Introduction
Mitchell reported in 1872 on bilateral symmetric burning pain and purple red congestion in the feet in four young adults, aged 21-40 years [1]. Mitchell described in 1878 sixteen cases with painful affections of the feet of various types and severity in his article “On a rare vasomotor neurosis of the extremities and on the maladies with which it may be confounded” [2]. The complaints begin with pain in the foot or feet and may start in the ball of the foot or of a great toe with extension to the dorsum and even leg. The burning pain and red congestion may be symmetric in both feet and legs or asymmetric limited to one or both soles toes or fingers. Mitchell stated that the foot and hand disorder might be conveniently labeled erythermalgia, deriving it from the Greek words erythros = red, melos = extremity and algos = pain [1]. The neurologist Mitchell attributed erythermalgia of the legs and feet to an undefined form of neuritis of the peripheral nerves or nerves within the spinal marrow.

Based on a detailed analysis of the 16 cases of Mitchell and 81 cases of his own, Brown defined in 1932 six basic criteria for the diagnosis of the primary and incurable variant of burning red congested extremities in the absent of any detectable underlying disorder [3]. In 1938 Smith and Allen substituted the term erythermalgia for another descriptive term, erythromelalgia, to denote the variability of disease manifestations and to emphasis the importance of heat = therm as a main important feature of red, burning and painful extremities [4]. Erythromelalgia patients seen by Smith & Allen noted that a single dose of acetylsalicylic acid (aspirin 500mg) produced marked relief of burning distress that persisted for a few days [4]. Since than both terms are used indiscriminately as synonyms in the primary and secondary forms, irrespective of aspirin-responsiveness and solely depending on the clinical absence or presence of an associated disease. Osler in 1908 and Brown in 1932 described cases of secondary erythromelalgia in polycythemia vera (PV) in which pain in the hands and feet with the extreme red congestion was suggestive for erythromelalgia of Weir Mitchell 1878 [1,5]. The etiology of erythromelalgia remained elusive for about one century until Michiels discovered between 1975 and 1980 aspirin responsive erythermalgia in thrombocythemia [6-8]. Based on analysis of the 16 cases of Mitchell and clinical observations in 81 cases in which burning pain in the hands or feet was a prominent or disabling symptom, Brown in 1932 postulated six basic criteria for the diagnosis of primary and incurable variant of burning red congested extremities [3].

1. Attacks of bilateral or symmetric burning pain occurring in the hands and feet.
2. The attacks were initiated or aggravated by standing, or exposure to heat.
3. Relief was obtained by elevation and exposure to cold.
4. During the attacks, the affected were flushed and congested.
Following the six postulates of Brown, Michiels recognized in 1988 the incurable and rare variant of red painfull extremities in the complete absence of any underlying disorder as a distinct clinical and congenital autosomal dominant entity and therefore labeled it aspirin resistant primary erythermalgia (PE) of unknown etiology [9,10]. Our experimental and research studies undoubtedly showed that the clinical manifestations of the primary incurable inherited erythermalgia were completely different from aspirin-responsive erythermalgia caused by platelet-mediated arteriolar inflammation and thrombosis in thrombocythemia of patients with essential thrombocythemia (ET) and PV (Figures 1, 2 and 3) [11-15]. In extension to the six postulates of Brown (1932), we could add in the 1990s four additional specific features of incurable inherited erythermalgia (Table 2) [3,9,10,16-22]. Incurable inherited erythermalgia spontaneously arises in children with symmetric bilateral localization in both legs and persists throughout life [9,10]. There is relative sparing of the toes because acrocyanotic ischemia or peripheral gangrene as the result of peripheral vessel (thrombotic) obstruction in skin biopsies in aspirin responsive erythermalgia is never seen in skin punch biopsies from cases with incurable hereditary erythermalgia [4,16-24]. The histopathologic findings in skin biopsies from erythermalgic areas of patients with incurable hereditary erythermalgia were non-specific, showed the complete absence of any underlying disorder, and did not reveal a clue to its pathophysiology (Figure 4) [25]. There are a multitude of clinical conditions without thrombocythemia associated with bilateral and symmetric red swollen and burning pain in the feet and hands. These other forms are referred to as secondary aspirin resistant erythermalgia, which originate from side effects of drugs (e.g. verapramil) or arise from various disorders including cutaneous vasculitis, vasculitis in lupus erythematoses, hypertension, rheumatoid arthritis and autoimmune diseases of undetermined significance [25-28].

**Aspirin responsive platelet-mediated erythermalgia in thrombocythemia**

The relief of burning pain and red congestion by one dose of aspirin (500 mg) for a few days appeared to be a pathognomonic diagnostic clue of erythermalgia in thrombocythemia (Figure 1) [6-8]. At that time it was known that acetylsalicylic acid (aspirin) did inhibit arachidonic induced platelet aggregation for a few days due to irreversible inhibition of platelet cyclo-oxygenase (COX-1) activity. Double blinded clinical experiments showed that sodiumsalicylate, other analgesics and the other platelet inhibiting agents including ticlopedine and dipyridamol did not inhibit platelet COX-1 activity and had no effect on erythermalgia (Figure 1) [7,11]. This was the very first objective hint that erythermalgia must be caused by platelet-mediated processes in thrombocythemia of patients with ET and PV. Subsequent prospective platelet function and histopathology studies were initiated to unravel the underlying etiopathophysiology between Erythermalgia and Thrombocythemia in ET and PV patients [6-8,11].

**Figure 1:** In a prospective basic research study cases with erythermalgia in thrombocythemia were sequentially treated by sodium salicylatat 500 mg followed by aspirin 500 mg, phenylbutazon followed by aspirin, sulfon pyrazon followed by aspirin, or ticlopedine followed by aspirin and measured MDA production after stimulation of PRP with NEM in each of the experiments to assess the degree of platelet COX) inhibition [6-8,11,12]. The longlasting analgesic effect of a single dose of aspirin is in accordance with the length of inhibition of platelet COX activity as measured by inhibition of malondialdehyde dialdehyde (MDA) [12]. After a single dose of indomethacine 25 mg and 75 mg, the burning pain relieved for about 12 and 24 hours, which was in accordance with the length of inhibition of platelet MDA production. Sulfipyrazone 800 mg, dipyridamole (platelet cyclic AMP inhibitor) 400 mg, ticlopedine (ADP receptor inhibitor) 1000 mg or sodiumsalicylate 500 mg daily for 4 days, did not alleviate the erythermalgic signs and symptoms, but also had no effect on platelet MDA production. Thus, active platelet prostaglandin metabolism in thromboecytemic platelets is necessary for erythermalgia to develop in ET and PVT patients [6-8].

We introduced the method of Brian Smith (1976) to measure platelet COX-1 activity directly by measuring malondialdehyde (MDA) after stimulation of platelets in platelet rich plasma (PRP) with N-ethylmaleimide (NEM) [12]. NEM maximizes the arachidonic acid mediated cyclo-oxygenase pathway to form prostaglandin endoperoxides, thromboxane A2 and its endproducts thromboxane B2 and MDA (Figure 2). MDA production in NEM stimulated PRP reflects the degree of platelet COX-1 inhibition by aspirin to document prospectively that the longlasting effect of aspirin on erythermalgia indeed was due to irreversible inhibition of platelet COX-1 activity (Figure 1) [7,11]. Sodiumsalicylate and other platelet inhibiting agents which do not inhibit platelet COX-1 and do not have any effect on erythermalgic signs and symptoms [7,11]. Thus, active platelet COX-1 activity and the production of platelet prostaglandin products is necessary for erythermalgia to develop in thrombocythemia of ET and PV patients [7]. Reversible inhibition of platelet COX-1 activity by indomethacin 25 mg TID is an alternative to relief erythermalgia (figure 1). In subsequent studies we showed that coumamin and ticlopedine (platelet ADP-receptor inhibitor) are not effective in the treatment of erythermalgia because coumamin and ADP
receptor inhibitors do not inhibit the platelet COX-1 activity of hypersensitive platelets in thrombocythemia [7,11].

Erythromelalgic distress in thrombocythemia patients varies from prickling and ‘pins and needles’ sensations (acropresthesias) to burning pain and red congestion. The asymmetric and often unilateral localisation of red congested, warm and painful swelling affects one or more toe, the sole of the foot or sometimes the tips of the fingers (Figure 2A) [7,11]. If left untreated, blue ischemic spots in erythromelalgic areas, acrocyanosis or even digital gangrene of one or more toes often occurs in due course of time during long-term follow-up (Figure 2B). In contrast to arteriosclerotic circulatory obstruction, peripheral arterial pulses usually remain normal in thrombocythemia of ET and PV patients with erythromelalgia. In the 1970s very little was known about the histopathology of erythromelalgia as the opportunity to examine tissue from recently developed erythromelalgias before ischemic complications do occur has not been reported. Michiels & Ten Kate decided in the late 1970s to perform skin punch biopsies from freshly relapsed erythromelalgia a few days to one week after discontinuation of aspirin in symptomatic cases of ET (Figures 2 and 3 left) [6]. Skin punch biopsies were taken from relapsed erythromelalgia 1 to 3 weeks after discontinuation of aspirin, and from cases of untreated erythromelalgia complicated by acrocyanotic spot or acrocyanosis but no digital gangrene (Figures 2 and 3 middle panel) [6].

The histopathological appearances of a skin punch biopsy from areas of recently relapsed erythromelalgia one week after aspirin discontinuation show arteriolar lesions of fibromuscular intimal proliferation without involvement of venules, capillaries or nerves (Figure 3, left panels). The lining endothelial cells are swollen with large nuclei. The inner layer of the vessel wall was thickened by proliferation of cells, with narrowing of the lumen. With factor VIII antiserum an affected arteriole shows an inner single layer of fluorescent cells, and with an antisera against smooth muscle cells strong fluorescence a multilayer of proliferated cells in the media of the arteriolar vessel wall was seen indicating that ‘fibromuscular intimal thickening’ is caused by increased smooth muscle cell proliferation and breaking up of the membrana elastica interna of the vessel wall. Cellular intimal proliferation and swelling of cells with cytoplasmic vacuolisation narrows the lumen and is accompanied by perivascular oedema, vascular and perivascular fibrosis and slight perivascular infiltration by inflammatory cells [6,7]. Occlusive arteriolar thrombi were not seen in the first skin punch biopsy of recently relapsed erythromelalgia one week after discontinuation of aspirin (figure 3 right panels).

Histopathology from a skin area of relapsed erythromelalgia complicated by blue ischemic spots (figure 2B) after 3 weeks of aspirin discontinuation showed arterioles with pronounced ‘fibromuscular intimal proliferation’ with narrowing of the lumen and occlusive thrombotic lesions on top of ‘fibromuscular intimal proliferation’ in the reticular dermis with no involvement of venules or capillaries (figure 3, middle panels, black toe due to thromboangiitis obliterans). The affected arterioles with fibromuscular intimal proliferation are partially or completely occluded by organised thrombus in skin areas from bluish discoloured erythromelalgic area 3 weeks after aspirin discontinuation. Immunofluorescence with IgG, IgA and IgM antisera were negative. An antiserum against complement B1A, showed granular deposits in the walls of several vessels in the subendothelial and perivascular zones of some vessels indicative for a very non-specific inflammatory process [6,7].

Figure 2: A. Severe asymmetric burning pain and red warm congestion of big and little toe, and sole of forefoot of the right foot 1 week after discontinuation of aspirin. B. Burning, aching pain and mottled red-blue discoloration of the sole of the right foot 3 week after discontinuation of aspirin. C. Detail of an untreated painful and bluish big toe, of which the skin surface temperature was low (cold ischemic toe) [15]. D. Progression of painful toes to ‘black’ big toe and peeling of the skin of second and third toe in a 6 week period of coumarin treatment. E. Complete restoration of painful black ischemic toe within a few weeks by treatment with aspirin. F. Relapse of painful red and blue toes 2 weeks after discontinuation od aspirin [15].

To demonstrate the platelet-mediated origine of aspirin responsive erythromelalgia, we prospectively performed histopathological...
Molecular etiology of incurable inherited erythermalgia

Drenth & Michiels collected blood samples from European families and the large Finley family in the United States (Figure 4) with incurable inherited erythermalgia and a clear-cut autosomal dominant heritance [24]. Drenth et al could localize the incurable inherited erythermalgia susceptibility gene on the long arm of chromosome 2 (2q24.3) [30]. Yang, et al. (2004) studied a chinese family with incurable inherited erythermalgia in three generations and discovered that heterozygous gain of function mutations in the SCN9A gene on chromosome 2q coding for the high voltage dependent sodium channel alpha subunit (Nav1.7) segregated with the affected family members [31]. Heterozygous mutations in the SCN9A gene as the cause of incurable inherited erythermalgia has been confirmed in a Flemish family by Michiels, et al. in European families by Drenth et al, and in the large USA family with autosomal dominant penetrance of PE in 5 generations (Figure 4) in which linkage of the PE susceptibility gene to chromosome 2q was reported by Drenth et al [30,32-34]. Heterozygous gain of function mutation F1449V in the SCN9A gene (Nav1.7) was found in 14 of 14 affected members of the USA family (Figure 4) [34]. Michiels et al investigated 10 members of a Flemish family and found a novel heterozygous S241T mutation in the SCN9A gene (Nav1.7) in all 5 investigated affected family members (figure 5) [33]. The neurologist Waxman and his team extensively studied the electrophysiological properties of mutant (SCN9A) Nav1.7 sodium channels on the basis of which primary erythermalgia became a neuropathic disorder of the small peripheral sensory and sympathetic neurons caused by hyperexcitibility of Nav1.7. Nav1.7 is located in dorsal root ganglions and in nocireceptive peripheral neuron [35-39]. Untill to date the invalidating condition is incurable and refractory to any treatment, although some subjective relief is given by analgesics, cold environment and refrain from daily activities.

Figure 3: Skin punch biopsies from skin areas of recently relapsed erythromelalgia 1 week after discontinuation of aspirin (Figure 2A) in ET patients show arterioles with swollen endothelial cells and fibromuscular intimal proliferation (left) [7]. Skin punch biopsies from blue spots of skin areas with relapsed erythromelalgia 3 weeks after discontinuation of aspirin (Figure 2B) show arteriole with fibromuscular intimal proliferation with partial and complete occlusion of arteiole by fresh organized thrombus (middle upper two). Arteriole with complete occlusion of the arteriole in skin area of untreated erythromelalgia of an acrocyanotic toe (middle bottom) [6].

An arteriole occluded by a thrombus show a strong staining for von Willebrand factor (VWF, right upper) and a very weak staining for fibrin (right middle) indicating a platelet-rich thrombus. Positive fibrin staining of an arterial thrombus in a patients with lupus anticoagulant (right lower) [40].

The platelet mediated inflammatory component in aspirin responsive erythromelalgia

Superficial thrombophlebitis or livido reticularis is a skin manifestation of erythromelalgia in ET and PV patients [13]. The incidence of superficial thrombophlebitis was 14% in our cohort of 50 thrombocythemia (30 ET and 20 PV) patients [13]. The prostaglandin activity in fluid from artificially skin blisters can be regarded as an inflammatory component in tissues. We measured the prostaglandin activity in artificial skin blisters from areas with active erythromelalgia (2 patients), in a control person and in skin area during effective treatment with aspirin (Table 1). The total prostaglandin activity in fluid of skin blisters from area of erythromelalgic skin areas was very high as compared to control (Table 1) [14]. Effective treatment of erythromelalgic skin areas with aspirin in figure 6 was associated with reduction of total prostaglandin content in skin blisters to normal (Table 1).

Table 1: Prostaglandin E-like (PGE) activity in fluid of artificial blisters from skin areas with erythromelalgia (E+) and control without erythromelalgia (C→E-) and from skin areas after treatment of erythromelalgia with aspirin (E+→E-)

| Blister fluid | Total PGE | PGE/ml |
|--------------|-----------|--------|
| 1.19 ml E+   | 6.43 ug   | 5.40 ug|
| 1.29 ml E+   | 8.42 ug   | 6.53 ug|
| 1.02 ml C→E- | 0.82 ug   | 0.80 ug|
| 1.36 ml E+→E-| 1.35 ug   | 0.99 ug|

Figure 4: Cutaneous pathology in primary congenital and incurable erythermalgia [25]. Capillary blood vessels in the lower dermis show moderate thickening of the wall, moderately swollen endothelial cells, minimal to moderate perivascular inflammatory cells with the absence of obvious inflammatory disease (left panel) and a lamellar appearance with perivascular edema and thickening (middle panel) in case 1 with congenital erythermalgia caused by the C1185A gain of function mutation in the voltage-gated sodium channel alpha subunit Nav 1.7. Nav 1.7 is located in dorsal root ganglions and in nocireceptive peripheral neuron [35-39]. Untill to date the invalidating condition is incurable and refractory to any treatment, although some subjective relief is given by analgesics, cold environment and refrain from daily activities.
Family pedigree of the large USA pedigree with autosomal dominant primary erythermalgia (PE) [24,34]. Circles denote females; squares denote males. The proband is shown by arrow. Blackened symbols indicate subjects with PE. (+) denotes subjects heterozygous for the 4393G mutation and (-) denotes subjects without the mutation [34].

**Figure 5:** Autosomal dominant aspirin-resistant symmetric red warm and burning painfull lower legs and feet in incurable autosomal dominant erythromelalgia (familial erythermalgia) is a neuropathic disorder of hyperexcitable small peripheral and sympathetic neurons caused by the gain of function mutation S2417T (red/green) in the voltage-gated sodium channel alpha subunit Nav 1.7 (red/green) [33].

**Pathophysiology of erythromelalgia and microvascular thrombosis in thrombocythemia**

Van Genderen & Michiels prospectively performed platelet kinetics studies in 10 individuals with reactive thrombocytosis, in 10 patients with thrombocythemia vera complicated by erythromelalgia (E+) and in 10 patients with asymptomatic thrombocythemia (E-) [40]. Platelet kinetic studies were performed according to the protocol during the presence of erythromelalgia for about 7 to 10 days, and after aspirin treatment several months later. The survival times in the E+ group (4.2 days) were significantly shorter than in the group with RT (7.7 days) and E- group (7.2 days). Platelet survival studies were repeated in seven E+ patients while on treatment with aspirin, which relieved the erythromelalgic symptoms completely and lastingly. The survival time in symptomatic E+ patients of 4.0 days significantly increased to 6.9 days during maintained aspirin treatment which was paralled by a significant decrease of beta-TG and TM. In another study Van Genderen & Michiels showed that within 10 days after withdrawal of aspirin, 3 ET-patients developed endarterial thrombi in skin biopsies from erythromelalgic areas, which was associated with a 3-30-fold increase in urinary TXB2 excretion. Both the increased urinary TXB2 excretion and clinical signs of erythromelalgic microvascular thrombosis could be corrected with a platelet-specific very low dose aspirin regimen of 50 mg daily, which is sufficient to inhibit platelet cyclo-oxygenase (COX) for the prevention of platelet thrombi in symptomatic thrombocythemia patients [42]. We concluded that erythromelalgia (E+) in thrombocythemia of ET and PV patients was featured by increased plasma levels of platelet factor 4 (PF4), beta-thromboglobulin (ß-tg), platelet derived growth factor (PGDF) and increased thromboxane B2 (TXB2) excretion in urine and that the generation of thrombin is not essential for platelet thrombi formation in thrombocythemia patients with erythromelalgia and its ischemic complications [42]. This explains the observed inefficacy of coumadin derivatives in the prevention and treatment of erythromelalgia, erythromelalgic acrocyanotic ischemia and migraine-like atypical transient ischemic attacks (MIAs), in ET and PV patients [11,42-47].

If erythromelalgia is left untreated, ET and PV patients not on aspirin are at high risk of digital ischemia (black toe, figure 2), migraine-like atypical transient ischemic attacks (MIAs), stroke or acute coronary syndrome during long-term follow-up [11,42-47]. The presence of erythromelalgia in ET patients is characterized by significant higher plasma levels of platelet activation markers PF4, btg, and PGDF (Figure 6).

Van Genderen & Michiels performed histopathology of skin biopsies derived from erythromelalgic skin areas of 2 ET patients and showed that erythromelalgic thrombi stained strongly positively for von Willebrand factor opposed to no or weak fibrin staining (Figure 3 right pannels), which is indicative for platelet-rich thrombi formation in the endarterial circulation [41]. To demonstrate that erythromelalgia in thrombocythemia is characterized by platelet activation and endothelial cell damage as the cause of fibromuscular intimaproliferation (Figure 3 left pannels) but not by thrombin generation Van Genderen & Michiels measured in vivo platelet, endothelial and coagulation activation markers in ET patients with recently relapses erythromelalgia after discontinuation of aspirin. In a cross-section study we compared plasma levels of endothelial cell marker thrombomodulin (TM), platelet activation markers platelet factor 4 (PF-4), beta-thromboglobulin (beta TG), and coagulation markers prothrombin fragment 1+2 (F1+2) and total degradation products of fibrin (TDP) in 5 ET patients with erythromelalgia (E+), in 16 asymptomatic ET patients, and 20 control persons (Figure 6) [41]. The results before and after aspirin treatment were characterized by significant higher beta-TG and TM levels, but no significant differences were detected in either F1+2 or TDP levels (Figure 6). Disappearance of erythromelalgia with aspirin was paralled by a significant decrease of beta-TG and TM. In another study Van Genderen & Michiels showed that with recently relapses erythromelalgia after discontinuation of aspirin.

**Figure 6:** The effects of intervention with aspirin on platelet activation markers platelet factor 4 and beta-thromboglobulin, on the endothelial cell activation marker thrombomodulin, on the
coagulation activation markers prothrombin fragment 1+2 and fibrin/ fibrinogen degradation products, and on platelet counts in controls asymptomatic thrombocytemia (E-), thrombocytemia complicated by erythromelalgia (E+), and cure of erythromelalgia by aspirin (E+ → E-) [41-46].

Increase of PDGF released from platelet and the endothelial cell (EC) activation marker TM refers to increased platelet-EC-vessel wall interactions underlying the etiology of fibromuscular intimal proliferation (Table 2, figures 2 and 3) [41]. Erythromelalgia is provoked by (spontaneous) intravascular activation and aggregation of thrombocytemic platelets at high shear stress rate in the end-arterial circulation of the peripheral, cerebral, ocular and coronary circulation [6-8,11,42-46]. Erythromelalgia is never seen in reactive thrombocytosis and thrombocytosis in Ph-positive CML. This clearly indicates that not only a quantitative (platelets >350x9L), but also a qualitative ‘hypersensitive’ functional platelet defect (‘sticky’ platelets) is the underlying etiology of platelet mediated arterial thrombophilia in myeloproliferative thrombocytemia. A gain of platelet function (Sticky Platelet Syndrome : SPS) is postulated by Michiels & Van Vliet in the early 1990s as the underlying pathophysiology of platelet-mediated arteriolar microvascular erythromelalgic thrombotic complications in thrombocytemia [6-9,40-45]. If left untreated, the erythromelalgic microvascular circulation disturbances (including the migraine-like atypical TIAs) indeed do progress to major vascular complications in particular in circulation disturbances (including the migraine-like atypical TIAs) [6-8,11,42-46]. Erythromelalgia is never seen in reactive thrombocythemia (E-) and cure of erythromelalgia by aspirin (E+ → E-) [41-46].

JAK2V617F mutation is associated with no or slight increase of erythropoiesis in ET and prodromal PV (table 3). Homozygous JAK2V617F mutation in PV preferentially leads to pronounced constitutive trilinear activation in the bone marrow of megakaryo/ erythro/granulopoiesis due to a more pronounced hypersensitivity to EPO and GCSF (Table 3) [51-54].

Table 3: Model for disease heterogeneity of JAK2V617F Myeloproliferative Neoplasms. The JAK2V617F mutation occurs in the hematopoietic cells and gives rise to the onset of disease. The kinase activity of heterozygous JAK2V617F mutation is impaired by the presence of a normal JAK2 wild type allele. The disease generated by this low constitutively activated kinase activity in ET or forme fruste PV. A second event leading to an increased kinase activity occurs in a hematopoietic stem cell already carrying the mutation. The second event is caused by an amplification of the JAK2V617F activity locus through mitotic recombination resulting in homozygous JAK2V617F mutated MPN with 9p loss of heterogeneity. Sustained high levels of JAK2 kinase activity could lead to progression to PV from its peteciotic stage to spent phase complicated by splenomegaly and secondary myelofibrosis.

Molecular etiology of ET, prodromal & overt PV, granulomyelosis (ET with a hypercellular megakaryocytic granulocytic bone marrow (EMGM), platelet-mediated microvascular thrombosis, increased red cell mass & macrovascular thrombosis, and secondary myelofibrosis in JAK2V617F myeloproliferative disorders MPDs: Michiels 2005

Molecular etiology of thrombocytemia and platelet thrombophilia: Sticky Platelet Syndrome

With the advent of the JAK2V617F mutation as the driver cause of ET and PV it became evident that JAK2V617F mutated megakaryocytes are constitutively activated with increased hypersensitivity to TPO as the production of hyperreactive sticky platelet as the cause of platelet mediated arteriolar inflammation (platelet thrombophilia) in thrombocytemia (Table 3, Figures 2 and 3) [51-53]. Heterozygous JAK2V617F mutation in ET and PV is related to increase of low JAK2 mutation load in ET and PV (less frequent in PV) and JAK2V617F positive thrombocythemia vera patients, much less frequent in JAK2 positive patients (mutation load more than 50% in ET and PV) and JAK2V617F positive patients (mutation load above 50% in ET and PV) were older, had higher leukocyte counts, hematocrits and larger spleen volumes. Major thrombotic
events were recorded after diagnosis in the preceding years during follow-up when not on aspirin. Major thrombotic events included ischemic stroke, transient ischemic attacks, myocardial infarction, angina pectoris, deep vein thrombosis, abdominal vein thrombosis, and pulmonary embolism. Symptoms due to microvesSEL disorder migraine-like headache, acral paresthesia, erythromelalgia, transient neurological and visual disturbances were neglected and excluded in this retrospective analysis. One hundred seventy-six patients (18.3%) had a major thrombotic event not on aspirin at diagnosis with a similar frequency in PV (19.2%) and ET (17.8%). During long-term follow-up, major thrombosis (not on aspirin) occurred in 122 patients (12.7%), corresponding to 14.9% in PV and 11.6% in ET patients (Table 4). Hemorrhages at diagnosis manifested in 55 (5.7%) patients, 5.3% in PV and 6.0% in ET. Hemorrhages during follow-up was recorded in 45 (4.7%) ET/PV. The frequency of bleeding was higher in JAK2V617F homozygous PV patients (21.4%) than in wild type or heterozygous ET patients (3.1%) and 3.8%. There were no significant differences in the overall rate and type of major thrombosis in heterozygous PV and homozygous PV (Table 4).

Table 4: Major cardiovascular events at diagnosis or during long-term follow-up in 323 PV and 639 ET patients according to the JAK2V617F mutation status in the retrospective study of Vannucchi. Only major thrombotic events were retrospectively recorded not including the erythromelalgic peripheral and migraine like cerebral ischemic events.

| Patients | PV N=323 | ET N=639 |
|----------------|---------|---------|
| JAK2V617F mutation status | hetero homozygous | hetero wild type |
| Number of patients | 219 | 104 | 368 | 257 |
| At diagnosis | | | | |
| Major arterial events | 21% | 15.4% | 21.7% | 10.5% |
| Venous events | 6.4% | 2.9% | 7.9% | 4.7% |
| During 10 years follow-up (no aspirin) | | | | |
| Major arterial events | 10.1% | 12.5% | 6.3% | 5.8% |
| Venous events | 4.1% | 7.7% | 6.3% | 2.7% |
| Total during life time follow-up | | | | |
| Major arterial | 31.1% | 27.9% | 28% | 16.3% |
| Venous | 10.5% | 10.6% | 14.2% | 7.4% |

Expert opinion

In 1878 Mitchel defined erythromelalgia as a rare vaso-motor neurosis of the extremities [1]. Brown postulated in 1932 six basic criteria of the idiopathic variant of burning pain and red congestion in the absence of any detectable underlying disorder [4]. In 1938, Smith and Allen substituted the term erythromelalgia for erythromelalgia to denote the importance of heat-therme, and first reported that a single dose of acetylsalicylic acid (aspirin 500mg) produced marked relief of burning distress and red congestion that persisted for a few days [5]. Since than both terms are used indiscriminately as synonyms in the primary and secondary forms, irrespective of aspirin-responsiveness and solely depending on the absence or presence of a detectable disease. Between 1975 and 1985 Michiels et al discovered aspirin-responsive erythromelalgia causally related to thrombocythemia in ET and PV patients to be clearly distinct from aspirin resistant primary erythromelalgia (PE) [6-10]. Following the six postulates of Brown (Table 2), Michiels discovered between 1988 and 1990 that incurable PE in the absence of any detectable underlying disease in skin biopsy (Figure 4) is a novel distinct clinical entity and could add four additional features of PE (Table 2) [9-10]. PE as a novel dominant and incurable disease has been confirmed in 1992 by the publication of a large family with autosomal dominant PE (Finley et al, Figure 4) [24].

Table 5: Nosologic classification and molecular etiology of aspirin responsive erythromelalgia in acquired and congenital thrombocythemia caused by gain of function mutations in the TPO, MPL and JAK2 genes and incurable primary erythromelalgia (PE) a congenital dominant neuropathy caused by gain of function mutations in the SCN9A gene; from Mitchell 1878 to Michiels 2016.

| Discoverer | Year | Disease |
|-----------|------|---------|
| Brown [4] | 1932 | Primary erythromelalgia: PE |
| Smith & Allen [5] | 1938 | Erythromelalgia versus Aspirin responsive Erythromelalgia in thrombocythemia |
| Michiels [6-8] | 1985/2013 | Aspirin responsive erythromelalgia and migraine-like ischemic attacks: Sticky Platelet Syndrome (ET & PV) |
| Michiels [9] | 1988 | Incurable inherited Erythromelalgia in a |
| Michiels [10] | 1990 | congenital dominant disease |
| Drenth et al [30] | 2001 | erythromelalgia susceptibility gene on chromosome 2q |
| Molecular etiology | 2004 | Gain of function mutation SCN9A gene in PE. Yang et al 200431 |
| | 2005 | Gain of function mutation JAK2 gene in acquired thrombocythemia (ET & PV) |
| | 2006 | thrombocythemia (ET & PV) |
| | 2013 | Germ line gain of function mutation in |

Four sequential discoveries have contributed to the elucidation of the molecular basis for PE. Linkage analysis in 2001 by Drenth & Michiels of 5 European families and one large USA family with documented incurable dominant PE located the PE susceptibility gene on chromosome 2q32-32 [30]. In 2004 Yang et al first found two mutations within this locus leading to single acid substitutions in the SCN9A gene for the human Nav1.7 sodium channel in patients with familial PE [31]. The finding of gain of function mutations in the SCN9A gene for the human Nav1.7 sodium channel in the 5 European PE families and the large USA PE family are completely in line with the dominant inheritance of PE as first delineated by Michiels [9,10,32-34]. Incurable PE is the first inherited painful neuropathy and has become a model disease that could held lessons for other painfull conditions and for the development of rational, mechanism-based treatments for pain [31-39]. The Nav1.7 gain of function mutations are expected to increase the excitability the nociceptors of peripheral sensory neurons and sympathetic ganglion neurons [34-39]. Functional analysis using patch clamp recording...
showed that these Nav1.7 mutations cause a hyperpolarizing shift in activation of the sodium channel and a slowing of deactivation. This is accompanied by an enhanced response to small depolarizing changes that should confer hyperexcitability on nerve cells, which express the mutant sodium channels. The Nav1.7 sodium channels are not globally present within all neurons but are selectively expressed within peripheral sensory neurons in dorsal root ganglia (DRG). There are about a dozen SCN9A mutations in multiple families identified causing PE (Reviewed by Drenth & Waxman Figure 7) [58]. All PE mutations detected are missense mutations that change important and highly conserved amino acid residues of the Nav1.7 protein [58]. The majority of the gain of function PE mutations are located in cytoplasmic linkers of the Nav1.7 channel, and some (F216S and N395) are located in transmembrane domains of the channel (Reviewed by Drenth & Waxman, Figure 7) [58]. PE mutations contribute to the hyperexcitability of pain-signalling DRG neurons thus causing extreme sensitivity to pain (hyperalgesia). Genotype-phenotype analysis of the SCN9A gene showed that smaller effects on sodium channel activation are related to a smaller degree of DRG neuron excitability and later onset of clinical PE signs and symptoms [58].

Cox, et al. discovered SCN9A mutations that cause a loss of Nav1.7 function in 6 patients from 3 consanguineous Japanese families with a congenital insensitivity to pain (CIP) [59]. The mutations were identified in exon 10 (S495X), exon 13 (I767X, and exon 15 (W897X) Goldberg (2007) and Ahmed (2007) performed studies in 9 Western European and North and South American families and a third large Canadian family used linkage analysis is search for homozygous haplotypes identified the same gene and detected 10 truncating SCN9A mutations [60,61]. The majority of affected patients in these two studies were homozygous for SCN9A mutations and 2 patients were compound heterozygous for different SCN9A nonsense mutations. The Nav1.7 channelopathy-associated insensitivity to pain (CIP) is an autosomal recessive disorder. There is intact ability to distinguish between sharp and dull stimuli and to detect differences in temperature. CIP individuals are insensitive to pain beginning in infancy that leads to frequent painless injuries, fractures, burns, ultimately resulting in a shortened life expectancy. Affected individuals are either homozygous or compound heterozygous for loss of function (nonsense) mutations of the Nav1.7 protein. All loss of function mutations are randomly distributed across the SCN9A gene [58]. The mechanism behind this profound insensitivity to pain may stimulate the search for novel painkillers by targeted inhibition of impulses-travel from nociceptive (pain-signalling) dorsal root ganglia (DRG) neurons.

Sudden attacks of rectal, ocular, and submaxillary pain, first described in 1958, has been named as paroxysmal extreme pain disorder (PEPD) [58,62,63]. PEPD is an autosomal dominant disorder characterized by paroxysmal episodes of sudden onset pain at different body sites, accompanied by skin flushing. There are four well defined types of painful episodes in PEPD patients [62,63]. A genome-wide linkage search in one large pedigree with PEPD led to the PEPD susceptibility gene on chromosome 2q24.3 [64]. As this region contained SCN9A, the investigators sequenced the gene and found 8 heterozygous missense mutations in 8 families [64]. Each family possessed a unique PEPD mutation and one individual was compound heterozygous for R996C and V1298D (Figure 7) [58]. This individual was more severely affected than his heterozygous father. Functional analysis of 3 mutations (I1461T, T1464I and M1627K) were reported to impair inactivation of the Nav1.7 channel. The effects in response to provoking stimuli (such as stretching and exposure to cold temperature) of PE mutations enhance channel inactivation [58]. The effects in response to provoking stimuli of PEPD mutations impair channel inactivation. Such differences are predicted to contribute at least in part to the different clinical symptomatology in these two congenital pain disorders PE and PEPD due to gain of function

Figure 7: Heterozygous gain of function mutations in the sodium-channel subunit Nav1.7 that are associated with autosomal dominant pain disorders of primary erythermalgia (PE) (*), paroxysmal extreme pain disorder (PEPD) (^), and homozygous or double heterozygous loss of function mutations in the sodium-channel subunit Nav1.7 that is associated with chronic insensitivity to pain (CIP) (#) (A). Sodium-channel subunit Nav1.7 is encoded by the SCN9A gene comprising 26 coding exons (A). The mutations of PE and CIP are distributed over the entire gene sequence (A and B), but the mutations linked to PEPD are located closer to the 3’end of the SCN9A gene (A and B). The sodium-channel subunit Nav1.7 consists of 4 domains (D1-D4) each with 6 transmembrane segments. The locations of known mutations associated with genetic pain disorders PE (*), PEPD (^) and CIP (#) are shown. Source Drenth & Waxman [58].

Aspirin responsive erythromelalgia in congenital dominant thrombocythemia

The first well documented report on autosomal dominant congenital ET due to a gain of function mutation in the TPO gene was first described in a large Dutch family and confirmed in a Polish family [65-67]. Analysis of the TPO gene in the Dutch family was recommended by Drs Michiels and van der Maas and performed by Dr Skoda [66]. The C→G transversion in the splice donor site of intron 3 of the TPO gene on chromosome 3q27 co-segregated with the affected autosomal dominant hereditary ET (HET) in the Dutch and Polish families [66-68]. This mutation destroys the splice donor site in intron 3 and results in exon 3 skipping. The shortened 5′UTR gene resulted in a gain of function which leads to overproduction of thrombopoietin (TPO) by a mechanism of increased efficiency of the TPO mRNA translation. The in vivo increased TPO levels are responsible for the etiology of congenital ET by stimulating megakaryocyte production both in vitro and in vivo. Congenital gain of function mutation in the TPO gene in the Dutch and Polish families results in increased plasma TPO
levels, which induce a physiological activation of the TPO→MPL signalling pathway [66-68]. This results in hyperproliferation of large mature megakaryocytes and persistent increased platelet counts. The marked increased TPO levels in affected family members as the cause of increased platelet count (congenital thrombocythemia) is associated with microvascular circulation disturbances including erythromelalgia and atypical transient ischemic attacks similar to platelet-mediated thrombophilia in acquired thrombocythemia in ET patients as first discovered by Michiels et al in 1984/1985 [6,7,68].

Congenital dominant ET due to a germline gain of function mutation S505N in the MPL gene has been described in 2004 [69,70]. Teofili et al reported the clinical and hematological features of 41 patients with a congenital germline gain of function mutation S505N in the MPL (thrombopoietin = TPO receptor) gene in seven Italian families (21 ET patients with a proven MPL S505N mutation and 20 relatives with thrombocythemia) [70]. In 41 affected congenital ET patients with a proven or suspected MPL S505N mutation, 15 major thrombotic episodes in 14 members (34%) were reported as Budd-Chiari syndrome, deep vein thrombosis, ecchlampsia, stroke and myocardial infarction at ages between 31-81 years, median 52 years. Fourteen out of 21 well documented MPL S505N mutated ET patients had no splenomegaly and were free of major thrombosis during follow-up at ages between 2 and 76 years (mean 31 years) [70,71].

There are three novel molecular variants of a germline gain of function mutation in the JAK2 gene for congenital dominant ET: dominant ET caused by a heterozygous gain of function mutation JAK2V617I, JAK2R564Q and JAK2H698N in the JAK2 gene [72-75]. Mead et al described the germline mutation JAK2V617I as the sole genetic abnormality, sufficient to induce the ET phenotype of MPN in a family with congenital dominant ET complicated by microvascular ischemic events in some of the them [72,73]. Another novel heterozygous JAK2R564Q mutation has been identified by Etheridge et al in another unrelated family with congenital dominant ET [74]. The investigators demonstrated that JAK2V617I and JAK2Q564W heterozygous germline mutation are the sole driver for congenital ET in JAK2V617I-positive and JAK2Q564W-positive individuals. The clinical investigators nicely documented that peripheral blood and bone marrow histology in these two families were consistent with normocellular ET without features of PV [72-74]. The heterozygous JAK2V617I and JAK2Q564W mutated congenital ET patients had completely normal values for haemoglobin, haematocrit, erythrocytes, TPO and EPO levels [72-74]. Heterozygous JAK2V617I or JAK2Q564W gain of function mutation in affected congenital ET patients is sufficient to induce cytokine hyperresponsiveness of hematopoietic stem cells to stimulate megakaryopoesis and platelet production with the induction of a ET clinical phenotype. Congenital dominant ET caused by a heterozygous gain of function mutation in the JAK2 gene R564Q and V617I[72-74] did present with typical manifestations of dominant aspirin responsive Sticky Platelet Syndrome (SPS) similar as seen in acquired JAK2V617F mutated ET [6,7,54,72-74].

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