. Diagnostic investigations did not reveal any primary disorder, and therapeutic trials with analgesics and a tricyclic antidepressant were without effect.

She was then transferred to our department 15 days after the onset of symptoms. At this point her pain was yen severe, and she almost continuously soaked her hands and feet in ice cold water. Pulse frequency at rest was 100, blood pressure 140/90 mmHg and core temperature slightly elevated to 37.7C in spite of the active cooling.

Her disease was classified as acute primary erythromelalgic phenomenon (EPPA) (see below), severity group 6 (see below). Peripheral hemodynamics showed ultrasound Doppler velocity profile group 3 (chapter 7), laser Doppler flowmetry group 3 (chapter 7) and reduced transcutaneous oxygen tension. (chapter 7). For information on etiology, see chapter 5, on histopathology, see chapter 7, and on treatment see chapter 9.

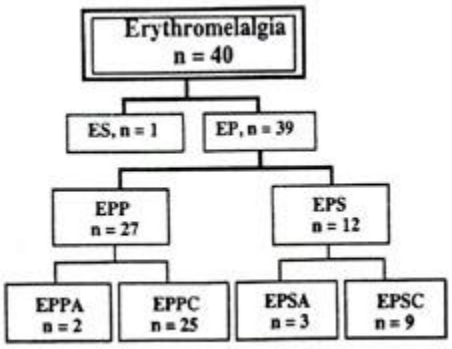

Fig. 2: Number of subjects in each category.

Case example 4

NN, male born 1953. He worked as a conductor in a tram car company. In 1972 he had an accident while mountain climbing and got a total luxation of the left knee with associated transsection of the popliteal artery. He was operated, and the artery was successfully reconstructed with a vein bypass. In May 1975 four friends planned a safe robbery, and NN was asked to use his car to carry the safe. After the job, he received his part of the profit, an amount of money corresponding to about six times his ordinary monthly salary. Four weeks later his four friends were arrested as suspects. NN was not arrested because he had only been the car driver, but the police informed his employer and he was therefore afraid of loosing his job. There was also a possibility that he would be imprisoned. He had previously never been in conflict with the police.

When his friends were put in jail, NN developed burning pain and erythema symmetrically in both hands and fingers. Cooling in cold water gave relief. He was admitted to the dermatological department of a university hospital in Oslo, and the condition was recognized as EM by an angiologist and a dermatologist. A therapeutic trial with i.v. infusion of propranolol gave some relief, and he was therefore treated with propranolol 40 mg three times a day and discharged from the hospital. The medication, however, gave only temporary relief. Symptoms increased again. and the patient was admitted to our hospital for one week. During this period, he was interviewed by a psychiatrist, who was informed by the patient of the story of the safe robbery. The psychiatrist found the symptoms to represent "a classical conversion neurosis". The "motive" for the symptoms was, according to the psychiatrist, to get a milder verdict in court. The reason for his fingers being affected was that the "Guilty" part of the body was affected-he had been "long fingered". The psychiatrist contacted the police department, and NN was informed that he probably would not be sentenced to jail. The symptoms then subsided gradually, he was exempted from meeting in court, and the charges were drawn.

This case is the only one in the present material which has not been examined by the author.
LJ's disease was classified as acute secondary erythroromelalgic phenomenon (EPSA) (see below), severity group 4 (see below).

Case example 5

Male born in 1946. He was healthy until 1982 when he acquired diabetes mellitus. Insulin was used for one year, until he stopped this treatment himself. He did not seek medical advice for the next five years, and treated himself by exercising and limiting his sugar intake.

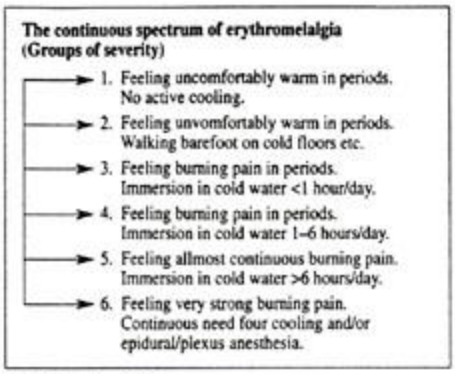

Fig. 3. Severity of EM

He was then admitted to the local hospital in April 1987 as an emergency case, suffering from hyperglycemia and diabetic ketoacidosis. Insulin treatment was again started. His general condition improved gradually, but he complained from paresthesia in the feet. He was dismissed from the hospital, but the feet gradually became more painful, warm, red and swollen. After 7 weeks he was readmitted to a local hospital because of burning pain in the feet. Cooling gave some relief, and the diagnosis was proposed to be EM. The neurologist did not find any evidence for neuropathy. Several drugs, including acetylsalicylic acid were without effect, and he was transferred to our department, where the disease was classified as acute secondary erythroromelalgic phenomenon (EPSA) (see below), severity group 4 (see below). Peripheral hemodynamics showed ultrasound Doppler velocity profile group I (chapter 7) and laser Doppler flowmetry group I (chapter 7). For information on histopathology, see table 1 in chapter 6.

Case example 6

Male born in 1916. In his young days he was an active wrestler, and had several shoulder injuries. For the last two years prior to examination, he had had pain and limited motion in his right shoulder. A radiographic examination revealed osteoarthrotic changes. In February 1989, he gradually got an increasing burning pain in the palmar aspect of the right hand. When the pain was predominant, he observed redness in color and the hand was warm. The burning pain was relieved by holding on a cold object. He also observed that the burning fluctuated synchronously with his shoulder pain. His disease was classified as chronic secondary erythroromelalgic phenomenon (EPSC), severity group 2 (see below). In the vascular laboratory, pathophysiological changes were shown in the affected arm by ultrasound Doppler velocity profiles (category 3, chapter 7) and laser Doppler flowmetry examination (category 2, chapter 7).

Case example 7

Female, born 1933. In her family there was no history of EM. She worked as a chemical engineer in a paint factory from 1956 until 1961, and later worked as a housewife. Previously she had allergic conjunctivitis and rhinitis in periods from 1975.

All her life she had had warm hands and feet. From 1983, at an age of about 50, she periodically felt burning pain in her feet in addition to being warm. The distress worsened

steadily during the following years, and she now suffers daily from a symmetrically located burning pain in the feet. Her burden is provoked by physical activity and by local heating or dependency of the feet. Relief is achieved by local cooling in cold or icy water for up to two hours a day, and to a certain extent by elevation of the feet. Mild analgesics have been without effect. Her social activities are limited because of her pain; she cannot for example sit for two hours in a theatre or during a family dinner.

Her disease was classified as chronic primary erythroromelalgic phenomenon (EPPC) (see below), severity group 3 (see below).

Clinical classification

The material presented by Babb et al. [2] is a review from The Mayo Clinic during a nine years period. In the present material, all cases were examined by the author during a period of seven years, and the material probably represents the largest published material seen by one doctor. When a certain number of patients were included, it was evident that the classification proposed by Smith and Allen (I] was not optimal, and that it would camouflage important information which could lead to a better understanding of the pathogenesis. An alternative classification is therefore proposed and used to describe the present material (Fig. 1).

The term syndrome is used when initial and gradually increasing symptoms appear in childhood or adolescence. The patients have affection of feet and leg skin, (i. e. involvement also of leg skin which normally does not contain microvascular AV anastomoses [8] [see chapter 61), and the disturbance usually gives continuous signs and symptoms, which can fluctuate in intensity. The disorder causes structural changes in skin microvascular architecture, and heredity may be involved as an etiological factor.

Phenomenon is used when the symptoms are intermittent, and no primary structural pathology is shown in the skin. The term *primary* is applied when no basic disease is apparent, and the term *secondary* if erythromelalgic symptoms are believed to be caused by a primary disease or disorder.

The term *acute* is applied if the disease reaches maximal strength within 4 weeks of the first symptoms. If symptoms have a more gradual appearance, the term *chronic* is used. A classification of patients into this scheme has to be based on judgement, and can in some few cases be difficult, but in most cases there has been little doubt as to which group patients belong.

The distinction between ES and EPPC can be difficult on the basis of clinical findings. An example is the family of case l, LHJ (see Fig. l, chapter 4). LHJ is classified as suffering from ES, while the cousin was classified as suffering from EPPC. The author has not, however, been able to suggest other clinical criteria for the classification, and has chosen to apply restrictive criteria for including patients as ES.

The distribution of the 40 cases in the present material is shown in Figure 2.

The author has been involved in the diagnosis and treatment of another two children with dramatic EPPA, one patient in Dundee, Scotland and one in Philadelphia. The history of the latter is described in chapter 4, and their treatment in chapter 9.

Severity of the disease

The severity of the burning pain varied considerably in this material. In the authors opinion, the patients can be classified in a continuous spectrum, according to the degree of involvement. For practical reasons a severity group scale was defined (Fig. 3), and used to illustrate the findings in the present material (Fig. 4).

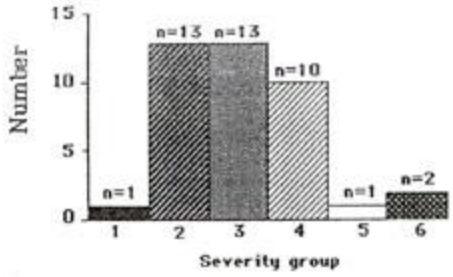

Fig. 4: Distribution of patients into groups of severity.

It is a well known clinical fact, that some healthy individuals "always" have cold hands and feet and feel cold, while others tend to be warm. It is a question of the individual's subjective feeling, as to when this warm or cold feeling is defined as a problem. In many such cases, no pathological signs are shown on clinical examination. If a patient, however, can tell of attacks where the digits "go dead", become pallid with shrunken pads and empty veins, it is probable that the doctor would think of a Raynaud's problem. If the patient tells about digits which are swollen, red and warm (or even burning) during attacks, it is possible that the doctor has heard about EM. It is in my opinion fruitful to think in terms of a continuous spectrum, not only of EM, but also of a warm/cold feeling as shown in Figure 5.

Table III: Sex distribution.

Category	Female	Male
ES	1	–
EPPA	2	–
EPPC	22	3
EPSA	1	2
EPSC	5	4
Total	31	9

Sex distribution

The sex distribution among the cases is shown in Table III. In the whole material there was a 3.5:1 ratio between females and males. A majority of females was found among both primary and secondary cases. A predominance of males in the ratio 2:1 was shown among "primary" erythromelalgic patients in the material presented by Babb et al. [6].

Distribution of symptoms

Table IV shows the number of patients in each category with affection of upper extremities, lower extremities or both. In this material primary disease is found both in upper and lower extremities. This is in contrast to the findings of Babb et al. [6], where patients with primary EM were found to be affected only in their lower extremities.

Table IV: Location of EM symptoms.

Category	Upper extremities	Lower extremities	Upper and lower extremities
ES	–	1	–
EPPA	–	–	2
EPPC	3	16	5
EPSA	1	2	–
EPSC	1	8	1
Total	5	27	8

The erythromelalgic involvement was symmetrical in all cases, except for two. One case of EPSA caused by cholesterol emboli syndrome, had symptoms in one foot only (see chapter 5), and one case of EPSC had burning pain in one hand secondary to osteoarthrotic affection of the shoulder (case example 6).

Duration of disease

Figure 7 shows the duration of disease before the first consultation at our department. The two cases with EPPA were referred 15 and 42 days after initial symptoms, while the three cases of EPSA were referred after 60, 80 and 231 days respectively.

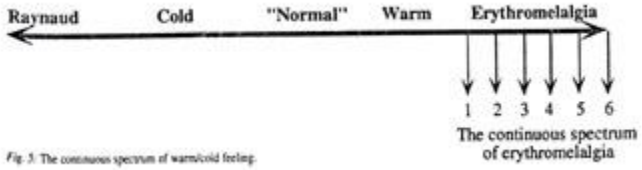

Fig. 5. The continuous spectrum of warm/cold feeling.

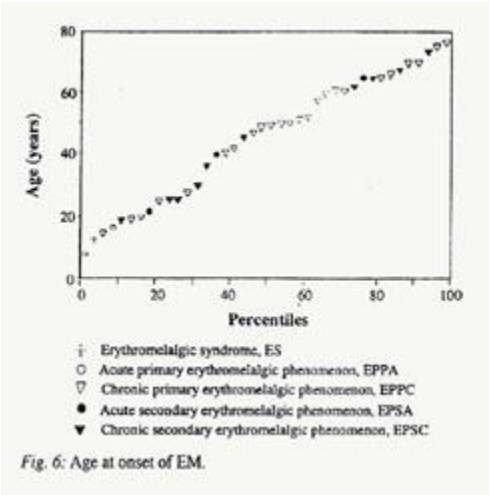

Fig. 6: Age at onset of EM.

Age of Onset

EM occurs in all age groups as shown in Figure 6. In the case of ES active cooling of the feet started at the age of 13 years (case 1), and the two girls with EPPA had a debut of symptoms at the age of 8 and 16 years. EPPC, EPSA and EPSC patients were diagnosed in both young, adult and in elderly subjects. The finding of Babb et al. that primary EM occurs at all ages was confirmed. In the present material also secondary EM was observed in subjects < 40 years, while Babb et al. found secondary disease only in subjects > 40 years old.

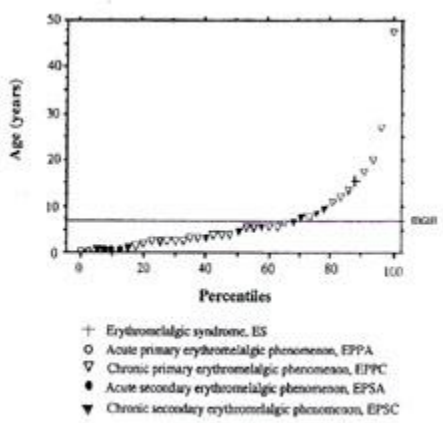

Fig. 7: Duration of EM before the first examination in our department.

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Chapter 4 - Incidence and Prevalence

In the literature, no reports of incidence or prevalence of EM exist to the author's knowledge. One explanation is that the disorder has not been well defined. and most doctors are probably not aware of the condition. Severe EM is probably, however, a rare occurrence. In a comment in The British Medical Journal in 1986 Housley states that he has not seen one convincing case over a time period of 16 years in the peripheral vascular clinic of the Royal Infirmary of Edinburgh, Scotland [I]. On the other hand, many subjects with milder involvement of EM (see Fig. 3, chapter 3) probably never consult a doctor.

The present material consists of 40 subjects from Norway, a country with just over 4 million inhabitants. All patients were seen during a time period of 7 years. The majority of cases contacted the author directly, without being referred by another doctor. They became aware of the author's interest in and experience with the disorder through a health program on-national radio'. The disease was only mentioned in one program broadcasted during or
ordinary working hours, and one would assume that only a minority of potential EM sufferers listened to the program. Approximately 50 %c of those who responded, were included as EM sufferers.

It is difficult to estimate the true incidence and prevalence of EM. The estimates are dependent on the criteria for the diagnosis and on severity of involvement. The present material consists of 40 subjects in a population of about 4 million people. The prevalence

must therefore be > 1/100000 inhabitants in Norway. An educated estimate could therefore be a prevalence of about 2/100000 inhabitants who suffer from EM with severity grade ≥ 2 (Fig. 3, chapter 3).

The mean duration of the disorder before consultation at our department was, in the present material, 6,5 years (median 3,5 years), (Fig. 7, chapter 3). If we assume that the mean duration of EM is 8 years, the incidence would be approximately 0,25/100000 inhabitants per annum.

References

Thanks are extended to Asa Rytter Evensen, M.D., Ph. D. and the editorial staff, « Sinn er livet», NRK, Oslo.

[11 Housley E. What is erythromelalgia and how should it be treated? BMJ 1986; 293: 117.

Chapter 5 - Etiology

Erythromelalgia is probably not one defined disease with a single etiological factor. The clinical picture varies considerably from patient to patient and, as pointed out in chapter 7, EM may represent a uniform vascular response to different etiological factors. In chapter 3, a clinical classification system is proposed, and etiological factors will be discussed for erythromelalgic syndrome (ES), and primary and secondary erythromelalgic phenomenon (EP) separately.

Erythromelalgic syndrome (ES)

Heredity

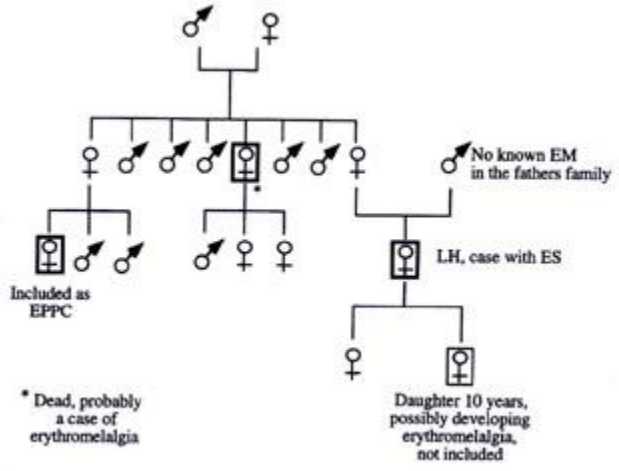

Fig. 1: The family of case example 1.

Several reports in the literature indicate that heredity is of importance in patients with ES. One example is a 14-yearold girl with severe erythromelalgic involvement of the feet and legs seen by Thompson et al. [1]. She had the first experience of burning discomfort in her feet and lower legs at the age of three years. The symptoms were initially mild and episodic, but soon became severe and constant. At the age of 13 she was admitted to the hospital with edematous, ulcerated and inflamed feet, causing

streptococcal septicemia and shock. An emergency bilateral knee disarticulation was performed.

Thompson classified this case as primary EM, but according to the author's description her disorder could probably be classified as ES (chapter 3). The girl had a mother and two older brothers who also had primary EM, but they were less severely affected. The father and two younger siblings were unaffected. There was no additional family history of EM.

Cross [2] reported a family where six members suffered from hereditary EM and nephritis. Autosomal dominant transmission with partial sex linkage was proposed, but the mode of heredity remains uncertain. Other reports [3-5] also show familial occurrence of EM-cases. Many of these reported cases would probably be classified as ES according to the criteria proposed in chapter 3.

In the present material only one case was included as ES. Figure 1 shows the patient's family tree. It may seem logical to classify the affected cousin as ES, but as mentioned in chapter 3, the author has chosen to apply restrictive criteria for classifying patients as such. In this family, however, heredity seems to be one etiological factor.

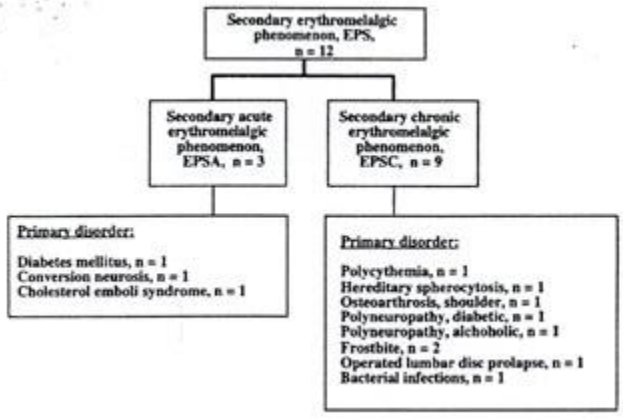

Fig. 2: Associated disorders in patients with secondary EM in the present material.

Psychological factors

Thompson et al. [1] performed an interview with the above mentioned 14 year-old girl after sodium amytal pre-medication, to try to determine if her pain was deafferentation or somatic in nature. Since the interview did not alter her situation, it was concluded that the symptoms were truly somatic. The etiology could, however, still be of a psychological nature. Our case of ES was examined by a psychiatrist, a clinical psychologist and a specialist in psychosomatic medicine without evidence of psychopathology or conversion neurosis.

Conclusion

Since the one case of ES in the present material and probably other cases in the literature which could be classified as ES have familial involvement of only the lower extremities, it is the author's belief that this syndrome is caused by an inherited disorder in skin vessels; a disorder that causes skin capillaries to proliferate, possibly as a response to hydrostatic distension pressure.

Secondary erythromelalgic phenomenon

The literature reports an association between EM and a wide variety of other disorders. Figure 2 shows associated conditions of the 12 subjects with secondary erythromelalgic phenomenon in the present material.

A review of associated disorders in literature is also given, but it is not within the scope of this presentation to discuss etiological factors for each of these associated illnesses

Conditions affecting the composition of and thereby the hemorheological properties of blood

Two cases of EM associated with myeloproliferative disorders were reported by Redding [6]. On the basis of these cases he presented the theory that abnormally rapid platelet aggregation could be the cause of EM, since: 1. histology showed thrombi probably composed of platelet aggregates, occurring arterioles; 2. EM symptoms reversed with drugs preventing platelet aggregation; 3. EM symptoms disappeared with adequate control of the myeloproliferative disease.

Michiels et al. [7] found EM to be the presenting symptom in 26 out of 40 patients with thrombocythemia. In skin punch biopsies taken from affected areas, typical arteriolar inflammation, fibromuscular intima proliferation and thrombotic occlusions were found. On the basis of these findings they proposed a casual relationship between EM and thrombocythemia. In another report of skin histopathological changes in patients with EM, Michiels et al. claim that EM always appears to be an expression of thrombocythemia [8], a statement which obviously is not in accordance with other reports in the literature, or with the findings in the present material.

In a recently published article, Kurzrock and Cohen [9] report a patient with chronic myelogenous leukemia associated with the development of EM. They also reviewed 60 cases of EM associated with myeloproliferative disorders published in the literature. In these cases symptoms of EM preceded the onset of a myeloproliferative disease by a median of 2112 years, and they therefore recommend all cases with EM to be monitored with periodic blood cell counts. Babb et al. reported one case where EM preceeded the full-blown myeloproliferative disorder by as much as 12 years [10].

In the present material one case with EPSC had a mild affection of hereditary spherocytosis, and one patient suffered from polycythemia.

All the above-mentioned disorders usually have disturbances in the hemorheological properties of blood, with an increased resistance to blood perfusion in small capillary tubes. This is because of an increased number of large and stiff white blood cells, an increased stiffness of red blood cells, a tendency towards rouleaux formation or formation of cell aggregates [11].

Diabetic ketoacidosis as in one case of EPSA (case example 5, chapter 3), also causes

increased stiffness of erythrocytes, and therefore pathological hemorheological properties of blood. This condition could probably also increase the blood/tissue diffusion barrier, or cause disturbances in the distribution of microvascular blood flow secondary to clinical undetectable neuropathy (see below).

Conditions which can increase the blood/tissue diffusion barrier

Eisler [12] showed an EM like eruption in nine out of 110 patients treated with bromocriptine medication for Parkinson's disease (also see below). Histopathological examination in three of these, showed a prominent perivascular lymphocytic infiltration and perivascular edema of the dermis, without vasculitis. The symptoms were reversible when bromocriptine medication was stopped.

An association with systemic lupus erythematosus is reported in two papers [13, 14]. In this condition vascular lesions may be encountered in any tissue or organ of the body [15]. The vascular changes are usually limited to small arteries or arterioles and consist of deposition of fibrinoid masses in the intima or the media.

A case of EM and coincident vasculitis of the feet is also reported [16].

Conditions which can affect distribution of microvascular perfusion

Vendrell et al. [17] studied one patient with acute diabetic neuropathy who developed EM. They noted an absence of histopathological lesions, and suggested EM to be caused by a disorder in vascular motility regulation caused by the severe neuropathy.

Polyneuropathy on the basis of high alcohol intake was believed to cause EM in one subject in the present material. He was a male of 68 years when first examined in our department. The duration of his EM had then been 71/ years, and he had classical EM, fulfilling both clinical and hemodynamic criteria (see chapter 6). He was seen on several occasions, in the following 31/- years. During this period, he developed a polyneuropathy, probably due to his consumption of alcohol, and at the last visit to our department, he did not fulfil the criteria for EM any more. Accordingly we think that EM symptoms preceded the clinical picture of polyneuropathy by about 10 years, and that this also was the duration of his EM.

Two cases of severe *frostbite* associated with EM are also included in the present material. The circulatory sequela secondary to a frostbite is probably complex, but it could be anticipated that the regulation of distribution of microvascular perfusion would suffer.

Cholesterol emboli syndrome [18] caused EM in one of our cases. Histological examination of a skin biopsy showed that large parts of the capillary bed were plugged by cholesterol crystals.

EM can also be provocated by drugs which have effects on vascular smooth muscle,

and thereby causes changes in blood microvascular distribution. Examples are bromocriptine and nifedipine [12, 19, 20]. Monk et al. reported two patients who received the ergot derivative pergloide as treatment for Parkinson's disease, and who developed EM [21].

One report refers to a patient with EM secondary to malignant thymoma [22]. In this case tumor secretion of serotonin was suggested by ultrastructural features of the tumor and increased urinary 5-hydroxy-indol-acetic acid (5 HIAA).

Psychogenic factors may be involved in some cases with secondary phenomenon (see aslo below). It is a well established fact that distribution of blood flow normally can be affected by emotions, examples are flushing and erection. Case example 4 in chapter 3 describes a male who got EM in his fingers after taking part in a robbery. The psychiatrist classified his disorder as a conversion neurosis, and postulated that he had a considerable secondary benefit from his EM - he did not have to go to jail, and he "punished" himself because of a bad conscience.

Other disorders which can induce EM

Hammer [23] described the association between plantar lesions of lichen scleroses and atrophicus and EM. In this condition the etiology is unknown, but drug sensitivity and psychogenic factors may be of importance [15].

EM has also been associated with astrocytoma [24], cerebral infarctions [25] and with one case of von Recklinghausen neurofibromatosis [26].

There was an epidemic of EM among secondary school students in Hubei. China, in February and March 1987. Among five schools, Zheng et al. [27] found an average prevalence of 12%. The disease was characterized by burning pain in the toes and soles of the feet and redness, congestion, and edema of the feet. 60.6% of the students had had a cold before the onset of EM and 91.2% had had pharyngitis. A poxvirus was isolated from throat swabs of five of the patients. This was a surprising finding, since human infection with poxvirus is uncommon today. Zheng et al. therefore postulated that the pathogenesis of EN1 may be connected with viral infection of the respiratory tract.

Primary erythromelalgic phenomenon

In the present material 25 cases were included as EPPC, while two cases were EPPA.

Some cases with EPPC could as mentioned above, be cases with the same etiological factors as ES. Other patients probably have primary disorders, and are true secondary phenomena. Symptoms of EM can, for example, precede the onset of a myeloproliferative disease by many years [9].

In the present material two girls with EPPA had severe symptoms. They were examined with a wide range of blood tests, but no probable etiological cause was found.

After treatment in our department they recovered completely and have since been free of symptoms of EM. One of these girls had a mild upper airway tract infection some weeks prior to EM (case example 3, chapter 3). and a virus etiology as proposed by Zheng could be one possibility.

In case example 4, chapter 3, EM was believed to represent a conversion neurosis. In the two girls with EPPA it is also possible that the disease was a result of a conversion disorder.

Can EM be a psychosomatic disorder?

Both girls with EPPA in the present material were examined by the same clinical psychologist[2]. and interesting observations were collected.

Case example 2. chapter 3 *(The case reports have deliberately been distorted.)*

NN was a eight year old female. When the psychiatrist examined the family situation she became aware of the following story: NN was born in USA. where her father was working as a carpenter. He suffered a myocardial infarction, and this event made the couple reevaluate their future. They chose to move back to Norway, where the father received a disability pension. He then worked at home, taking,. care of NN and the two older children, while the mother worked as a waitress and assistant nurse. When a turbulent family situation occured NN became seriously ill. For the next two months NN needed all her parents' time and attention, and they did not leave their daughter. When NN became healthy again, the disease had influenced the family situation and continues to do so 4 ½ years later - and NN is still healthy.

Case example 3, chapter 3

NN was a 16 years old female. She was clever at school, was physically, fit and actively taking part in cross country skiing competitions. She got her first EM symptoms at a training camp. just before the first test competition of the season. After dialogue with the family and "Thematic Apperception Testing (TAT)", the psychologist proposed the following psychodynamic theory for the cause of NN's disease:

NN's parents were talented with high intellectual potentials, but without higher education.

When the couple had children, the parents had great expectations of their achievements, both at school and in sports activities. For NN. the youngest child, these expectations were a heavy burden. When the ski season started she became ill with alarming acute EM symptoms, and could not continue her training. After treatment at our hospital, she recovered from EM, but had sequela with an increased tendency towards Raynaud's phenomenon. This disorder made further active spars at a high level of ambition, impossible.

When she was treated pharmacologically, and the symptoms of EM improved considerably. she regressed mentally and for a period had to be treated as a small child. At this point she also showed signs of apathy and depression. After a few weeks, she became her old self again, and has now been observed for 4 years without serious problems or signs of psychical disturbances. She has now started an academic education.

Discussion

Conversion neurosis with alarming symptoms has previously been described in children [28]. Selzer [29] has proposed the term: The conversion family, to describe a family with at least one child or adolescent member who exhibits a disabling physical disorder for which no corresponding organic problem can be found. In these families a conversion family culture with interrelated material and ideational dimensions is proposed, and major links between family history and symptoms can be described. Superficially almost nothing deviant, conflicting or problematic has ever been registered about these families. They appear almost "super-normal". Selzer also in these cases proposes a treatment regime based on a psychotherapeutic basis. In case 2, we treated her EM by pharmacological means, and her psychic imbalance did not need any professional psychiatric treatment.

The family members of case 1, chapter 3, the only case with ES in this material, were also examined by the same psychologist, but without obvious signs of any conversion disorder. These two cases with EPPA imply that EM can be the consequence of a conversion mechanism, and can be a psychosomatic disorder in some cases.

Other experiences

The author has been involved in the treatment of another case of EPPA.[3]

Case example 8 *(The case reports have deliberately been distorted.)*

NN was a 17 year old woman who was admitted to The Children's Hospital of Philadelphia. USA in 1986 because of severe burning pain in her hands and feet. She was in her usual state of good health until about four weeks prior to admission when she developed a cough, sore throat, and upper airway respiratory symptoms. EM symptoms then developed over a few days, about 2 weeks later. No underlying disorder was discovered during investigation at the hospital.

NN was the fourth and youngest child in an intact family. There was no history of problems between NN and the other members of her family. She was characterized as a "quiet and loving" child. NN reported considerable frustration at school. There were difficulties with her room-mate. She was also worried about getting into college, and about her grades (she was an average student). She reported the degree of stress as being very high, she was coping with the stress, but by a narrow margin.

In this case a conversion disorder could be one explanation for the symptoms. In such a

case, there would be a secondary, benefit from the disease - severe illness allowed her to be away from school for over two months.

Psychological mechanisms probably play an important part in the experience of pain in many cases of EM, as is the case with most chronic pain conditions. The case of ES (case 1, chapter 3) reports that her symptoms get worse when she has problems in her relation to her husband. An EPSC patient in the present material with a husband suffering from mania has symptoms that fluctuate with his disease. She also experienced a positive effect from dialogue with her chaplain about her marital problems.

[2] Thanks are extended to Wencke J Seltzer, clinical psychologist at the Child and Adolescent Psychiatric Section, Department of Pediatrics. The National Hospital, University of Oslo, Norway.
[3]Information obtained from Barbara Shapiro. M.D., Associate Director, Pain Management Program, Dept. of Pediatrics, The Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, Philadelphia, USA.

Conclusion

In conditions like venous thrombosis and inflammation, a variety of etiological factors can be involved. In the author's opinion, this is also the case in EM, and the proposal of this monograph is that many etiological factors can produce physiological disturbances leading to the symptom of EM. These etiological factors can be classified as disturbances which l. affect the composition, and thereby hemorheological properties of blood, 2. increase the blood/tissue diffusion barrier or 3. affect distribution of microvascular perfusion (see chapter 7).

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Chapter 6 - Histopathology

No uniform description of histopathological changes in patients with EM is found in the literature. Standard textbooks of pathology do not mention the diagnosis at all [1, 2]. In published papers, some authors do not find pathology on histological examination of biopsies from affected skin [3], while others claim that arteriolar pathology is obligatory [4].

Findings in literature

Secondary ervthromelalgic phenomenon

In patients with EM secondary to thrombocythemia, skin biopsies from affected skin show arteriolar inflammation, fibromuscular intima proliferation and thrombotic

occlusions [5]. When these patients were treated with acetylsalicylic acid, their symptoms improved. In biopsies, one to three weeks after discontinued treatment, major changes were still found in the arterioles [4]. The endothelial cells were often swollen with large nuclei. A narrowing of the lumen occurred by proliferation of smooth muscle cells with vacuolisation and swelling of the cytoplasm and deposition of intercellular material. The internal elastic lanvna appeared to be split between the proliferated cells. This gave rise to the appearance of fibromuscular intimal arteriolar proliferation which was often occluded by thrombi of varying age. Ultimately the arterioles became completely fibrosed.

A histopathological examination was performed on 3 patients with EM - like eruption secondary to use of bromocriptine [6]. A prominent perivascular lymphocytic infiltration and perivascular edema of the dermis, without vasculitis were found. When medication was stopped, symptoms and histopathological findings were reversible. Vendrell describes one case of EM secondary to acute diabetic neuropathy. Histological examination showed an absence of pathological lesions. [3].

Cross [7] reported a family where six members suffered from hereditary EM and nephritis. Histology of the kidney revealed a combination of chronic glomerulonephritis and pyelonephritis. Glomeruli had varying degree of hyalinization, atrophy and hypertrophy, but Cross was unable to demonstrate any gamma globulin deposition.

Peripheral autonome nerves in EM

Blanchard et al. [8] showed a slight and questionable reduction of the density of autonomic adrenergic nerve terminals in the periarterial and glandular plexuses in a skin biopsy of one patient, and partly on this basis suggested the hypothesis that EM could be explained by an abnormality of distal autonomic axons. Uno and Parker [9] have also shown degeneration of autonome nerve plexuses in skin affected with EM, compared to unaffected skin in the same individual and in one control person.

In both these reports the observed changes are not necessarily primary, but could as well be secondary to for example tissue hypoxia, as proposed in chapters 7 and 8.

Own Experiences

Six of the patients in the present material were examined with biopsy and histopathological sections from

Table I: Histopathological findings in the present material.

Number	Name	Diagnosis	Histopathological finding
1	LHJ, case 1 chapter 3	ES	Increased number of small vessels, mainly clustered in small groups. Deeper in corium and in subcutis: dilated small vessels.
2	NN, case 5 chapter 3	EPSA (Diabetes)	Possibly increased number of small vessels in upper corium. No thrombi.
3	ABB	EPSC (infections)	Dilated, but not proliferated small vessels in upper corium. No thrombi. Some perivascular lymphocyte infiltration, some interstitial edema.
4	NN, case 3 chapter 3	EPPA	No pathology.
5	RI	EPSC (polyneuropathy)	No pathology.
6	ÅK	EPSA (cholest. emboli)	Arterioles and capillaries loaded with athero-emboli, Cholesterol emboli syndrome.

affected skin. A summary of the findings is presented in Table I.

The findings in the biopsy from case example 1, chapter 3, LHJ the only case with ES, is of particular interest. Standard light microscopy showed marked proliferation of small vessels in the upper corium[4] (see fig. 1). These thin walled vessels were mainly clustered in groups, and had varying diameters. The pathologist therefore concluded that they probably represented capillaries and small veins. Deeper in the corium and in subcutaneous tissue dilated small vessels were found, but no proliferation was observed. No hemosiderin deposits or thrombus formation were found. Skin biopsy from unaffected skin of the thigh showed no pathology.

Immunhistochentical examination was also performed[5]. The sections were stained for deposits of IgG, IgA, IgM, C3, fibrin, Factor VIII and alkaline phosphatase. The proliferated vessels were clearly shown in sections stained for Factor VIII, usually found in epithelium. Only few areas showed alkaline phosphatases in the endothelium. There were small amounts of fibrin and IgM in some vessels, but marked immunological deposits were not demonstrated. The pathologist concluded that since alkaline phosphatase is regarded as a marker of vessels of the arterial side of the capillaries, the vessels in this section represent proliferation of the venous side. The changes were also described as being similar to the pathological vessels found in primary telangiectasia (Osler-Weber-Rendu disease).

Since transcutaneous oxygen tension measurements and clinical observations (see chapter 7) indicate tissue hvpoxia, it was important to look for a pathologically increased blood-to-tissue diffusion barrier. Electron micrographical studies were therefore performed in the same cases'. These sections showed no major pathology. The basal lamina varied somewhat in thickness, but were thinner than what is usually seen on the arterial side of capillaries. Some vessels had a multi layer basal lamina, which is compatible with the venous side of capillaries and venules [10]. No morphological diffusion barrier was found.

An important clinical observation in the present material is that all cases with erythromelalgic phenomenon, were affected only in their hands distal to the wrist and/or in the feet, distal to the ankle. The structure of skin microcirculation in these areas is different to the vascular anatomy in the rest of the upper and lower extremity. The vessels in the digits and palmar/plantar parts of hands and feet have a rich supply of arterio-venous (AV) anastomoses, subserving a thermoregulatory function (see Fig. 1, chapter 8). These AV anastomoses are innervated by the sympathetic trunk [11]. In leg and thigh skin and in the upper and lower parts of the arm such anastomoses are not described [12]. This observation suggests that AV anastomoses can play a part in the pathogenesis of ervthromelalgic phenomenon.

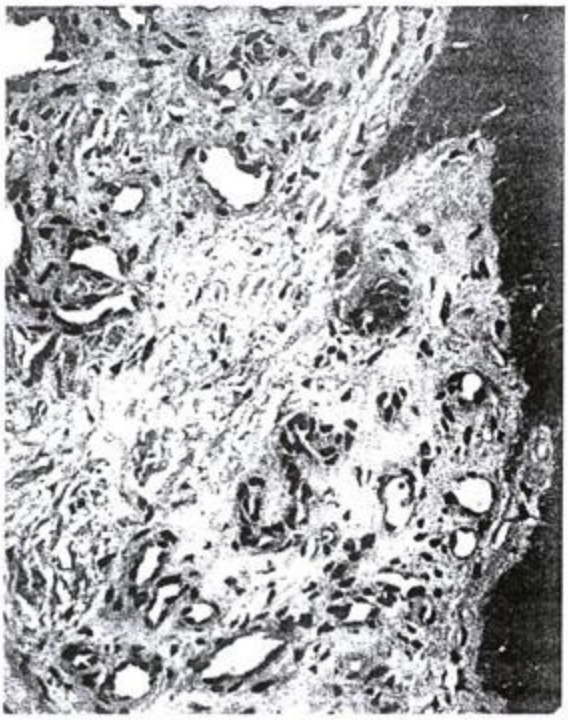

Fig. 1: Histology section of a skin biopsy from a patient with ES (case example 1, page 8). Nests of proliferating vessels serving as microvascular arterio – venous shunts are clearly seen.

Conclusion

EM is not, in the author's opinion, one defined disease. It is therefore not surprising that some reports describe pathology of skin vessels, while others do not find any pathology on histological sections.

The available literature and the findings in the present material does not offer any conclusive histopathological diagnostic criteria.

[4] *Examination performed by Nils Raknerud M.D., Dept. of Pathology, Aker Hospital, Oslo, Norway.*

[5] *Examination performed by Per Brandtzaeg Ph. D., Institute for Pathology, The National Hospital, University of Oslo, Norway.*

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Chapter 7 - Pathophysiology

Erythromelalgia was described more than 150 years ago, at a time when few methods for objective assessment of physiological parameters were available. The rapid capillary refilling time after anemisation has shown clinicians that affected skin is hyperperfused. Today equipment which can be used for detailed physiological studies of the circulation exists. So far, however. few reports on pathophysiology of EM have been published.

Findings in the literature

Skin temperature studies

Temperature studies have been performed by Babb et al, in 31 patients with EM, to determine a possible relation of distress to elevation of skin temperature [1]. The patients were first observed in a cold room, and the skin temperature in affected areas was recorded. Thereafter the patient was brought into a room with a temperature of 31 to 33°C. A correlation was found between skin temperature and distress; increased skin temperature induced the burning distress, and the return to a lower temperature made the distress disappear. Lewis claimed that a fairly constant critical temperature at which the pain occurs exists in each patient [2]. In most patients this critical point lies within the range of 32 to 36°C. It is also shown that temperatures which cause distress in patients with EM, do not provoke any discomfort in healthy controls [3].

Other physiological investigations

Brown pointed out that increased elimination of heat was a consequence of vasodilatation, and showed increased content of oxygen in the venous blood from the affected extremity of these patients [4].

In one case where the drug nifedipine had induced EM, the authors claimed that skin temperature increased but photoplethysmography did not show increased blood flow [5]. This statement is not a correct interpretation of the results in the authors view, since photoplethysmography does not measure blood flow, but changes in tissue hematocrit during a pulse wave. In cases with low peripheral vascular resistance the amplitude of the photopletysmography signal can be small in spite of a large blood flow.

Lazareth and co-workers are to the author's knowledge, the only group which so far has applied more sophisticated non invasive methods in an attempt to gain more knowledge about the physiology of EM [6]. They used capillaroscopy to examine the patients, but found this method to be of little help in diagnosing the disease.

Discussion

Lewis found that the critical skin temperature point for the provocation of pain lies

within the range of 32 to 36°C. An interesting observation in this context was performed by Walmsley and Wiles [7]. They quantified skin perfusion with laser Doppler flowmetry (see below) in healthy controls. With local heating they observed an initial gradual rise in perfusion followed by a later rapid rise in skin blood flow. In all subjects examined, this change in the sloop of the graph occurred at temperatures above 33°C. It therefore looks as if both healthy individuals and patients with EM have a critical temperature where skin microcirculation increases rapidly, for example by opening of microvascular AV anastomoses and other vessels mainly sub-serving thermoregulatory perfusion. In healthy controls heating above this level does not cause burning pain, but in patients with EM it does - possibly because of a lack of ability in patients to increase nutritional capillary blood flow (see chapter 8).

Own experiences

In this study several non-invasive methods have been applied on patients with EM to evaluate objectively their peripheral circulation, in search for a more thorough understanding of pathophysiological mechanisms. The microcirculation of affected skin has been evaluated by laser Doppler flowmetry (LDF) and of muscle perfusion by single-fiber laser Doppler flowmetry (SF-LDF). The macrocirculation in the affected limb has been examined by ultrasound Doppler flow velocity measurements and strain gauge plethysmography, whereas effects on central hemodynamics have been studied by thermodilution measurements of cardiac output. The effects of flow disturbances on skin nutrition (transcutaneous oxygen tensiometry), and on total body thermoregulation (calorimetry, body temperature measurements) have also been evaluated.

Methods

Studies of blood flow

Laser Doppler flowmety

The principles governing measurements of blood flow by LDF have been described in detail elsewhere [8.9]. Essentially, coherent light from a 2 mW Helium-Neon laser is brought to the skin by an optical fiber and undergoes multiple scattering and absorption in a small hemispherical volume of tissue with a radius of approximately 1 mm [101. When scattering occurs from a moving object such as an erythrocyte (RBC) the wavelength of the light is changed (Doppler effect) and the light reflected from the illuminated volume will therefore consist partly of unchanged and partly of Doppler shifted light. Some of the illumination will be directed out of the tissue and picked up by optical fibers in the head of the probe and guided back to the instrument for signal processing. The Doppler shifted part of the signal is isolated and converted into a voltage output signal which is linearly related to the flux of RBC [9, 11].

All measurements were performed with a Periflux® (PFIc or Pfld) laser Doppler flowmeter (Perimed KB, Stockholm, Sweden). The flowmeter output signal was recorded in the present studies with a linear recorder (Graphtec mark VII®, Graphtec Corp.,

Tokyo, Japan), the flux values being expressed in arbitrary Relative Flux Units (RFU). The zero level was obtained by placing the laser probe against a white reflecting surface, while 40 % of full scale level with gain 10, was defined by calibration against a standardized latex solution, as recommended by the manufacturer. At Periflux® gain 10 and full flowmeter deflection the flux was defined as 10 RFU; at gain 100 the related flux value was 1 RFU. Periflux filter settings of 4 kHz and 0.2 s were used in all measurements.

Laboratory procedure

The LDF measuring probe was fixed to the skin with the help of a plastic sleeve, using double adhesive tape. When postocclusive hyperemia was recorded, limb ischemia was created by a pneumatic tourniquet placed directly above the patella or at the level of the ankle and rapidly inflated to a pressure of 300 mm Hg. This pressure was maintained for three minutes and then suddenly released. The width of the cuff was approximately 30 % of the thigh circumference. The laser Doppler output was recorded continuously before, during and for five minutes after release of the tourniquet.

Single fiber - laser Doppler flowmetry (SF-LDF)

The technique of SF-LDF was first described by Salerud and Oberg [12]. In this study a standard laser Doppler flowmeter (Perifluxo PfId, Perimed KB, Stockholm, Sweden) was used as the basic equipment for the signal processing. Instead of the standard multifibre probe, a single fibre probe was used[6]. In this LDF system, light is transmitted bidirectionally through one optical waveguide without mixing its inherent frequencies. The step-index plastic waveguide (ESKATM, SH2001, Mitsubishi Ltd, Japan) chosen in this study had a diameter of 0.5 mm and a numerical aperture (NA) of 0.5. SF-LDF has previously been shown to be a method which can be used for continuous measurements of human muscle blood perfusion [13, 14].

[6]*Thanks are extended to Goran Salerud Ph.D., Dept. of Biomedical Engineering, University of Linkoping, Sweden, for constructing the equipment and making the prototype available for the author.*

Laboratory procedure

Only the case with ES (case 1, chapter 3) was examined. The patient was recumbent for 15-20 minutes in a room with an air temperature between 22 and 24°C before measurements. A standard cannula (Microlance, 0.9 * 40 mm, No. 1, B-D R) was introduced into the anterior tibial muscle 12 cm proximal to the ankle joint. The SF-LDF probe, sterilized in ethylene oxide, was then brought into the muscle tissue through this cannula, and positioned to protrude 0.5 cm from the cannula tip. The proximal end of the probe was connected to the laser Doppler flowmeter. In a juxtaposed position skin perfusion was simultaneously evaluated with another laser Doppler flowmeter. This LDF probe was attached to the skin, using a standard probe holder and double adhesive tape. The recordings were made with a pen writer (Graphtec mark VII®, Graphtec Corp.,

Tokyo, Japan).

Ultrasound blood pressure measurements

Brachial- and ankle blood pressure were recorded with an ultrasound flow detector (Model 802-A, Parks Electronics Lab.). The ratio between ankle- and brachial systolic blood pressure, the ankle pressure index (API) was calculated. An index < 0,95 indicated the existence of stenotic involvement of the lower limb arteries.

Ultrasound flow velocity measurements

The basis for measurements of blood flow velocities using ultrasound Doppler technique is described elsewhere [15, 16]. The flow velocity measurements were performed with a pulsed wave Doppler ultrasound flowmeter (Alfred©, Vingmed, Norway). Non-invasively a probe with an ultrasound frequency of 10 MHz was used at the level of the ankle and foot, whereas other arteries were investigated using a 5MHz probe.

Laboratory procedure

The ultrasound probe was placed on the skin at an angle of 45° against the blood flow direction, using a coupling gel (Aquasonice) for transmission of the ultrasound waves. All recordings were made with a pen writer (Graphtec mark VII®, Graphtec Corp., Tokyo, Japan).

From the flow velocity curves maximal (V_a) and minimal speed (V_b) were measured. Mean velocity was also recorded. From these data the Pulsatility Index ($PI = V_a - V_b)/ V_{mean}$) was calculated in some cases (Fig. 1).

Strain gauge pletysmography

The basis for measurements of limb blood flow with strain gauge pletysmography was given by Whitney [17]. The pletysmograph consisted of an electrical and pneumatic part. Extensible mercury-filled fine bone silastic tubes served as a double stranded strain gauge, which formed one arm of a Wheatstone bridge. The bridge circuit was equipped with electrical volume calibration [18], which permitted repeated calibrations in between measurements. A linear relationship between the extension of the gauges used in our study, and recorded volume have previously been shown at our laboratory [19].

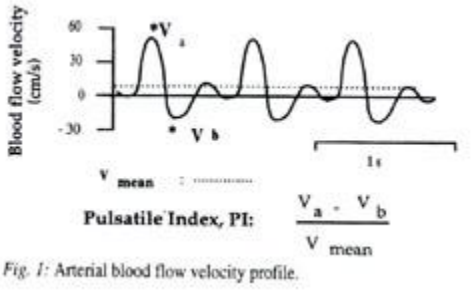

Fig. 1: Arterial blood flow velocity profile.

Laboratory procedure

The gauges were placed around the greatest circumference of the calf with the lowest tension necessary to maintain good contact with the skin. The venous occlusion cuff was applied just proximal to the patella. Venous collecting pressure of 50 mmHg was obtained by inflation of compressed air in the course of 1-2 s, and was maintained for 5-10 s. The recordings were made with a pen writer (Graphtec mark VII®, Graphtec Corp., Tokyo, Japan). Blood flow was calculated from the linear part of the plethysmographic curve-and was expressed in ml/min and 100 g of tissue.

Cardiac output

Cardiac output was estimated according to the thermodilution technique described by Gantz et al. [20]. During this procedure, blood samples for analysis of oxygen saturation were also collected[7].

[7] *Measurements performed by Otto Orning MD, Dept. of Medicine, Akter Hospital, Oslo, Norway.*

Studies of tissue nutrition

Transcutaneous oxygen tensiometry, $TCpO_2$

$TCpO_2$ measurements are based on an electrochemical reaction between 0_2 having diffused through the skin and an epicutaneous sensor. An electrochemical reaction takes place in the sensor and produces an electrical current proportional to the amount of diffused oxygen [21]. Measurements were made using a Kontron Roche 632 monitor equipped with a Clark-type electrode. The sensor temperature was set at 45°C. Calibration and membrane change procedures are described elsewhere [22].

Laboratory procedures

Prior to sensor application, the skin was washed with alcohol. By the use of double-sided adhesive rings, the sensors were attached to the skin before recordings were started. In some recordings a postocclusive hyperemic test was performed-see procedure for LDF above. Measurements were also performed before and after breathing 100 % oxygen.

Studies of bode heat balance

Calorimetric

To evaluate the effect of active cooling in cold water on the total body heat balance, calorimetry was performed in the case of ES (case 1, chapter 3). A water filled two

chambered thermobox was used as calorimeter. The calorimeter was filled with water with a temperature of 18.0°C, the temperature usually used for cooling by the patient. The feet were then immersed in the water, one foot into each chamber. Water temperature measurements were then performed at 10 minute intervals for 30 minutes, and the heat loss was calculated in cal/min and 100 g of body tissue.

Results and discussion

Studies of blood flow

Resting skin perfusion

Measurements were performed on 39 subjects on the toe pulp and anterolaterally on leg skin, 10 cm proximal to the ankle joint. In summary, resting skin perfusion in unaffected areas was not different from reference values at our laboratory [23]. In affected areas skin perfusion during attacks was considerably increased in all patients.

Case example 1 with ES was examined on twelve occasions during six years, and had pulp perfusion varying between 7 and 9 RFU (reference values 1.5 [0.9-3.0], median with 95 % confidence interval). In affected leg skin the patient's values varied between 4.5 and 6 RFU (reference values 0.48 [0.38-0.62]). In controls there is a marked difference in flux values between pulp and leg skin perfusion as shown by the reference values. This finding is believed to be caused by differences in skin microvascular architecture [23]. Arterio-venous (AV) anastomoses subserving a thermoregulatory function is located in the pulp, while these shunts are absent in leg skin [24]. In the ES patient, however, extremely high perfusion was recorded both in pulp and leg skin, probably because the proliferated vessels shown in the skin biopsy (see chapter 6), have a shunt function.

In patients with erythromelalgic phenomenon leg skin values above 0.7 RFU were never observed (reference values 0.48 [0.38-0.62], median with 95 % confidence interval). In pulp skin perfusion values varied considerably according to whether measurements were performed during attacks or not. Resting values between 1.0 and 7.5 RFU were observed (reference values 1.5 (0.9-3.0). In all cases examined during attacks, values > 4.0 RFU were found.

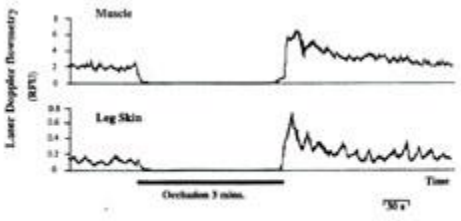

Fig. 2: LDF recording during a postocclusive hyperemic test in muscle and skin in a human control.

Postocclusive hyperemic perfusion

Skin perfusion was measured continuously both on the toe pulp and on leg skin before, during and for 5 minutes after 3 minutes of tourniquet occlusion in 37 patients. An example of a LDF recording of a postischemic reactive hyperemic response in skin and muscle in a healthy control is shown in Figure 2.

In repeated recordings at different occasions from affected skin in the ES patient, no

hyperemia above resting flux levels were recorded after tourniquet occlusion for 3 min. (Fig. 3), indicating that this patient had maximal vasodilatation in affected skin. Perfusion is either maximal or absent (during tourniquet occlusion); the curve has an "on or off" pattern.

One way of describing postocclusive hyperemic curves is to relate peak hyperemia to preocclusive perfusion level (hyperemia index, HI). In young healthy controls this index is 2.9 (median) with a range of 2.4-5.9. (95% confidence interval) in leg skin [14], while no corresponding reference values are available for pulp skin. The findings in toe pulp in the present material was classified according to this index into three groups, Table I. HI < 1.2 was classified as "on - off' response (group 3), while values > 1.5 were considered as normal (group 1). Borderline cases (group 2) were patients with 1.2 < HI < 1.5.

Approximately 50% of the patients had marked pathology with nearly maximal vascular dilatation at rest. There seems to be a positive correlation between symptoms and signs, and LDF hyperemic findings, since all patients with burning pain during examination had HI < 1.2. Patients with HI > 1.5 were examined in periods of no pain. In unaffected leg skin the hyperemic response was within normal limits in cases with EM phenomenon. Figure 4 shows an example of one case where pulp perfusion (skin containing AV anastomoses) has an "on or off" pattern, while HI in the unaffected leg skin is 3.3. The pathological findings of skin microcirculation accordingly seems to be confined to the affected skin areas.

Distinct vasomotion flow pattern [25] was observed in leg skin in patients with EM phenomenon (Fig. 4). Vasomotion was sometimes difficult to identify in affected pulp skin during attacks (Fig. 3), but was sometimes seen (Fig. 4).

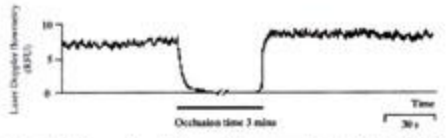

Fig. 3: LDF recording of "on or off" response in a patient with EM.

Single fiber - laser Doppler flowmetry (SF-LDF)

In the literature, the author has not been able to find examinations or comments on the question of whether EM is a vascular disorder in skin only or in both skin and other tissues. In patients with primary EM phenomenon it is, as discussed in this monograph (chapter 6, 7 and 8), reasonable to relate the disorder to malfunction of AV anastomoses, subserving thermoregulatory skin perfusion. The anastomoses are located only in certain areas of skin and these patients probably have normal vascular function in other tissues. In the case with ES, marked structural pathology was found on skin biopsy examination (chapter 6), and in this patient muscle tissue underlying the affected skin, could have the same vascular changes. We have recently published the first results of continuous measurements of microvascular perfusion in human muscle, using SF-LDF [13. 14]. The result of recordings of the case with ES is shown in Figure 5. The on-off pattern is clearly shown in the leg skin, while the underlying anterior tibia] muscle shows a normal response with an HI of 4.1,

reference values are 3.6 (median) with 2.9-5.3 (95% confidence interval) [14]. This finding implies that the pathophysiology of microcirculation in EM is found only in affected skin.

Ultrasound blood pressure measurements

Table I: LDF patterns found in the present material.

Category	No pathology (group 1) HI > 1.5	Borderline (group 2) 1.2 < HI < 1.5	On-off response (group 3) HI < 1.2
ES	–	–	1
EPPA	–	–	2
EPPC	14	1	9
EPSA	1	–	1
EPSC	2	2	4

In his material from the Mayo Clinic, Babb [1] had three patients with pathology of pedal pulses evaluated clinically, but the cause of the pulse abnormality is not mentioned in his publication. Apart from this report, the author has not found any comments on the relation between atherosclerosis and EM. Ankle blood pressure measurements with the help of an ultrasound flow detector is the most commonly used laboratory method for evaluation of lower limb atherosclerosis [261. In the present material six patients had the combination of EM and pathologically reduced API, Table II. When the atherosclerotic involvement was asymmetrical, EM was still symmetrical. In the only case with asymmetrical involvement of EM, API showed a similar degree of atherosclerosic disease. Lower limb atherosclerosis accordingly does not seem to cause EM.

Ultrasound flow velocity measurements

Clinical examination of EM patients shows rapid capillary refilling time after anemisation and LDF shows high capillary perfusion values. In the case with ES, angiography showed normal arteries, but unusually rapid passage of contrast to the venous side. Flow velocity pattern in the arteries at the level of the ankle were therefore examined in 38 patients.

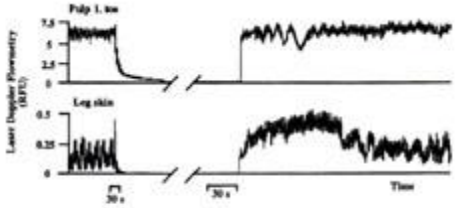

Fig. 4: LDF recording in leg and pulp skin with "on or off" response in affected toe pulp and normal response in leg skin. Vasomotion waves is seen in both curves.

An example of the blood flow velocity profile of the common femoral artery of a healthy control at rest and after exercise is shown in Figure 6[8]. At rest a three-phasic velocity pattern is seen in > 95 % of recordings in the posterior tibia] artery in healthy controls [27, 28]. During hyperemia induced by exercise, a monophasic velocity profile is recorded, and even during diastole the blood moves in the distal direction. It is also a well known fact that in parts of the circulatory system with low vascular resistance, for example internal carotid artery and brain circulation, a similar flow pattern with positive diastolic flow is found [29].

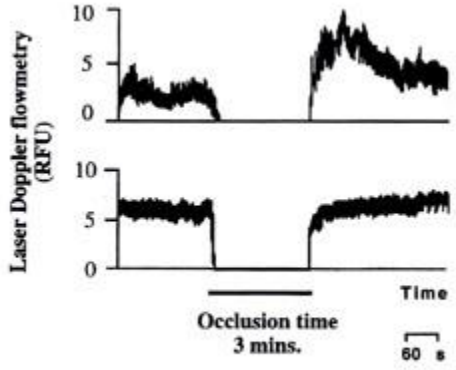

Fig. 5: Simultaneous LDF recording in leg skin (lower curve) and in under-lying muscle (upper curve) in the patient with ES.

Figure 7 shows a recording of maximal and mean velocity of the posterior tibial artery in a patient with EP. In this case the LDF pulp hyperemia profile showed an on-off response. The figure shows a maximal velocity of of 33 cm/s (reference: 23.0 cm/s [8.11, mean and SD [28]), a minimal velocity of 15 cm/s (reference: -5.5 cm/s [2.2]), and mean velocity of 17 cm/s (reference 2.7 cm/s [1.1]). Since there was no sign of atherosclerosis in the artery, and the blood pressure was within normal limits, the result indicates a marked hyperemic flow pattern with extremely low peripheral vascular resistance. Table III shows results of measurements in the different categories of EM. Group 1, "normal" means a three-phasic flow velocity profile with negative diastolic flow velocity. Patients in group 3, "low peripheral resistance" had monophasic curves with positive diastolic flow, while patients with curves fluctuating during a period of 1 minute between positive and negative diastolic velocity were named "borderline", group 2. One patient with EPSC and group 3 velocity profile was classified as group 2 LDF skin hyperemia response. In all other cases, patients had the same group classification with ultrasound Doppler velocity measurements and laser Doppler flowmetry.

[8] *After Jorgen J. Jorgensen, J Oslo City Hospital 1984:34: 109-114*

Studies of skin nutrition

Table II: Patients with lower limb atherosclerosis and EM in the present material.

Name/sex age	Category Symmetry of EM?	API Dext.	API Sin.	Severity index	LDF category	Velocity profile
HS, male 76 years	EPPC symmetrical	0.45	0.60	3	3	3
RI, male 65 years	EPSC (polyneuropathy) symmetrical	0.82	0.76	4	3	3
ÅK, female 65 years	EPSA (cholesterol emboli) asymmetrical	0.64	0.72	4	3	3
GN, female 61 years	EPPC symmetrical	0.93	0.96	2	1	1
KN, male 62 years	EPSC (polycythemia) symmetrical	0.70	0.76	2	3	3
FW, male 67 years	EPSC (diabetes polyneuropathy) symmetrical	1.0	0.67	1	1	2

Transcutaneous oxygen tensiometry, $TCpO_2$

Measurements of transcutaneous oxygen diffusion ($TCpO_2$) with the equipment currently available on a commercial basis, have several limitations. First of all recorded values are dependent on skin quality, and measurements are not possible in thick skin, for example in the plantar aspect of the foot. To enhance recorded values in skin of dorsal aspects of the foot and the leg, local heating to 45°C is used, and measurements are therefore not performed under physiological conditions. The measuring probes used at our lab. are also too large to be applied on fingers and toes.

Measurements were performed in unaffected leg skin of eight EM patients, and all results were within the range of reference values of age-matched healthy controls.

Recordings in affected skin, were for the above mentioned reasons, only achieved in two patients who had no signs of lower limb atehrosclerosis: Case example 1 with ES and case example 3 with EPPA.

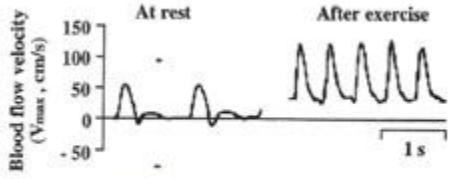

Fig. 6: Arterial ultrasound velocity profile at rest and during hyperemia.

In the ES patient repeated measurements were performed during a time period of six years. Values in affected leg and foot skin were within the range of 0-3.3 kPa, reference values at our lab are 9.2 (7.7-9.5) (median with 95 % confidence interval) in healthy controls < 30 years [221. The patient's skin was not pathologically thick, as evaluated clinically or by light microscopy of biopsy (chapter 6). This surprising finding was observed in skin which on LDF post-occlusive test showed an "on or off" response.

The reference level for $TCpO_2$ at the dorsum of the foot in a group of subjects with critical ischemia secondary to severe atherosclerosis was 0.9 (0-4.0) [22]. This group of patients all had critical ischemia, i.e. ischemic rest pain, ulcerations or gangrene and API ¡Ü 0.4. A recording of 0 kPa. can be found without the existence of gangrene [30]. The reason is believed to be that the currently available measuring probes consumes oxygen, and measurements at low levels of available oxygen can therefore be erroneously low [31, 32].

In one recording in the same patient, a stable level of 1.9 kPa was observed. When inspiratory gas was changed from air to 100 % oxygen, nothing happened for the first 30 s, and then a rapid increase in recorded value was observed until a new stable level of 34 kPa. This value is within normal limits in healthy controls [33].

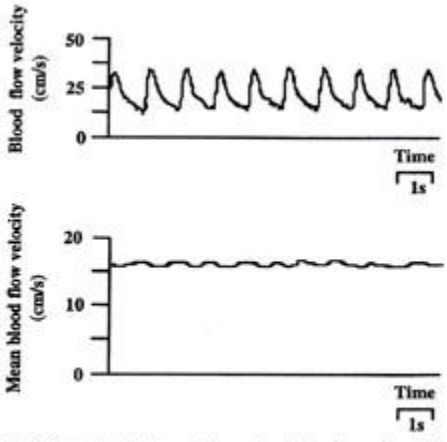

Fig. 7: Posterior tibial artery ultrasound velocities in a patient with EM.

Case example 3 had affection mainly in the soles of the feet, toes, palms of the hand and fingers. On the dorsum of the foot there was also some redness and pain, and in measurements on the dorsal aspect of the foot, between 1. and 2. metatarsus, repeated measurements performed on separate days showed severely low values, down to 0.6 kPa, reference values 9.2 (7.7-9.5), (median with 95% confidence interval).

Clinical observations

In case 2, chapter 3 with EPPA, it was not possible to obtain $TCpO_2$ measurements from affected skin. Three months after her serious disease and successful treatment, the

girl had no signs of EM. On examination of all her toe nails and partly on some finger nails, semilunar ridges were found in the middle part of the nail. In the author's opinion, these ridges probably represented growth disturbances in the nail during the disease period, disturbances which could be caused by hypoxia.

Case example 1 with ES also had two other important clinical findings. In periods with severe distress from EM, the patient got small skin ulcers without any causative trauma. Twice such exacerbations were improved by treatment with intermittent inhalation of 100% oxygen and infusion of prostaglandin El (see chapter 10). During clinical remission, the ulcers healed. The site for the biopsy of affected skin in this patient healed very slowly during a period of nine months.

One patient with EPPC and one with EPSC also had small ulcers in affected skin. Both were successfully treated with Surall prostaglandin El (see chapter 9), and after treatment the ulcers healed.

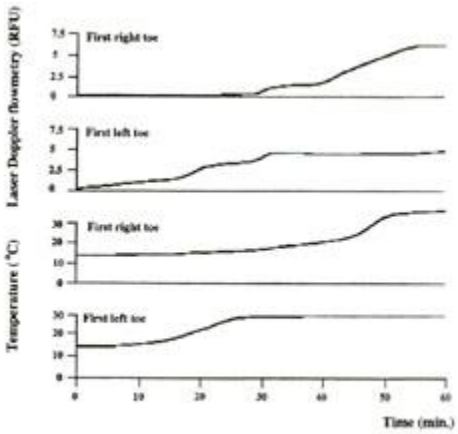

Fig. 8: Skin perfusion (LDF) and temperature in case example 1 with ES.

Discussion

The observations of low $TCpO_2$ in affected skin, the growth disturbance of the nails in case example 2, the small ulcers and the slow healing after biopsy in case example 1 are all findings indicating the existence of hypoxia in affected skin. The pain, which in many of the patients is difficult to relieve by opiates, could also be caused by hypoxia. Supporting this interpretation is the well known clinical fact that ischemic pain is often difficult to relieve by narcotics. For example a recognized clinical guide-line for surgeons is that patients with acute continuous abdominal pain which is not relieved by large doses of opiates, often have intra-abdominal ischemia.

Blood oxygen saturation

Blood oxygen saturation was measured in case example 1 during heart catheterization. During cooling of the lower limbs (vasoconstriction),.a mixed venous oxygen saturation in the pulmonary artery was found to be 70 %. In the common femoral vein, mixed blood from the limb showed oxygen saturation of 86 %.

Table III: Ultrasound velocity patterns found in the present material.

Category	Normal (group 1)	Borderline (group 2)	Low peripheral resistance (group 3)
ES	–	–	1
EPPA	–	–	2
EPPC	14	1	9
EPSA	1	–	1
EPSC	3	1	5

After the limbs had been taken out of the bucket of water and rewarming and vasodilatation started, both these values fell. After 35 minutes, pulmonary artery oxygen saturation was 65 %, and common femoral vein saturation was 84 %. Fifty minutes after stopping of the active cooling, pulmonary artery saturation was 60 % and common femoral vein 80

%.

During this period of time the cardiac index increased from 3.6 (cooling) to 4.02 (30 minutes after cooling) to 4.36 (45 minutes after cooling). Reference values for Cardiac index = Cardiac output/m^2 is 2.5-4.2 [34].

Discussion

The AV oxygen extraction in the lower limbs seems to be low; only 14 % during cooling. This could be caused by two factors. Firstly, the metabolic needs of cold skin are low. Secondly, the abnormally rapid microvascular passage time shown in the hemodynamic studies implies microvascular shunting of blood. When the skin was rewarmed, the temperature raised about 18°C. Since the metabolic needs increase about 130 % for every l0°C [34], the patient's skin increased the metabolic needs of oxygen by about 235 %. In spite of the increase in perfusion during rewarming, an increase in AV oxygen extraction to 20 % was observed. This augmented AV extraction is probably caused by a rise in the blood-tissue oxygen tension difference, i. e. an increased tissue hypoxia after rewarming.

The effects of cooling on hemodynamics and body heat balance

Case example 1 with ES was studied with several techniques during rewarming after cooling her feet in cold water for 30 minutes. She had been treated with a lumbar sympathectomy on the left side 10 months previously. Before this treatment, the severity of the disorder was symmetrical. Differences in results between the two lins, therefore also gives an impression of the effect of sympathectomy.

Measurements of skin temperature, skin perfusion on the toe pulp (LDF), calf blood flow (strain gauge plethysmography), common femoral artery blood velocity profile and PI were performed bilaterally for 50 minutes. Heart catheterization was also performed and cardiac output estimated.

Skin perfusion and temperature during rewarming

Figure 8 shows simultaneous recordings of skin perfusion (LDF) and temperature. It is obvious from the figure that cooling induces vasoconstriction in affected skin. After cooling in water, there is a gradual rewarming, and the left limb which was sympathectomized 10 months previously was rewarmed more rapidly. This is also the most troublesome limb for the patient.

Calf blood flow

Calf blood flow was measured with the help of strain gauge plethysmography, and the values expressed in ml/100 g and min., (Fig. 9). After 12 minutes a steady increase was observed in both legs. The minimal level recorded in both legs was 5.0 m1/100g and min. in the right leg and 5.2 ml/ 100g and min. in the left leg, and the stable level after rewarming was around 11.2 ml/100g and min. Reference values at our lab. (men of 24 years) are 4.1 (SD: 0.8) ml/100g and min. [35], so the patient had approximately a 2.8 times increase in leg blood flow at a steady state without cooling.

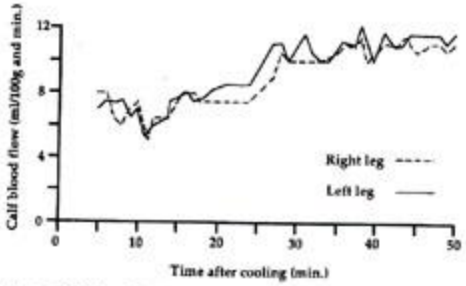

Fig. 9: Calf blood flow in case example 1 with ES.

Ultrasound flow velocity measurements

Blood velocity was examined in the common femoral artery during warming up, using the ultrasound Doppler flowmeter. Figure 10 shows the mean flow velocity and Figure 11 the calculated PI during rewarming. PI has been shown to be a parameter on vascular resistance in health controls [28].

Mean flow velocity increased in our case of ES from 15 to 32 cm/s while PI decreased from 7.6 to 3.3 during rewarming. Reference values for mean resting velocity in the common femoral artery are at our lab. (healthy controls, 30 years) 9.0 (SD. 4.4) cm/s and for PI 8.2 (SD 1.9) [28]. The reference value at rest for PI in the common femoral artery is 8.2 (1.9 SD) at our laboratory, while it is reduced in the same reference group to 2.6 (0.9 SD) after exercise (25 knee bendings carried out during a period of 30 to 45 seconds). Since no marked changes were observed in blood pressure, the results show a reduction in peripheral resistance during warming up, to a level with a very low resistance: This low resistance is probably caused by opening of constricted arterioles, and a marked perfusion in the patient's skin microvascular shunts, see chapter 8.

Cardiac output

Cardiac index measurements showed an increase from 3.6 during cooling to 4.36 after rewarming (see above). This represents an increase in cardiac output of 21 %. Reference values for Cardiac index = Cardiac output/m^2 is 2.5-4.2 [34].

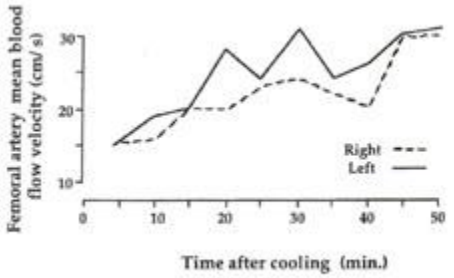

Fig. 10: Mean blood flow velocity in common femoral artery in case example 1 with ES.

Body heat balance

Rectal temperature in case 1, chapter 3 with ES was found to be between 33.3°C and 35.5°C on repeated measurements during six years . The patient often complained of

feeling cold, and wanted to have a room temperature of 27-30°C. In the hospital we often observed the patient sitting sleeping in her chair and cooling her feet in cold water. It is possible that this sleep was a compensation for lack of sleep during the night, caused by intermittent pain and cooling. Another possibility is that this sleep was related to the low body temperature. During conversations, she would from time to time have small periods of "absence"; this could also be caused by reduced cerebral function because of low body temperature.

Cases 2 and 3 (chapter 3) with EPPA used active cooling almost continuously in periods. In spite of the cooling, they had slightly elevated body temperatures of 37.5 to 37.7°C.

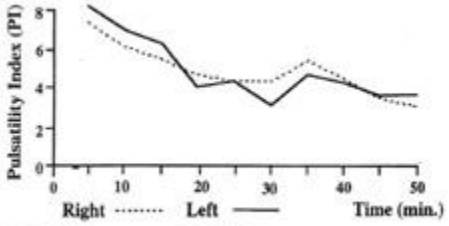

Fig. 11: PI in case example 1 with ES.

They also had tachycardia with frequencies of 100 to 130 at rest, and it is probable that their body temperatures without cooling would have shown fever.

The heat loss in the case with ES was measured in the calorimeter, and the result is shown in Figure 12. The heat loss is most marked in the left sympathectomized limb.

Conclusion

The results indicate a coexistence of hyperperfusion and tissue hypoxia in affected skin, caused by microvascular shunting. The hemodynamic effect of this shunt flow is shown both at the level of the affected skin, leg blood flow, femoral artery blood flow and even on the cardiac output. Cooling induces increased vascular resistance by vasoconstriction and reduced skin temperature.

The burning pain is reduced in all patients by cooling the affected skin. An explanation could be that the tissue hypoxia is reduced with cooling, since skin metabolism is diminished by cooling (down to 15°C), and increases manifold by warming.

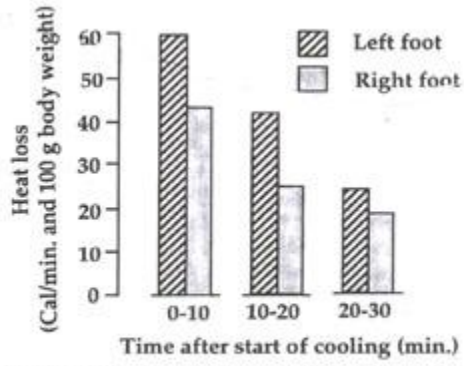

Fig. 12: Heat loss from the legs and feet during cooling in case example 1 with ES.

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Chapter 8 - Pathogenesis

Few reports on the pathogenesis of EM are available so far. Many patients with mild degrees of EM have probably been rejected by their doctor. When doctors have been consulted by severely ill patients, however, they have been obliged to try some kind of treatment. Because of a lack of an adequate theory of pathogenesis. their therapeutic choice may have been unfortunate. Some patients have probably been made worse by treatment, as in the case in our patient with ES who was sympathectomized on one side.

This chapter presents a theory of pathogenesis of EM, based on information in the previous chapters.

Findings in the literature

Brown showed an increased content of oxygen in the venous blood coming from the affected extremities of these patients, and interpreted the finding as a result of vasodilatation causing spontaneous attacks of burning distress [1]. Allen, Barker and Hines [2] also claimed that vasodilatation was the direct cause of spontaneous attacks of burning distress but that increased blood flow was "not an integral part of the mechanism causing distress". This conclusion was made on the basis of the observation by Lewis [3], that the symptoms induced by increasing the temperature above the critical point (see chapter 7), remain unchanged even if the blood flow is interrupted by a proximal pressure cuff. This fact was overlooked by Ivlufson [4], who believed that the distress was due to increased blood pressure in the minute skin vessels.

Lewis and Hess [3, 5] claimed that the skin of EM patients was unusually sensitive to warmth. They called this the "susceptible state" and believed that increased heat - susceptibility was due to damage' to the skin. From a pathogenetic point of view,

however, Lewis claimed that EM should be included among inflammatory conditions [3].

In a report on histopathological changes in skin in patients with EM. Michiels et al. claimed that EM always appears to be an expression of thrombocythemia. [6], a statement which is obviously not in accordance with other reports in the literature or with the findings in the present material.

Uno and Parker [7] have shown degeneration of autonome nerve plexuses in affected skin in one subject with EM compared to unaffected skin in the same individual and in one control person, and Blanchardet al[8] showed a slight and questionable reduction of the density of autonomic adrenergic nerve terminals in the periarterial and glandular plexuses in a skin biopsy of one patient. On the basis of this, the hypothesis that the disorder of EM could be explained by an abnormality of distal autonomic axons was suggested. A degeneration of autonome nerves does not have to be the cause of EM, however. It could also be a consequence of tissue hypoxia caused by the disorder (see below).

The symptoms of EM are promptly relieved in some patients when treated with acetylsalicylic acid [9,10]. Since one of the actions of acetylsalicylic acid is to potently block prostaglandin synthesis, Jorgensen and Sondergaard examined whether prostaglandins might be involved in the pathogenesis of EM [11]. They found evidence for an increased rate of prostaglandin synthesis in the affected skin of EM patients, and concluded that prostaglandins might be the main chemical mediator involved. There are, however, only a few cases with EM that have this striking effect of acetylsalicylic acid (only one in the present material). Prostaglandin El has in the present material also been shown to be a valuable drug in the treatment of some patients (see chapter 10).

In an article by Mandell et al. one case where the calcium channel blocker nifedipine had induced EM was described [12]. The authors proposed the possibility that increased tone in precapillary arterioles diverts blood to subdermal AN shunts, and that the skin is therefore chronically ischemic. In the author's opinion they base their supposition of skin ischemia on an erroneous interpretation of skin photoplethysmography recordings (see chapter 7). The theory of disturbance in microvascular distribution of blood can, however, explain many of the observed facts in EM patients.

Theory of pathogenesis of erythromelalgia

Circulation through the skin subserves two major functions: first, nutrition of the tissue and, secondly. conduction of heat from the body core to the skin so that the heat can be removed from the body [13]. Figure 1 shows an illustration of the vascular structures of skin. where the nutritive part of perfusion is in the capillaries, and the thermoregulatory part is in the dermal vascular plexuses. These plexuses can be filled from arterio-venous anastomoses located

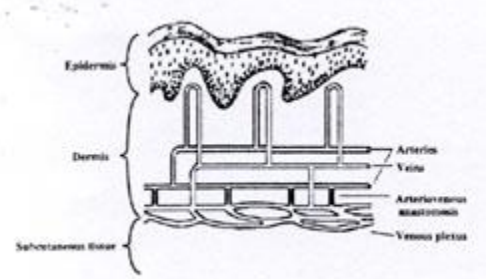

Fig. 1: Diagrammatic representation of the skin circulation.

in some skin areas [14], (see also chapter 6).

The clinical and epidemiological findings in the present material suggest that EM is not a separate disease entity. The pathohysiological findings, however, indicate that the pain is caused by tissue hypoxia.

If these shunts are opened at the same time as precapillary sphincters increase their tone, a maldistribution of slain microvascular perfusion with increased thermoregulatory flow and reduced nutritional flow will be the result (Fig. 2). Patients with primary EM phenomenon may have this mechanism, leading to tissue hypoxia.

In the patient with ES (chapter 3). proliferated vessels cla.~tered in groups were shown on histology. and these vessels probably also represent shunts leading to maldistribution of flow and tissue hypoxia.

In addition to blood flow through the nutritional capillaries, there exist in most tissues direct vascular connections between the arterioles and venules that do not participate in the transport of nutrients: thorough fare channels [15]. In patients with EM secondary to the plugging of capillaries (polycythemia wixh an increased tendency towards rouleaux formation [16], myeloproliferative disorders with an increased number of stiff and large unflexible white blood cells [17, 18], spherocytosis with stiff erythrocytes [18], cholesterol emboly syndrome [19]), only few capillaries/mm^3 are perfused. In these cases the tissue can be h-, poxic because of increased diffusion distances, and the perfused capillaries will have increased blood flow velocities. Such increased velocities can cause the passage time of erythrocytes to be too short for allowing equilibration of oxygen with the surrounding tissues. The remaining capillaries can therefore be functional shunts, thorough - fare channels.

Pathologically increased blood-tissue diffusion barrier (vasculitis [20], diabetes mellitus. bromocriptine use [21]), can also cause tissue hypoxia and the flow will be "shunted" through the capillaries.

It is important to realize that a tissue does not necessarily have to have a homogeneous oxygen content. but that small volumes in a certain tissue can be hypoxic while other parts have adequate oxygen tension.

The vicious circle that maintains EM

Figure 3 illustrates the consequences of tissue hypoxia. Tissue hypoxic causes a compensatory arteriolar dilatation, and thereby increased microvascular perfusion pressures. The concomitant flow increase is, due to maldistribution, shunted through AV shunts or "physiological" shunts, and leads to increased skin temperature. When the temperature increases, the metabolic rate will increase (about 130% for every 10°C [20]), the oxygen consumption will increase accordingly, and the hypoxia will be maintained.

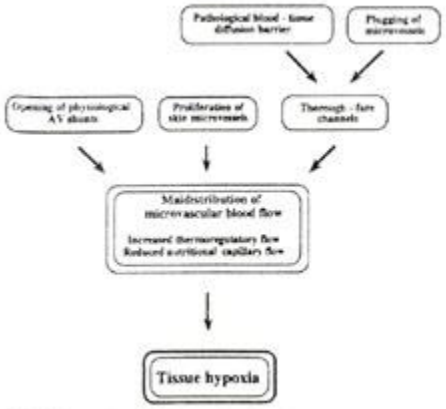

Fig. 2: Mechanisms leading to tissue hypoxia.

Can the proposed hypothesis explain observed facts?

The effect of cooling

All patients benefit from cooling of affected skin. According to the presented hypothesis this is because cooling decreases the metabolic rate and tissue oxygen consumption.

The effect of treatment of the primary disease.

Successful treatment of myeloproliferative disorders results in the relief of EM symptoms [23]. The explanation must be that when the plugging of nutritional capillaries is abolished, the shunting effect decreases and tissue oxygenation improves.

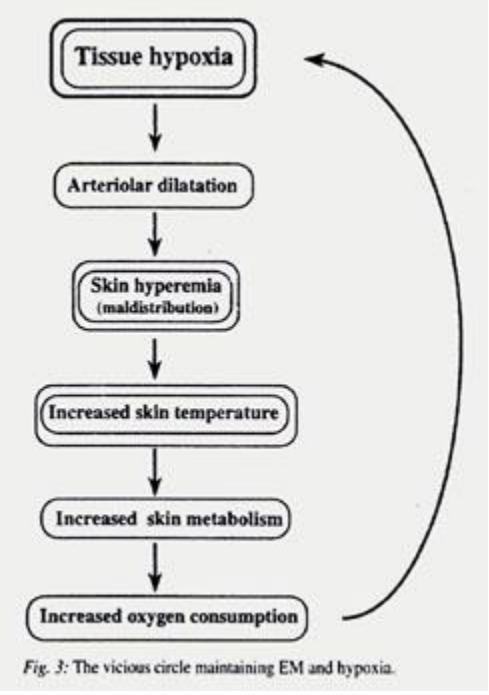

Fig. 3: The vicious circle maintaining EM and hypoxia.

The effect of vasodilators treatment

Vasodilatation has been shown to be effective as treatment in some cases of acute primary erythromelalgic phenomenon (see chapter 10). It is the author's belief that these cases have a primary maldistribution of blood flow because of opening of the microvascular AV shunts and closure of the nutritional capillaries. When the nutritional capillaries are opened by potent vasodilatory drugs, the symptoms disappear, tissue oxygen tension increases, and the supplying arterioles constrict to normal tone with the consequence that the total tissue perfusion decreases (see chapter 9).

The effect of vasoconstrictor treatment

Vasoconstrictor drugs can induce EM [24]. The mechanism is probably that tissue hypoxia is produced by a reduction in nutritional capillary blood flow.

Figure 1, chapter 9 illustrates the deterioration of skin nutrition induced by intra-arterial infusion of metaraminole, a potent alpha-stimulator and skin vasoconstrictor.

Conclusion

Many reports in the literature refer to an association between a wide variety of diseases and drugs, and EM. Some theories have been postulated as an explanation of pathogenesis, but they often seem to be contradictory to each other.

The present theory seems to be in accordance with clinical findings, pathological and physiological observations. Rudolf Virchow (1821-1902) summarized the pathogenesis of venous thrombosis in a triad, saying that thrombosis could be initiated by 1. changes in the vein wall (endothelial damage), 2. changes in the composition of blood or 3. disturbances of blood flow, especially stasis [25].

In an analogous manner, the present theory implies that tissue hypoxia can cause EM, and that the hypoxia can be caused by 1. changes in the capillary wall (with diffusion barrier), 2. changes in the viscosity of blood (for example polycythemia) and 3. a primary disturbance in the distribution of blood (opening of AV anastomoses and closure of nutritional capillaries).

Only a few patients with one of the three disturbances proposed by Virchow develop venous thrombosis, and fortunately only a few patients with one of the three disturbances of microcirculation develop EM. With the present level of pathogenetic understanding, it is not possible to predict which patients will develop EM. Future studies will probably give results which can serve as a basis for an improvement of the present theory of pathogenetic mechanisms.

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Chapter 9 - Therapy

Relief of burning pain by cooling of the affected skin is by definition one criterion for the diagnosis of EM (chapter 3), and the vast majority of patients have discovered this kind of treatment themselves. The effect of treatment proposed by doctors has in the past been quite variable and the results inconsistent for several reasons. The prevalence of the disorder is low, and few doctors have therefore gained experience from the condition. The clinical classification systems have not been optimal. and no objective laboratory criteria for the diagnosis have been available. Clinical criteria for the evaluation of the severity of the disorder have been lacking. Spontaneous remissions have occurred without treatment, thereby causing further confusion. Most important is, however an insufficient understanding of the pathophysiology and the pathogenesis of EM.

Finding in the literature

Secondary erythromelalgia

Management of secondary EM is dependent on the treatment of the primary disorder. and successful treatment of the primary disorder may provide relief of the symptoms. Babb reported three cases secondary to polycythemia who got relief after appropriate treatment of polycythemia, and a recurrence of the EM followed a recurrence of the polycythemia [11. Another example is presented by Eisler [2], who showed an EM-like eruption in patients treated with bromocriptine medication. The symptoms were reversible when the medication was stopped.

Primary erythromelalgia

Medical treatment

Epinephrine reduces cutaneous blood flow by constricting precapillary vessels and subpapillary venules [3] and in one report it is claimed to be of value in the treatment of EM [4]. The same effect is reported for sublingual isoproterenol, the most potent of the sympathomimetic amines [5]. This drug acts almost exclusively on the β-receptors [3]. β-blocade with pmpranolol has, on the other hand, also been reported to be effective [6]. but has been without effect in other cases [7]. Phenox),benzamine hydrochloride, an α-blocking agent enhances cutaneous blood flow in cold environments with a high degree of sympathetic tone. In a warm environment, however, sympathetic vaso-constriction normally exerts little restraint on cutaneous blood flow [3]. This drug has also been reported to be a therapeutic alternative [8].

The 5-hydroxytryptamine antagonist methysergide has been useful for the prophylactic treatment of migraine and other vascular headaches [3], and may be of value in some cases of EM [9, 10].

Nitroglycerin is a dilator of arterial and venous smooth muscle [3], and has been reported to be of value when applied locally as nitroglycerin ointment [4].

Acetylsalicylic acid

Acetylsalicylic acid (ASA) given as a single dose of 650 mg. has been used in some cases with a benificial effect lasting several days [11, 12]. Babb [1] found that 25 of 35 patients responded well to this regime. Mandell and associates, however, tried ASA agents in the treatment of an 11-year-old girl in addition to prednisone, hvdantoin, phenobarbital, chlorpromazine hydrochloride and carbamazepine, without significant improvement [13].

Sodium nitroprusside

Özsoylu [14] reported a nine year old girl with acute EM starting three days prior to admission to hospital. His clinical description is similar to cases 2 and 3 in the present material, and this girl could be classified as an acute primary erythromelalgic

phenomenon (EPPA) with severity group 6 (see chapter 3). She had severe symptoms with continuous burning sensation in her hands and feet up to the wrists and ankles respectively. The affected skin was swollen without pitting, red and warm to touch. She continuously kept her extremities in cold water. Treatment with sodium nitroprusside, 1 μg/kg * minute was started intravenously for two days without any effect on the pain, redness or edema. The dose was then increased to 3 and then to 5 μg/kg * minute. The burning pain gradually became less. and the redness and increased skin temperature were reduced. After one week of treatment she was without any pathological signs or symptoms.

Özsoylu claims that the reason for starting this regime was the reported effect of the drug on patients with ergotism [15], a disorder with peripheral vasoconstriction, but he does not give further arguments for his therapeutic choice. Later on the same group reported one further child with EM and elevated blood pressure, who also was successfully treated with sodium nitroprusside administration i.v. [16].

Surgical treatment

Few reports on surgical treatment have been presented. Teleford [17] reported favorable results following lumbar sympathectomy in three patients with primary disease. Others have not confirmed the beneficial effect of sympathectomy [4].

Peripheral nerve block with phenol or alcohol has been tried without success [11].

Some patients have required amputations because of ulceration of affected skin with secondary infection and sepsis [7].

Symptomatic treatment

Cooling the affected skin gives relief in all cases. Thompson et al. [10] were forced to perform bilateral knee disarticulation amputations on a 13 year old girl with EM, because of streptococcal septicemia with shock and progressive gangrene. The burning discomfort migrated to the distal aspects of her stump and in cooperation with the National Aeronautical and Space Administrations (NASA) they constructed a rapidly adjusting cooling unit (refrigerator), working on the principle of heat exchange with an attached liquid perfused garment for affected skin areas. This battery-powered portable unit gave good relief, and could be attached to the patient's wheelchair.

Other regimes

Typhoid vaccine [18] and administration of posterior pituitary extract [19] have been advocated, along with biofeedback regimes [20] and heat desensitization [21].

Conclusion

Since EM is more of a symptom complex than one defined disease, it is not surprising

that the consistent value of one drug has not been found. Many doctors have concentrated their attention on the observed skin hyperemia and tried to reduce perfusion. The reports of Özsoylu [14, 15] are of particular interest, because the group used a potent vasodilatory drug. Some effect of ASA also seems to be documented in many cases.

Own experiences[9]

Vasoconstrictor therapy

Vasoconstrictor treatment was reported to be of value, and before an understanding of pathogenetic mechanisms were obtained, a therapeutic trial in case example 1 with ES was performed.

Skin perfusion was continuously recorded with laser Doppler flowmetry in affected skin, while skin nutrition was monitored with transcutaneous oxygen tensiometry. Metaraminol, a potent vasoconstrictor was then given intra arterially in the common femoral artery in increasing doses. A low dose gave a small reduction in perfusion, but a dramatic decrease in TCpO2 (Fig. 1). Increased doses showed that perfusion could be reduced, but that this effect was ac companied by a severe and dangerous fall in oxygen available to the tissue.

In the author's view vasoconstrictors should not be given in cases with ES. On the basis of the pathogenetic theory presented in chapter 8, vasoconstrictors should not be given to other EM patients either.
Figure 1 is an example of objective evaluation of the therapeutic effect, using laser Doppler flowmetry and transcutaneous oxygen tensiometry. These techniques have also been used in the present material to test other therapeutic regimes.

[9] *Discussions with and advice from Tom Skomedal, MD, Ph.D., Institute for Pharmacology, Medical Faculty, University of Oslo, and appreciated.*

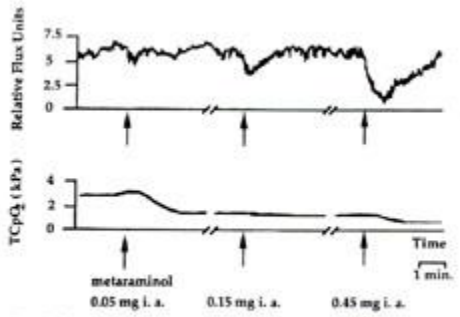

Fig. 1: Simultaneous recording of skin LDF and $TCpO_2$ during i. a. infusion of metaraminol.

Acetylsalicylic acid

All patients in the present material tried ASA. In 39 cases no response was recorded. One case, a 64, years old female suffering from EPCP has a dramatic effect of ASA. She has had her symptoms for nearly 11 years, and has been observed by the author for nearly four years. Her symptoms are severe without treatment (severity group 3. chapter 3) and both her laser Doppler flowmetry and her ultrasound velocity pattern are in group 3 (see chapter 7). When taking 75 mg of ASA she experiences relief of burning pain after approximately one hour. her feet are no longer red and warm, and both hemodynamic tests normalize to group 1 patterns. The duration of the effect is about two days.

Vasodilator treatment

When the pathogenetic mechanisms presented in chapter 8 were understood, it was logical to try to improve tissue oxygenation by enhancing nutritional blood flow. Two vasodilatory drugs were therefore tried: Sodium nitroprasside and Prostaglandin E1.

Sodium nitroprusside

This drug directly relaxes both arteriolar and venous smooth muscle, decreasing both preload and afterload. Its mechanism of action appears to be the same as that of nitroglycerin [3]. Nitroprusside must be given parenterally. The onset of action is maximal within 1 to 2 minutes, and the effect dissipates quickly when an intravenous infusion is stopped. One reason for trying this drug was reports of cure of EPPA cases, using nitroprusside [14, 15]. The drug has also been of value in the treatment of ergotism, a vasospastic disorder [22].

Results

Case example 2 in chapter 3 was a girl of eight years with EPPA. severity group 6. She was fist treated with an infusion of prostaglandin El (see below) for three days in doses increasing from 6-1014 ng/kg*min. This regime was without any obvious effect evaluated clinically, by laser Doppler flowmetn (LDFI and ultrasound velocity profile measurements (see chapter 7). It was then decided to chan_~e treatment to scxiium - nitroprusside infusion. This drug was given for seven days in doses increasing from 1-3-5 mikrogram/kg* min. During this period the girl's blood pressure was around 100/60 and pulse frequencies between 120 and 1s0. Clinically she gradually improved, and was without pain after five days. The girl did not tolerate postocclusive hyperemic tests with 3 minutes of tourniquet occlusion, and we were therefore only able to record resting skin perfusion values. The LDF values at rest showed persistent high values between 6.0 and 9.0 RFU (see chapter 7)for the whole period of therapy. The ultrasound velocity profile changed from category 3 to category 2 the second day, and was then unchanged until the infusion was sopped. at this point she was without pain, she started eating normally, gained weight and could take a bath in hot water. She was discharged from hospital two days later. Her LDF hyperemic index was then 1.6, which was normal (see Table 1. chapter 7), and ultrasound velocity profile were in group 2 (see Table II chapter 3). Four weeks later she was examined, still without symptoms of EM, and with normal hemodynamic tests. She has now been obsewed for 4 years and 2 months, and is still in good health.

Case example 8, presented in chapter 5 was also a girl with a dramatic EPPA. She was treated by dr. Shapiro in Philadelphia with the same sodium-nitroprusside regime for eight days. Three days after the commencement of the therapy, cooling in iced water was stopped, and analgesics were gradually reduced. Over a period of five days, her hands and feet became normal in color and temperature, and there was no swelling. She has continued to be without pain for an observation period of almost one year.

Prostaglandin E1

Prostaglandin E1 (PGE1) is a potent vasodilator, involving arterioles, precapillary sphincters and postcapillary venules. In addition it inhibits aggregation of human platelets [3, 24]. In spite of one report where an increased rate of prostaglandin synthesis was shown in skin affected with EM (25], see chapter 8), this drug was tried. The reason for this was that the drug is a potent vasodilator, and also because of the interesting reports of the use of PGE1 in the treatment of extremity ischemia in atherosclerotic patients. In 1973 Carlson and Olsson reported the first trials with PGEI infusion in the femoral artery of the diseased leg in patients with severe ischemic disease [26]. A beneficial effect was observed, and later on they showed that intravenous. infusion in small doses also exerted a positive effect [27]. They were, however, unable to explain this positive effect.

Little is still known about the effect of PGE, on the distribution of flow between muscle and skin, or the effects in ischemic skin. In a study in ischemic canine hind limbs, Pasch et al. found that PGE1 increased the absolute nutrient flow rather than opening arteriovenous shunts, and that skin flow was more influenced by PGE1, than muscle blood flow. They concluded that PGE1 might be useful in situations where vasospasm is a prominent feature [24]. Martin and Tooke examined the effect of PGE1 on skin micro vascular hemodynamics in patients with Raynaud's phenomenon secondary to progressive systemic sclerosis. They observed a beneficial effect, and concluded that the reason was improved nutritive capillary perfusion by lowering precapillary resistance, since they observed both increased transcapillary pressure gradients and increased nutritional capillary red cell velocity. The effect was still observed six weeks after infusion, which was only given as continuous infusion for 72 hours. (dose up to 10 ng/kg and min.) [28]. Clifford et al. showed similar effects in patients with small vessel arterial disease and rest pain or gangrene: improvement in both digital perfusion pressure, digital skin temperature and in symptoms [29]. The effects could be demonstrated even six weeks after infusion. An increased delivery of nutrients to peripheral tissues secondary to increased capillary permeability has been proposed as a mechanism for the observed effects [30].

Results

Case example 3, in chapter 3 was a girl of sixteen years with EPPA, severity group 6. Based on the experiences with case example 2, treatment with nitroprusside infusion in doses of 1-3-5 mikrogram/kg * min. was started..4fter three days no clinical or measured hemodynamic improvement had occurred. $TcpO^2$: values were around 0.7 kPa, and both LDF and ultrasound velocity profiles were in group 3 (see chapter 7). At this point the patient's pain was so severe, that she was transferred to the intensive care unit and was treated with continuous epidural administration of mepivacaine hydrochloride (Carbocaine®) and morphine. Six days after nitroprusside infusions were stopped, PGE1 infusions were started in doses increasing from 6-10-14 ng/kg*min. After three days of therapy, her situation had improved considerably (from severity group 6 to group 4, see chapter 3). PGE1 was stopped, but the improvement did not continue, and the treatment

was therefore started again after four days, and continued for a further three days. At this point she was without burning pain in three extremities, but still used iced water to cool her right foot. After some days it became evident that she did not suffer from EM in the right foot any more, but that she was suffering from damage to the skin caused by the cooling. She complained of a cold, but painless foot during cooling. When the foot was taken out of the water, the skin had a temperature of 13 to 14°C, and the foot became edematous, red and painful, and further cooling in turn gave relief. She was treated with elevation and analgesics, and developed petechiae on the dorsal and lateral aspect of the foot. After some few days she was discharged from the hospital, was treated with ambulant physiotherapy, and was able to walk normally and return to school after another two weeks.

Her mental state fluctuated during her stay in hospital. When an improvement of EM started, she got a depression, and had several consultations with the clinical psychologist.

Her mental state fluctuated during her stay in hospital. When an improvement of EM started, she got a depression, and had several consultations with the clinical psychologist.

Further experiences with PGE1

Table I shows the results of a further nine patients, where PGE1 treatment was given as continuous infusions for three days. The regime was to increase the dose each day, starting with 6, then 10, and finally 12 ng/kg*min. Apart from phlebitis when the drug was given in peripheral veins, no serious complications were recorded.

Table I: 9 Patients where PGE1 treatment was given as continuous infusions for 3 days

Name/sex age	Clinical group	Primary disease	Severity group	PGE1 infusion	Therapeutic effect
LHJ, female 29 years	ES		5	1 * 3 days	Clinically some remission with ulcer healing. No change in hemodynamic parameters.
LCH, female 17 years	EPPC			1 * 3 days	Total remission with healing of a small ulcer. During pregnancy new symptoms first trimester then spontaneous remission. Without EM symptoms 2 years after delivery
OMI, female 24 years	EPPC		4	2 * 3 days	Total remission from treatment. duration 3-4 months
IU. female 57 years	EPPC		3	3*3days	Total remission with duration of 3--t months LDF changed from group 2 to 1, and ultrasound parameters from 3 to 1.
RA, male 40 years	EPSA	Diabetes mellitus	4	2*3days	Clinically some remission after first treatment. Almost without symptoms after second treatment.
AK, female 65 years	EPSA	Cholesterol emboly	4	1 * 3 days	Total remission. LDF and ultrasound parameters changed from group 3 to group 1. Without EM symptoms after 1 year.
SS, female 28 years	EPSC	Frostbite	3	1 * 3 days	Total remission of EM. Healing of small ulcers. Without symptoms of EM after 2 years.
ABB, female 46 years	EPSC	Bacterial infections	3	1 * 3 days	Total remission: effect started after 4 days. back to work as a nurse. New infection after 2 years induced new EM symptoms.
RI, male 68 years	EPSC	Polyneuro -pathy	4	1 * 3 days	No effect of treatment

In the case with ES the patient was treated during a period of major problems and small ulcers in affected skin.

The impression was that a

certain remission was induced, and the ulcers healed during the three weeks following the infusion. Her skin was, however, severely damaged, and it is the author's belief that her nutritional capillaries had partly gone into involution and that a good result could not be expected.

The rest of the patients, except one, had benefit from the treatment. The improvement started after some hours in some patients, but not until day three or four in others. Some patients have enjoyed the effects for several years. In these cases it is possible that a vicious circle has been broken. Other patients have had a relapse of symptoms. In these cases remission has had a duration of at least three months. A long term improvement of skin nutritional blood flow has also been shown in other studies [28. 29].

Sympathectomy

Operative sympathectomy was in the present material performed in the case with ES, but only on one side. This treatment made the patient worse, and the sympathectomized leg is still bothering the patient more than the other leg after 5½ years. The unwanted effect of sympathectomy is clearly shown in Figures 8-12 in chapter 7.

From a theoretical point of view, and from personal experiences with laser Doppler and transcutaneous oxygen tensiometry monitored percutaneous chemical sympathectomies, performed in patients with Raynaud's phenomenon and atherosclerotic patients, this treatment is not correct. The reason is that sympathetic block increases thermaregulatory blood flow, and does not increase nutritional blood flow; it may in fact induce a further maldistribution in patients with tissue hypoxia.

Other kinds of treatment

Cooling of affected areas with water is effective in all cases. To avoid humidification of the skin, it is wise to first put the affected parts in a plastic bag, and then into the water.

Cooling with air is also an alternative. The car of case example 1 with ES was equipped with an air condition system, which makes it possible for her to drive for long distances without the bucket of cold water.

Inhalation of 100% 0_2 increases transcutaneous oxygen diffusion, and probably increases tissue oxygenation in some patients. This could be one way of inducing remission in severely affected patients. Hyperbaric 0_2 treatment in a pressure tank could also be of value in selected cases. Such treatment could possibly induce angioneogenesis in severely damaged skin.

Conclusion

In cases with secondary EM the treatment should aim at the primary disorder. In patients still suffering from EM, acetylsalicylic acid should be tried in all cases without contraindications, since the drug is easy to administer.

In severe acute EM nitroprusside or PGEI should be tried. In chronic EM patients with severe burning pain. infusions with PGE1 should be tried.

Both nitroprusside and PGE1 have to be administered as intravenous infusions. In the last few years several studies have successfully used prostacycline infusions in patients with severe ischemia secondary to atherosclerosis. This drug has effects similar to PGE. In the near future. prostacycline analogues will probably be available for peroral use.

Such drugs could be of value in the treatment of patients with EM.

Vasoconstrictor therapy or sympathectomy should probably not be tried.

Recommendations for future therapy studies

EM patients should be classified according to the guidelines presented in Figure 1. chapter 3. and therapy effects should be evaluated according to the severity group scale (Fig. 3. chapter 3). If possible, therapeutic trials should also be monitored with measurements of skin perfusion (for example laser Doppler flowmetry). skin nutrition (for example transcutaneous oxygen tensiometry or dynamic capillaroscopy if applicable). and artery blood flow velocity profiles (ultrasound Doppler).

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Egil Seem was the most important of the colleagues taking part in the research process. First of all he is a competent circulation physiologist, but also our discussions about the interpretation of the results were very valuable for the proposed theory of pathogenetic mechanisms. Several colleagues and experts have helped analysing the data; references to their contributions have been made in the text.

One of the reasons for the relatively large number of patients in this material, was that my work was mentioned by Asa Rytter Evensen in the programme "Sånn er livet" in the Norwegian Broadcast Association (NRK). Many frustrated erythromelalgia patients contacted the author after having heard the program.

In 1988 King Olav V of Norway through the Faculty of Medicine. University of Oslo, invited researchers to write a paper demonstrating how modern technological equipment had been used to improve the understanding of pathogenetic mechanisms of a disease. The present monograph was rewarded with the King's gold medal in 1990.

I would like to express my gratitude to the patients, who agreed on participating in the investigations, and to colleagues and nurses for their cooperation. Finally I would also thank my wife Randi and our four daughters Kjersti, Mari, Anne Kari and Ida for continuous encouragement.

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Addendum 1.

From a historical point of view, the basis for practice of medicine was purely empirical. Doctors then used the hypothetico-deductive method to analyse clinical, epidemiological. structural and physiological findings in healthy and sick individuals, and theories of mechanisms of disease were proposed. Such theories could often be tested by experiments and clinical therapeutic trials. The pathogenetic theory could then be modified according to these results, and serve as a basis for further studies and therapeutic regimes.

The theories of one of this centuries most marked philosophers of science, Sir Karl Popper (born 1902) have, however, widened my understanding of the clinical research process. Popper claims that scientists should observe, describe and classify data (pre-scientific phase). but should then bravely use-creative intuition to formulate theories unambiguously (scientific phase), so as to expose them as clearly as possible to refutation. This is because he thinks that knowledge only consists of our theories, and that knowledge can only advance through criticism and improvements of the theories. One aim for a clinician should therefore be to retain her/his curiosity and ask questions about the mechanisms of disease, not only to be concerned with descriptive reports of an empirical nature.

The present monograph first presents the author's clinical observations of 40 patients with erythromelalgia. Modern equipment for objective assessment of morphology and physiology of the circulation was then applied. On the basis of these results and the findings in the literature, a theory of pathogenesic mechanisms is presented according to the "reason to best explanation" principle. The theory was then tested against the results of therapeutic trials. I sincerely hope that the present theories will stimulate discussion and criticism and it is my conviction that future studies will give knowledge that can be used to improve the present theory of pathogenesis. and thereby the knowledge of how to give the best help to patients suffering from erythromelalgia.

Addendum 11.

Erythromelalgia is a rare disorder. My belief is, however, that the maldistribution of blood flow postulated as the basic mechanism for the condition, is also an important factor in development of other disorders of skin circulation. In the diabetic foot with neuropathy and microangiopathy, in skin with venous leg ulcers and in sclerodermic fingers there is evidence of arteriovenous shunting. The basis for the beneficial results of prostaglandin E l and prostacycline in the treatment of pain and ulcers in patients with critical ischemia caused by severe atherosclerosis, could also be a redistribution of microvascular perfusion from shunt flow in favour of nutritional capillary perfusion. In the hyperemic phase of septic shock, extensive microvascular shunting is probably also an important factor in the pathophysiology. Erythromelalgia may therefore serve as a model disease, and studies and increased knowledge of the pathophysiology of erythromelalgia may be useful also for the handling of patients with the above mentioned diseases and conditions.

Addendum 1I1.

Francis of Assisi (1181-1226) was the first known human who had marks on the skin resembling those made by the nails on the body of Jesus at His crucifixion (i. e. stigmata). Since then about 90 subjects have experienced the same phenomenon. In several of the cases outlined in this study there is strong evidence for psychological factors causing maldistribution of skin circulation. It is possible that subjects with stigmata have erythromelalgia like mechanisms, with local maldistribution of skin perfusion, reduced nutritional blood flow, local skin hypoxia and development of skin ulcers, induced by religious and emotional experiences. The perfusion can probably also be redistributed by psychological mechanisms, with the consequence that the skin ulcers heal.