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# Aspirin Responsive Thrombotic Complications in Thrombocythemia Vera. A Novel Platelet-Mediated Arterial Thrombophilia

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## ABSTRACT

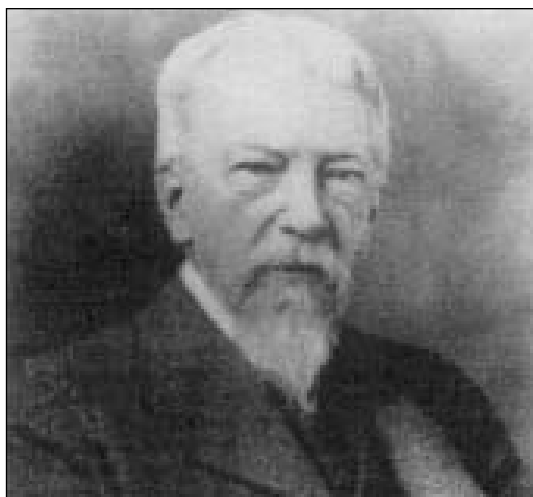
Erythromelalgia is the main, pathognomonic and presenting symptom in patients with Essential Thrombocythemia and thrombocythemia associated with Polycythemia Vera. Complete relief of erythromelalgic and acrocyanotic pain is obtained with the cyclooxygenase inhibitors aspirin and indomethacin, but not with sodiumsalicylate, dipyridamol, sulfipyrozone and ticlopedine indicating that platelet-mediated cyclooxygenase metabolites are necessary for erythromelalgia to develop. Local platelet consumption in erythromelalgic areas became evident by the demonstration of arteriolar fibromuscular intimal proliferation and occlusions by platelet-rich thrombi in skin biopsies, by the findings of shortened platelet survival times, significant higher levels of platelet activation markers  $\beta$ -thromboglobulin ( $\beta$ -TG), thrombomoduline and increased urinary thromboxane B2 excretion in thrombocythemia patients suffering from erythromelalgia. Aspirin treatment of erythromelalgia in thrombocythemia patients resulted in disappearance of the erythromelalgic, thrombotic signs and symptoms, correction of the shortened platelet survival times, and significant reduction of the increased levels of  $\beta$ -TG, PF IV, thrombomodulin and urinary T x B2 excretion to normal. Erythromelalgia is frequently preceded or followed by atypical transient neurologic, ocular or coronary ischemic symptoms, which specifically responds to low-dose aspirin or reduction of platelet counts to normal. The broad spectrum of acroparesesias, erythromelalgia and acrocyanotic ischemia together with the episodic and transient atypical TIAs and ocular or coronary ischemic symptoms all are the consequence of one underlying disorder of aspirin-responsive and platelet-mediated arterial thrombophilia precipitated by spontaneous activation and aggregation of hypersensitive platelets in the endarterial microvasculature involving the peripheral, cerebral and coronary circulation of thrombocythemia patients.

Key Words: Erythromelalgia, Arterial thrombosis, Transient ischemic attacks, Aspirin, Thrombocythemia.

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## INTRODUCTION

In his lecture entitled "On a rare vaso-motor neurosis of the extremities and on the maladies with which it may be confounded" Silas Weir Mitchell reported in 1878 16 cases with painful affections of the feet of various types and severity<sup>[1]</sup>. In a footnote on the title page of his manuscript Mitchell stated that the burning painful and red congestion of the foot and hand disorder might conveniently be labelled erythromelalgia, deriving it from the Greek words erythros= red, melos= extremity, and algos= pain (Figure 1). As the pathologic basis of erythromelalgia had not been established, the original concept outlined by Mitchell in 1878 remained elusive for more than one century. Based on Mitchell's description of 16 cases, Brown postulated in 1932 six basic criteria for the diagnosis of the idiopathic variant of burning pain and red congestion in the extremities in the absence of a detectable underlying disorder<sup>[2]</sup>. Brown separated the group of typical cases with the primary variant from those cases in which there was burning pain in the hands and feet secondary to diseases. The hot burning disturbances of acral portions as a frequent precursor or an early presenting symptom of polycythemia vera were mentioned as the most prominent and typical variant of secondary erythromelalgia. In 1938 Smith and Allen substituted the term erythromelalgia for another descriptive term, namely, erythermalgia, to denote the importance of heat=thermé<sup>[3]</sup>. Smith and Allen discovered that a single dose



**Figure 1.** Silas Weir MITCHELL, 1878. Discoverer of erythromelalgia.

of acetylsalicylic acid (aspirin) produced marked relief of the burning distress that persisted for a few days<sup>[3]</sup>. Between 1975 and 1981, Michiels et al discovered that the specific subset of patients with burning painful red extremities, who experienced clinical relief with aspirin, all had elevated platelet counts associated with thrombocythemia in its primary form or associated with polycythemia vera<sup>[4-6]</sup>. Moreover, the long-lasting effect of aspirin could be attributed to its irreversible inhibition of platelet cyclooxygenase activity (Table 1, Figures 2, 3). This form of aspirin-responsive red congestion and burning pain asymmetrically located in toes or fingers, foot sole or handpalm is defined as a distinct entity by Michiels as erythromelalgia (Figure 4)<sup>[4-6]</sup>.

Following the six postulates of Brown, Michiels et al have recognized the rare and incurable variant of red burning pain and warm congestion of lower leg and feet in the absence of any detectable underlying disorder<sup>[7-9]</sup>. This incurable variant arises in children or adolescents, persists throughout life and is defined by Michiels et al as idiopathic erythermalgia to emphasize the prominent symptoms of heat and redness (Table 2)<sup>[7-12]</sup>. There are a multitude of clinical conditions without thrombocythemia to cause symptoms of symmetric red, warm, swollen and burning pain in the feet or hands, which do not respond to aspirin. These other forms, which are labelled by Michiels et al as secondary erythermalgia, originate from side effects of drugs or arise from various disorders including cutaneous vasculitis, vasculitis in lupus erythematoses, hypertension, rheumatoid arthritis and many other conditions<sup>[7-20]</sup>.

Both terms, erythromelalgia and erythermalgia, are currently 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<sup>[21]</sup>. In this document we introduce the historic differentiation of this syndrome to aspirin-responsive erythromelalgia vera and idiopathic erythromelalgia/erythermalgia (Table 1, Table 2, Figure 4). Aspirin-responsive erythromelalgia vera appears to be utterly dissimilar from idiopathic and secondary erythromelalgia/erythermalgia, in which the prompt relief of aspirin is lacking and therefore to be used as a differential diagnostic test.

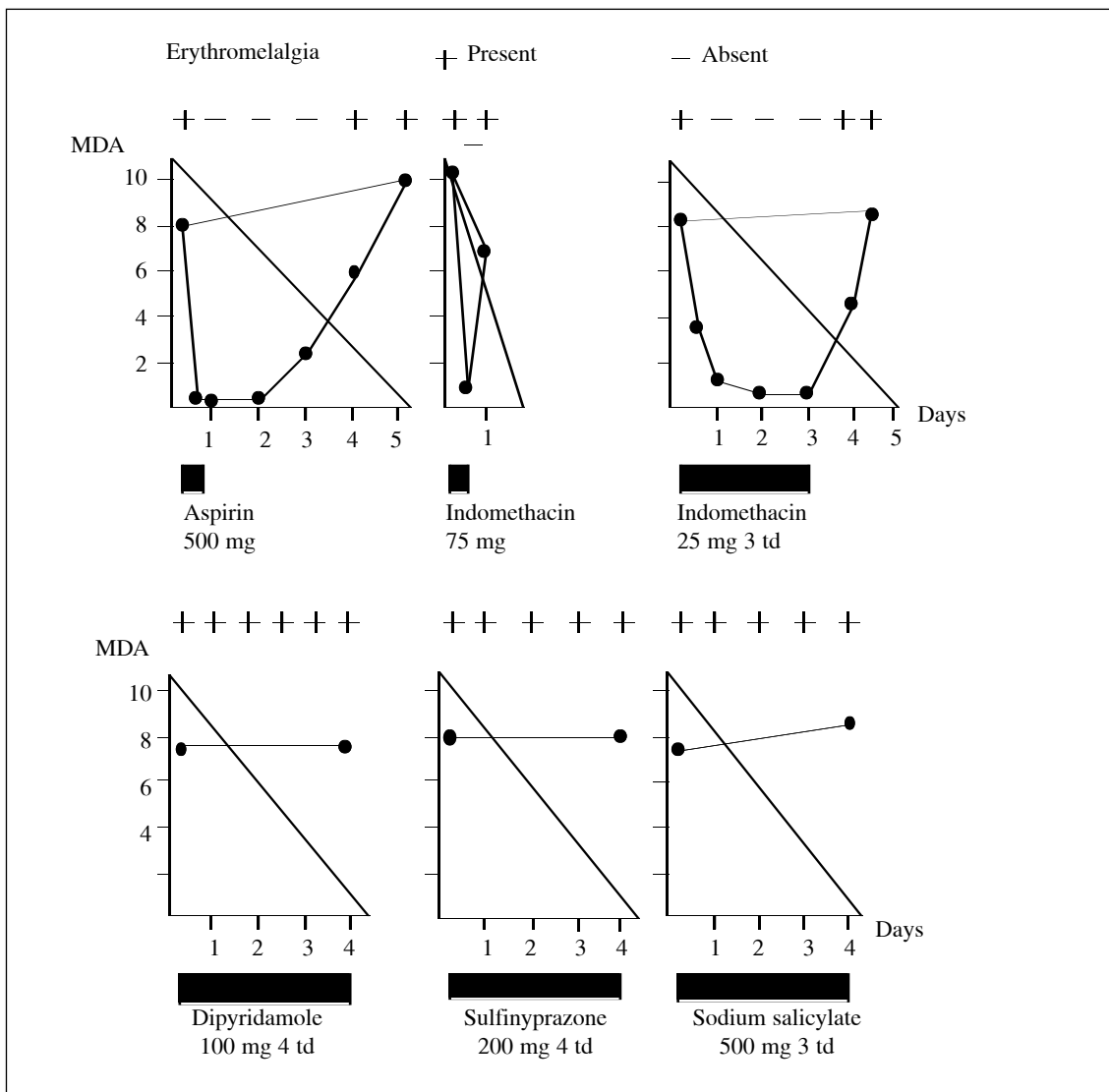
### **Erythromelalgia: A Pathognomonic Microvascular Thrombosis in Thrombocythemia**

Classical erythromelalgia or erythromelalgia vera is characterized by red congested extremities and painful burning sensations with preferential asymmetrical involvement of the forefoot sole and one or more toes or fingers (Table 1). Acroparesthesias, for example tingling, "pins and needles" sensations and numbness in the toes or fingers, usually precede the disabling and burning distress. If left untreated, erythromelalgia frequently progresses to painful ischemic acrocyanosis or even peripheral gangrene. Aspirin promptly relieves pain for approximately 3 days. This long-lasting effect of a single dose of aspirin (500 mg) is so specific that it can be used as a diagnostic test (Figure 2). In contrast to coumadin, a daily low-dose of aspirin not only cures the erythromelalgic distress quickly and lastingly but also reverses the ischemic circulation disturbances, coinciding with the complete inhibition of platelet cyclooxygenase activity. Dipyridamole, sulfinpyrazone, and sodiumsalicylate have no effect on erythromelalgia or platelet cyclooxygenase activity as measured (Figure 2). Thus active platelet prostaglandin metabolism is a prerequisite for erythromelalgia to develop.

The histopathological appearances of a skin punch biopsy in a patient with full blown erythromelalgia without ischemic complications show arteriolar lesions without involvement of venules capillaries or nerves<sup>[22,23]</sup>. Sections of arterioles showed pronounced vessel wall thickening by fibromuscular intimal proliferation and degeneration with narrowing of the lumen, the lining endothelial cells were swollen with some large nuclei, but occlusive thrombi but occlusive thrombi were not seen (Figure 3). The histopathological appearances from an area of relapsed erythromelalgia of a second patient 3 weeks after discontinuation of aspirin showed one affected arteriole with proliferative intimal thickening with partial occlusion by a thrombus. Another affected arteriole, which showed pronounced fibromuscular intimal proliferation, was completely occluded by thrombus (Figure 3). Immunohistochemically, these thrombi in erythromelalgic areas stain strongly for von Willebrand factor while there is a very weak fibrin staining<sup>[24]</sup>. This is consistent with platelet-rich thrombi. These clinical results imply that intravascular activation and aggregation of hypersensitive platelets in symptomatic patients with thrombocythemia vera are paramount in the etiology of both erythromelalgic inflammatory signs and thrombotic occlusive disease of the acral microvasculature, without evidence of

Table 1. Ten diagnostic criteria of aspirin-responsive erythromelalgia vera

1. Attacks of unilateral or bilateral but asymmetric burning pain and red warm congestion of footsole, handpalm, or one or more toes or fingers
2. The attacks aggravate by standing, exercise, and/or exposure to heat
3. Relief is obtained by rest, by elevation of the involved extremities, and by exposure to cold
4. During the attacks, the affected parts are red, blue and congested and exhibit local heat
5. Erythromelalgia vera is linked to thrombocythemia in various myeloproliferative disorders and caused by platelet-mediated inflammation and thrombosis in the end-arterial circulation
6. Low-dose aspirin cures erythromelalgia and prevents recurrences
7. Aspirin-responsive erythromelalgia arises at adult age
8. Aspirin-responsive erythromelalgia vera in thrombocythemia is an acquired condition and has also been documented as a congenital condition in association with hereditary thrombocythemia
9. There is preferential involvement of forefoot sole and one or more toes or fingers and it usually progresses in acrocyanotic ischemia or even peripheral gangrene
10. The histologic findings in skin biopsies from erythromelalgic areas are specific, showing fibromuscular intimal proliferation and thrombotic occlusions of arterioles or small arteries in the absence of preexistent vascular disease



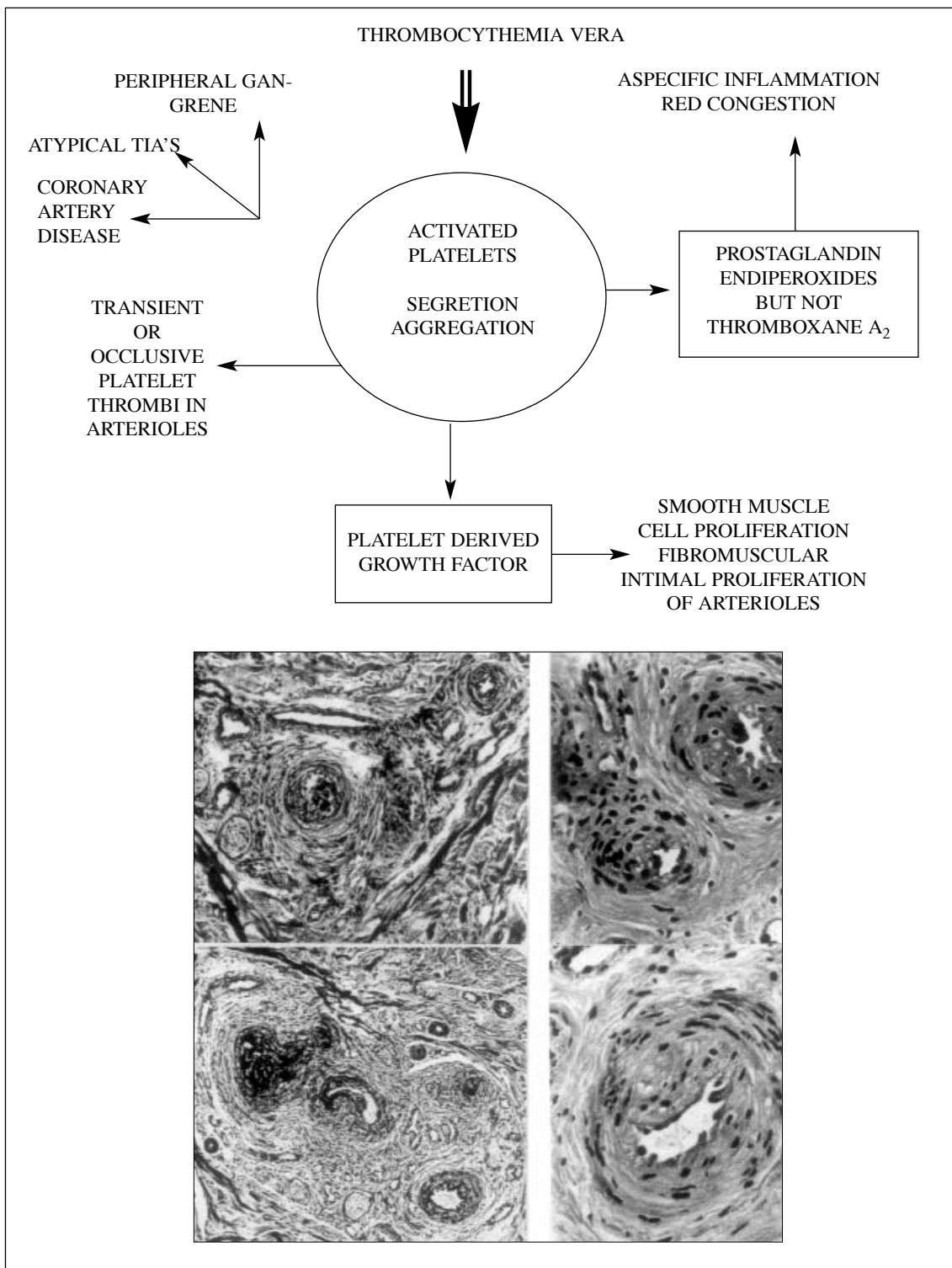
**Figure 2.** The effect of aspirin (acetylsalicylic acid), indomethacin, dipyridamole, sulfinyprazone and sodiumsalicylate on erythromelalgia and on platelet cyclooxygenase activity as measured by malondialdehyde (MDA) production by arachidonic acid stimulated platelets in platelet-rich plasma of patients with essential thrombocythemia.

preexisting vascular disease or atherosclerosis.

**Aspirin-Responsive Platelet-Mediated Arterial Thrombophilia in Thrombocythemia**

Our clinical observations and histopathological studies indicate that in thrombocythemia the platelets are primarily involved in the etiology of thrombotic occlusions of the acral microvasculature<sup>[5,22,23]</sup>. In contrast, erythromelalgia and acrocyanosis are not a fe-

ature in patients with reactive thrombocytosis. Further evidence for local platelet consumption in thrombocyt-hemic erythromelalgia stems from our platelet kinetic studies<sup>[25]</sup>. We performed platelet kinetic studies in symptomatic thrombocythemia patients suffering from erythromelalgia before and after intervention with aspirin, in asymptomatic thrombocythemia patients, and in a control group of patients with reactive thrombocytosis. Platelet kinetic studies using Cr-labeled autolo-



**Figure 3.** The etiology of erythromelalgia as caused by platelet-mediated arteriolar inflammation, fibromuscular intimal proliferation and thrombosis was first conceptualized by Michiels and van Vliet in 1978.



**Figure 4.** Jan Jacques Michiels, MD, PhD. 1981.

Discoverer of erythromelalgia vera caused by platelet-mediated arteriolar inflammation and thrombosis in thrombocythemia as a novel aspirin-responsive arterial thrombophilia 1989.

Description of idiopathic erythromelalgia/erythermalgia: An incurable congenital disorder.

gous platelets showed a significantly decreased platelet survival ( $4.2 \pm .4$  days) in 10 symptomatic thrombocythemia complicated by erythromelalgia as compared

with 10 asymptomatic thrombocythemia patients ( $6.6 \pm 0.3$  days,  $p < 0.001$ ) and 6 patients with reactive thrombocytosis ( $8.0 \pm 0.4$  days,  $p < 0.001$ )<sup>[25]</sup>. After treatment of erythromelalgia with aspirin 500 mg per day in 7 symptomatic thrombocythemia patients, platelet survival increased significantly from  $4.0 \pm 0.3$  days to  $6.9 \pm 0.4$  days ( $p < 0.001$ ) thereby causing a significant rise of the platelet count of about  $200 \times 10^9/l$  in each of the aspirin treated thrombocythemia patients<sup>[25]</sup>. Continued treatment with low dose aspirin, inhibiting platelet cyclooxygenase activity normalized platelet survival by suppressing platelet consumption, resulting in complete relief of erythromelalgic stress and restoration of the ischemic thrombotic circulation disturbances. In contrast, coumadin failed to improve platelet survival in erythromelalgia, which is consistent with the clinical experience of the ineffectiveness of coumadin in the treatment of erythromelalgia. In subsequent studies we could demonstrate that erythromelalgia, as compared with asymptomatic ET-patients and control subjects, was characterized by significant higher levels of the platelet activation markers  $\beta$ -thromboglobulin ( $\beta$ -TG) and platelet factor IV (PF IV) and endothelial cell marker thrombomodulin (TM), but no significant differences were detected in either prothrombin fragments F1 + 2 or total fibrin/fibrinogen degradation products (TDP) levels<sup>[24]</sup>. Treatment of erythromelalgia with aspirin was paralleled by a significant decrease of  $\beta$ T-G, PF IV and TM levels<sup>[24]</sup>. Thus, the generation of thrombin appears not to be essential for the formation of platelet-rich thrombi in erythromel-

**Table 2.** Ten diagnostic criteria of idiopathic erythromelalgia/erythermalgia

1. Attacks of bilateral and symmetric burning pain and red warm congestion in the feet, lower legs, or hands
2. The attacks are initiated or aggravated by standing, exercise, or exposure to heat
3. Relief is obtained by rest, by elevation of the extremities, and by exposure to cold
4. During the attacks, the affected parts are red, congested, and exhibit local heat
5. There is no treatment available
6. Idiopathic erythromelalgia/erythermalgia spontaneously arises in children and adolescents and persists throughout life
7. A hereditary basis of idiopathic erythromelalgia/erythermalgia has become evident
8. There is relative sparing of the toes and acrocyanotic ischemia is not a feature
9. Peripheral gangrene is never observed
10. The histologic findings in skin biopsies from erythermalgic areas are nonspecific showing the absence of an underlying disorder and do not reveal a clue to its pathophysiology

gia, thereby giving a plausible explanation for the inefficacy of comadin-derivatives and heparin in the prevention and treatment of erythromelalgia in thrombocythemia vera. In a subsequent study we could demonstrate that within 10 days after discontinuation of aspirin, 3 ET-patients developed arterial microvascular thrombosis of the extremities (erythromelalgia), which was preceded by a 3 to 30 fold increase in urinary T x B2 excretion as compared with 3 ET-patients who remained asymptomatic after discontinuation of aspirin<sup>[26]</sup>. The increased urinary TxB2 excretion and the clinical signs of erythromelalgia could subsequently be inhibited by a platelet-specific low-dose aspirin regimen of 50 mg daily without affecting vascular cyclooxygenase<sup>[26]</sup>. These observations clearly indicate that platelets were the main source of increased T x B2 generation in ET-patients complicated by erythromelalgia and provide a rationale for using a very low dose of aspirin 50 mg daily for the prevention of microvascular circulation disturbances in thrombocythemia patients<sup>[26]</sup>.

Our clinical, histopathological, platelet-kinetic and experimental studies using activation markers for platelets, coagulation and endothelial cells are in line with the concept that indeed platelet activation and endothelial cell damage are essential factors in the etiology and formation of platelet-rich thrombi in erythromelalgic areas of symptomatic thrombocythemia patients (Figures 3, 4)<sup>[5,22-26]</sup>.

#### **Transient Cerebral and Ocular Ischemic Manifestations in Thrombocythemia Vera**

We studied the presenting, neurological and visual ischemic symptoms in 22 patients with essential thrombocythemia<sup>[27,28]</sup>. Erythromelalgia preceded or followed the neurological symptoms in 10 patients. All patients presented neurological and/or visual ischemic symptoms. Eleven ET-patients had focal symptoms: Transient monocular blindness in 3, transient mono- or hemiparesis in 6 and both of these in 1, migraine accompaniments in 1 and partial stroke in 1. Nonfocal symptoms occurred in 14 ET-patients: Transient postural instability in 13, dysarthria in 8 and scintillating scotomas in 5. The transient focal and nonfocal neurological and visual symptoms all had a sudden onset, occurred with a march rather than all at one time, lasted for a few seconds to several minutes and were usu-

ally associated with or followed by a dull or pulsatile headache. This clinical presentation is very atypical for transient ischemic attacks caused by atherosclerosis, but the striking similarity with migraine accompaniments supports the crucial role of platelets in the pathogenesis of ischemic neurological disturbances in essential thrombocythemia (Figure 3). During continuous treatment with low doses of aspirin (250 to 500 mg daily) for 1 to 9 years, no recurrence of vascular events occurred in 14 ET-patients<sup>[27,28]</sup>. Eleven ET-patients maintained remissions of ET (platelet counts < 350 x 10<sup>9</sup>/L) for 3 to 7 years after treatment with busulfan and remained asymptomatic<sup>[27,28]</sup>. Fröhli nicely documented the prophylactic effect of low dose aspirin on vascular complications in 22 symptomatic patients with thrombocythemia vera due to either ET or PV in remission after bloodletting (n= 13) or ET (n= 9) at platelet counts between 400 to 1000 x 10<sup>9</sup>/L<sup>[29]</sup>. Under low dose aspirin (250 mg/day) during a total period of 45 patient-years acral microvascular ischemia disappeared completely in 11 patients and atypical TIAs including unstable gait, dizziness and blurred vision were completely abolished in 12 of 13 patients<sup>[28]</sup>. Discontinuation of aspirin was followed by prompt recurrence of the peripheral and cerebral microvascular circulation disturbances<sup>[27-29]</sup>.

#### **Coronary Artery Disease in Thrombocythemia**

We studied 9 cases of coronary events as the presenting symptom of ET included myocardial infarction in 4, and unstable angina pectoris in 5<sup>[30]</sup>. Cardiac catheterisation was performed in 8. Three patients with myocardial infarction had normal coronary arteries. Five patients with unstable angina had coronary disease (one vessel disease in 2 and two vessel disease in 3) underwent coronary by-pass surgery. During continuous treatment with low doses of aspirin (500 mg/day) there was no recurrence of vascular events in 4 patients for 1 to 5 years at platelet counts of 650, 800, 860 and 1000 x 10<sup>9</sup>/l. Five patients maintained complete remission of ET (platelet counts < 350 x 10<sup>9</sup>/l) for more than 1 to 6 years after treatment with busulfan and remained asymptomatic.

#### **CONCLUSION**

We have produced very good clinical and experimental data that control of platelet function with aspi-

rin and correction of platelet number to normal by platelet lowering agents are effective in the prevention of platelet-mediated microvascular circulatory disturbances in thrombocythemia vera. In case of reactive thrombocytosis erythromelalgia has never been observed, which indicates that not only a quantitative but also a qualitative disorder of platelet function appear to contribute in the etiology of microvascular ischemia or thrombosis in thrombocythemia vera. The mechanism whereby patients with thrombocythemia vera develop microvascular circulation disturbances under the prevailing high shear stress conditions in the end-arterial microcirculation remains to be determined. The broad spectrum of acroparesis, erythromelalgia and acrocyanotic ischemia together with the episodic and transient atypical TIAs and to a less extent also acute coronary ischemic syndromes all are the consequence of one underlying disorder of aspirin-responsive and platelet-mediated arterial thrombophilia precipitated by spontaneous activation and aggregation of hypersensitive platelets in the endarterial circulation involving the peripheral, cerebral and coronary circulation of thrombocythemia patients (Figure 2).

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