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# PATHOPHYSIOLOGY OF WHITE FINGERS IN WORKERS USING HAND-HELD VIBRATING TOOLS

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## ABSTRACT

The pathogenic events and the localization of the primary lesion in white fingers among persons using hand-held vibrating tools are still unclarified. A "vibration disease" has been proposed to be due to damage to the limbic system and other brain structures which causes autonomic dysfunction. Current common opinion regards the pathogenesis of white fingers to be a result of longterm exposure to various physical and psychological environmental stressors, but the relative importance of one stressor or other is unknown. Observations indicating a chronic autonomic disturbance include changes in cardiac functions, excessive hearing loss in persons with VWF, and reduced toe skin temperature also in the absence of acute cold or vibration exposure. Sympathetic hyperactivity alone has long been postulated to account for vibration-induced white fingers, but damage to vasoregulatory structures and functions in the finger skin now also seems to be involved. An abnormal level of sympathetic efferens is likely to be important for producing the symptoms in white fingers. Recent findings, however, indicate that the pathogenesis also involves changes in alpha-adrenergic receptor mechanisms as well as endothelial damage with deficient function of endothelial-derived relaxing factor. The role of vessel lumen reduction due to organic changes and an increase in whole blood viscosity remains unclarified. The understanding of the influence of confounders such as cold exposure, smoking habits and variations in individual susceptibility is also lacking. In particular, the physiological complexity of the response to cold is so great and the interaction between various vasoregulatory mechanisms so intricate that only a multifactorial etiology and pathogenesis is likely for Raynaud's phenomenon in persons using hand-held vibrating tools. A model is suggested for the manifestation of abnormally strong vasoconstriction and white fingers as a result of a narrowing of the gap between the individual symptom threshold and the level of sympathetic activity.

Key words: Adrenergic receptors, Autonomic functions, Cold, Hand-arm vibration syndrome, Endothelial-derived relaxing factor, Hearing loss, Raynaud's phenomenon, Stressors, Vibration disease, Vibration exposure, White fingers

## INTRODUCTION

Vibration from hand-held tools — largely absorbed in the skin of the hand — may cause a circulatory disturbance called "vibration-induced Raynaud's phenomenon", also popularly known as "vibration white fingers" (VWF). The mechanism behind the acute attack is well known: an abnormally strong contraction of skin blood vessels. The question of where the primary site of the lesion is localized, however, is controversial. Although, not long ago, the pathophysiology of vibration white fingers (VWF) seemed to be regarded as a clearcut case of sympathetic hyperactivity, it is not that simple anymore. A picture is emerging where several possible, probably concomitant, pathogenic processes have to be taken into account together with a number of confounding factors and effect modifiers. Although enhanced sympathetic activity is likely to be important in many cases, it now seems that vascular and vasomotor nerve structures in the finger skin are also heavily involved.

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The purpose of this paper is to review and discuss these various matters. This survey complements another review of the pathophysiology and pathogenesis of VWF recently published.[1)]

## NOSOLOGICAL CONCEPTS

A Hand-Arm Vibration Syndrome (HAVS) has been defined to include only the peripheral circulatory, sensorineural and locomotor manifestations, interpreting "neurovegetative" symptoms as well as signs of "autonomic dysfunction" as psychosomatic manifestations of the effect of various stressors.[1–3)] Other researchers prefer to gather the disturbances occurring in vibration-exposed workers into a nosological entity, a stress-induced "vibration disease."[4,5)] This disease notion includes all those disorders that may be caused by working with hand-held tools and which are, consequently, pathogenically connected with vibration, cold, noise, ergonomic and biodynamic conditions, and emotional stress in work.[6–8)] The damage is considered to involve the limbic system (especially the hypothalamus) and the cerebral cortex, and through these structures to cause neuropsychiatric symptoms like headache, insomnia, and impotence, but also tinnitus and hearing loss. By way of hormonal mechanisms mediated by the adrenal medulla, the cardiovascular system is thought to be affected, with such manifestations as heart enlargement and bradycardia.

In both these nosological concepts, stressors in the form of physical and psychological work environment factors are regarded as important for the pathogenesis of disorders that commonly occur in subjects working with hand-held vibrating tools. This concept will receive prime attention in the present review.

The question whether there is in fact a functional-anatomical brain lesion in persons with chronic autonomic dysfunction is unsettled. In a recent study by Hirata et al.,[9)] however, evidence seems to have been obtained, in patients with vibration-induced disorder, of a locus of damage in the CNS. It was seen as prolonged latency in response to click sound testing of a component (P300) in the so-called event-related brain potential. This component is associated with cognition and selective attention and has been studied also in persons affected by solvent vapor and manganese exposure. No theory was offered as to how such a lesion may have been caused.

An effect on the P300 latency in military aircraft pilots has also been investigated,[10)] but the influence of whole-body vibration and noise could not be separated from those of age, and of ergonomic factors related to aircraft flying, such as cumulative exposure to hypoxia and G forces, and possible effect of other stressors were not explicitly addressed. Intriguing data have been obtained in studies by MRI of male aviation ground personnel (22–59 yrs old) long-term exposed to vibration and noise from pneumatic hammers and nut runners.[11)] These authors identified so-called hyperintense foci in the basal ganglia and the brain stem, which were considered to be related to the vibration and noise exposure. It was emphasized, however, that similar lesions may be observed as an age-dependent finding in otherwise normal individuals and in certain diseases.

## CENTRAL OR PERIPHERAL MECHANISMS IN WF PATHOGENESIS?

The decisive role of sympathetic hyperactivity alone has long been taken for more or less granted. Thus, according to Olsen,[12)] VWF is basically "caused by a primary closure of all proper digital arteries in the cooled segment of the affected finger" due to "a transient

vasoconstriction...predominantly mediated by central sympathetic reflex mechanisms" — a manifestation of "hyperreactivity", induced by "activation, over a long time of vibration exposure, of central sympathetic reflex mechanisms". As also mentioned by Olsen in a more recent paper,[13] the vasospasm may have other explanations as well: "active" processes, mediated by "local, humoral or central sympathetic reflex mechanisms", and "passive" processes, for instance thromboembolism in a vessel with damaged endothelium, or changes in the viscoelastic properties of the arterial wall and its response to cold. Additional possible pathogenic mechanisms were suggested, such as "abnormal adrenergic receptor activity of the smooth muscle cell" or hypertrophy of vascular smooth muscle cells, that may contribute to some extent.

As will be treated in more detail below, these quotations summarize quite well the multifactorial view that now is most commonly favored.

## "AUTONOMIC DYSFUNCTION"

Three types of chronic condition indicating a chronic disturbance in autonomic nervous functions have been observed in persons working with hand-held vibrating tools: (1) changes in cardiac and hemodynamic functions, (2) excessive hearing loss in persons with VWF, and (3) reduced toe skin temperature, due to the influence of prolonged exposure to stressors, also in the absence of acute cold or vibration exposure, in persons exposed to hand-arm vibration.

*Changes in cardiac and hemodynamic functions*

Orthostatic hypotension observed by Färkkilä and collaborators[14] in forestry workers with VWF was regarded as a sign of "autonomic failure", the symptoms and signs of which resembled those induced by mental and physical stress.[15] The lesion behind the VWF in those lumberjacks was considered to be on the afferent side of the sympathetic nervous system, because the vasoconstrictor response to stressors was found to prevail.

Bovenzi, in an investigations of grinders, did not explicitly mention stressors as etiologic factors, but the effects of the vibration exposure were of the same kind as in the study by Färkkilä and collaborators just mentioned. Bovenzi[16] recorded blood pressure, heart rate and systolic time intervals in response to a battery of typical "stress" tests for sympathetic tone. From the results of, for instance, systolic time intervals, he concluded that excessive sympathetic reflex activity plays an important role in the pathogenesis of VWF. Other potential vibration effects, like neurologic disturbances, were not included in this study.

A vibration-induced autonomic dysfunction was also discussed in the report of Heinonen and collaborators in a study of chain-saw workers.[17] In this investigation, however, an enhancement of sympathetic vasomotor tone was suggested to result from an imbalance between opposing autonomic influences which stemmed from a depression of parasympathetic activity.

It should be emphasized that there is no simple or general relation between the functions of the sympathetic and parasympathetic nervous systems. Intricate processes govern catecholamine-related reactions,[18,19] and the pathogenic mechanisms behind cardiac effects of various stressors therefore cannot be easily understood. It is well known that stressors induce a CNS reaction which results in physiological changes mediated by neurogenic and neuroendocrine systems. Enhanced sympathetic activity causes a release of catecholamines from the adrenomedulla, and an increase in RR variability.[20] This reflects an autonomic imbalance in the form of a relative reduction in the activity of the parasympathetic part of the ANS. The confounding and effect modification of psychological and other factors in such conditions have not been clarified,

and generalizations about the effect of one physical environmental factor or the other should be avoided.

*VWF and excess hearing loss*

Evidence of autonomic involvement causing effects on other organ functions also comes from the results of studies of aggravated noise-induced hearing loss in vibration-exposed persons suffering from white fingers.[21–25] It has been postulated that hand-arm vibration causes changes in the autonomic nervous system which will affect audiological function, perhaps by increasing the susceptibility of the inner ear to noise. There are various possible mechanism by which this could occur. One proposition considers sympathetic hyperactivity causing ischemial damage to the hair cells due to abnormally strong vasoconstriction.[23]

*Stressor exposure and chronic reduction of toe skin temperature*

Epidemiological results obtained by Sakakibara and collaborators[26–28] have shown that the presence of VWF is correlated to an increase in the occurrence of coldness in the legs and lower skin temperature in the toes even without acute exposure to cold or vibration. This condition is ascribed to ANS dysfunction in the form of a generally elevated level of sympathetic activity due to prolonged influence of exposure to hand-arm vibration as well as other factors that can induce vasoconstriction in the extremities. It is also suggested that the ensuing repeated vasoconstriction in the foot may eventually lead to hypertrophy of smooth muscle and consequent arterial stenosis. A contribution to the pathology may also come from changes in endothelial vasoregulatory mechanisms. The theory described here is hypothesized to be a possible explanation for the observations of Raynaud's phenomenon in feet that have not been exposed to vibration.[29]

## DAMAGE TO VESSEL WALL VASOREGULATORY STRUCTURES AND FUNCTIONS

Recent extensions of our knowledge of endothelial vasoregulatory mechanisms have led to a natural focusing of interest on anatomical structures and functions in the endothelium of the vessel wall as plausible targets for harmful effects of hand-arm vibration. The damaging mechanism may be of a mechanical nature, but other factors in the working environment, such as cold, may contribute.

*Functional adrenergic receptor changes*

An intricate set of adrenergic vasoregulatory mechanisms operate in the finger skin. Important observations on these functions have been made in studies by Ekenvall and collaborators, where vasoactive substances were administrated to the finger skin by iontophoresis.[30] The findings suggested that Raynaud's phenomenon in persons damaged by vibration is caused by a selective damage to alpha-1 receptors, resulting in abnormally strong vasoconstrictory response to skin cooling resulting from a predominance of alpha-2 adrenoceptors. In other similar experiments,[31,32] it was concluded that vasoconstriction on local cooling in the human finger skin is mainly mediated by alpha-2 adrenoceptors and that substances inhibiting them may be of therapeutic value in patients with VWF.

*Endothelial damage*

Other damage to vessel wall mechanisms may also merit further research. Results of

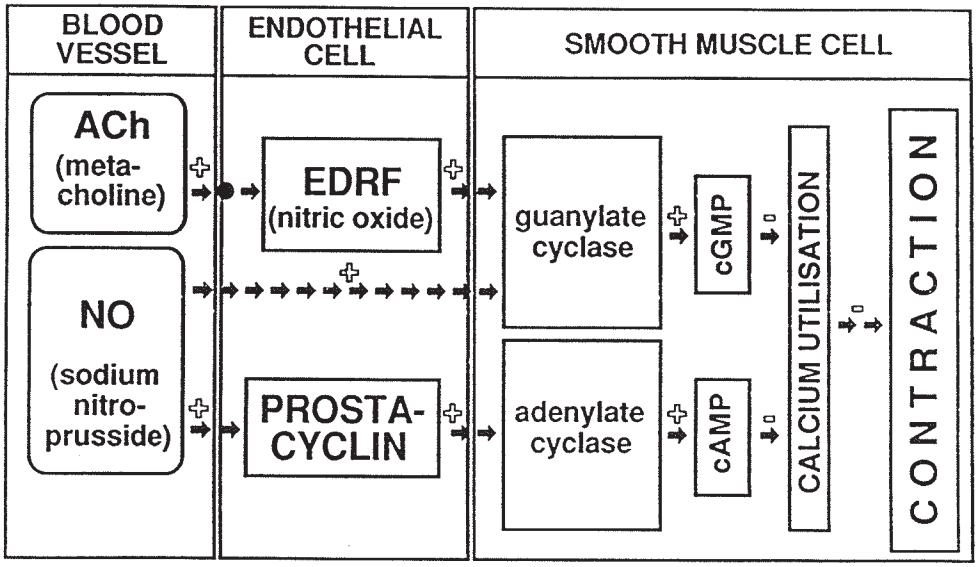


Fig. 1. Schematic representation of endothelial vasodilatory mechanisms.

experiments[33] with iontophoresis of sodium nitroprusside and metacholine into the finger skin of subjects with and without VWF and laser-Doppler recording of blood flow indicate that vibration exposure may cause functional damage to endothelial vasoregulatory mechanisms. The background of these experiments is that peripheral vasoregulation partly depends on the integrity of factors residing in the endothelium,[34] namely the two vasodilating mechanisms mediated by EDRF (endothelial-derived relaxing factor) and prostacyclin (prostaglandin $I_2$). Acetylcholine — as well as the metacholine of the experiment — stimulates the release of EDRF, which reduces the calcium available for smooth muscle contraction by increasing the activity of guanylate cyclase and cGMP (Fig. 1). A vasodilating effect is also mediated by nitric oxide (NO) — and the NO-releasing nitroprusside used in the experiment — along two paths: one directly on the muscle cell and one by stimulating prostacyclin.

Three groups were studied: chain-sawyers who had never experienced white finger (A; n=25); those with WF up till two years earlier (B; n=7), and those with current WF(C; n=7).

In their capacity of vasodilators, both MCh and NP elicited an increase in blood flow in the majority of subjects.

The most interesting finding was that the vasodilation in response to metacholine — but not to nitroprusside — was considerably weaker in the combined group B+C than in group A. This agrees with the physiological premises described above. It would also be consistent with the notion of an endothelial damage that causes a deficiency in vasodilation due to a disturbance of the EDRF, mediated vasodilatory function. As indicated in Fig. 1, metacholine induces relaxation only through EDRF, while NO also has direct access to the smooth muscle.

The relative blood flow increase at MCh iontophoresis was greater in group A than in group B, and the group C response to MCh was consistently smaller than that in group B. This gradient suggests that other vasodilatory mechanisms may have compensated for the loss of vasodilation suffered by a deficiency in endothelial smooth-muscle relaxation.

## OTHER PERIPHERAL CHANGES RELATED TO VASOREGULATORY PROCESSES

The complexity of finger skin vasoregulation by means of receptor mechanisms operating in the vessel walls is also compounded by other possible factors of importance.

There is, for instance, the suggestion of a pathoanatomical mechanism that only secondarily requires a strong sympathetic activity, namely a reduction in the width of the skin blood vessels in VWF subjects because of either hypertrophy of the vessel wall smooth muscle layer and/or intimal thickening,[35–40] If such changes occur, a proportionately stronger reduction of blood flow would be the result of normal or only slightly elevated sympathetic activity. A study by Hashiguchi et al.[41] showing hypertrophy of finger vessel walls in VWF subjects lends some support to such a mechanism, although in these experiments the presence of the anatomical changes was not well correlated with the occurrence of white fingers.

That trauma to the skin by vibration can result in local organic changes has also been suggested[42] because of the observation that there was a slower rewarming rate in vibration-exposed persons after finger cooling, even when dilation was enforced with oral administration of alcohol.

Persistent lumen reduction from organic or functional causes may result in diminished capacity to dilate the vessel in a warm environment, which would be manifested as a vasodilatory deficiency in response to hand vibration, as shown in VWF subjects by Nakamura et al.[43] This kind of pathophysiology would also be consistent with results obtained in finger blood flow recordings in a climate chamber.[44] In the stage of maximal vasodilation (room temperature 45°C and anesthesia of the digital sympathetic nerves), the arterial blood inflow to the finger after arterial occlusion with a cuff was considerably lower in the VWF subjects than in persons without Raynaud's phenomenon.

A significant elevation in whole blood viscosity (but not in plasma viscosity) has been observed in vibration-exposed subjects with VWF as compared with those without,[45] as well as in vibration-exposed rats.[46] A reduced vessel diameter drastically increases blood viscosity, but other factors related to vessel diameter and viscosity (for instance turbulence) also strongly influence blood flow.[47] It is a cautious contention that increased blood viscosity may be an important contributing factor for producing the vasospasm in VWF but it may occur only when there is endothelial damage with consequent platelet aggregation.

*Influence of cold on the development of white fingers*

An obvious clue to the pathogenesis of white fingers should be looked for in the fact that Raynaud's phenomenon is typically elicited by environmental cold by way of local as well as central sympathetic mechanisms, especially when the whole body is cooled. This, of course, does not necessarily make cold pathogenic, but it is at least highly possible that cold exposure contributes to the development of VWF. The possibility that there is an enhanced response of the vasomotor receptors (or effectors) to a cold stimulus is pathogenically important but unclarified, largely because of the complexity of peripheral vasoregulation. Manifest white fingers have not been reported from countries with a warm climate. In an epidemiological study of the occurrence of vibration-induced disorders in a tropical rain forest,[48] no clear evidence of an excessive occurrence of white finger cases was obtained. Not even cold provocation with hand immersion in water at 10°C for 10 min could elicit Raynaud's phenomenon of the kind that is typical in VWF. The implications of this is not clear: is it necessary, for VWF to develop, that the environment is cold, or is it habitual vasoconstriction in a cold climate that paves the way for WF in long-term vibration-exposed persons?

Although no evidence has been produced for the pathogenic importance of cold in man, some indication comes from animal experimentation. Endrich[49] reported on extensive endothelial damage, as seen by electron microscopy, in capillaries and venules (but not in arterioles) of a dorsal skin fold in hamsters exposed to non-freezing cold for five consecutive days.

Studies have been made of substances that, in an oversimplified way, may be considered as indicators of autonomic activity connected with cold-induced finger skin vasoconstriction, but the results are inconclusive. This is not surprising, since there are many inherent difficulties in experiments of this kind. Harada et al.[50] investigated vibration-exposed men with and without WF and found that cold exposure of the whole body caused a relatively greater rise in blood cAMP and cGMP than in healthy controls. In view of the above-mentioned mechanisms — by which an increase in these substances cause a decrease in smooth muscle contraction — the significance of this interesting finding, however, needs further clarification.

It should also be borne in mind that the complexity of peripheral vascular response to cold is astounding.[51] In addition to the adrenergic, cholinergic and purinergic receptor systems, serotonergic mechanisms have been shown to interact with other systems,[52,53] and there are several subtypes of specific receptors.[54,55] Endothelium-dependent substances such as NO, EDRF, and prostacyclin — as well as endothelin, a potent vasoconstrictor — relate to many of the other systems. Cold, like vessel wall injury, causes platelet aggregation and skin vasoconstriction as a net effect of the liberation of various vasoactive substances.[56] Intimal damage may become a site for platelet aggregation — further enhanced by both local cooling and warming — and consequent release of vasoconstrictor substances such as thromboxane, serotonin, and thrombin.[53]

In experimentation on humans it is difficult to control the several mechanisms operating simultaneously in response to cold stimulation of the skin. This, if not other circumstances, should indicate to researchers that no single theory is likely to offer the sole explanation to the vasoregulatory events in VWF, no more than in Raynaud's disease.[57]

*Confounding factors and effect modifiers*

It is a fact that many persons habitually experience cold and, consequently, diffuse pallor in their fingers and toes together with lower than normal skin temperature. Persons with such a disposition (which may be termed "constitutional Raynaud") are likely to be included in any occupational group exposed to hand-arm vibration. This consequent confounding may very well influence the outcome of epidemiological studies, and may be present together with the uncontrolled affect of stressors in experimental studies as well.

The pathogenic importance for the development of VWF of such a constitutional disposition has not been epidemiologically clarified. It is physiologically reasonable that persons with this trait are more susceptible to harmful influence from various vasoconstrictory stimuli, as the general sympathetic level of activity is likely to be elevated in these subjects.

Insufficient control in epidemiological studies of factors related to the individual explains the very wide variation in VWF prevalence observed in many occupational groups. Interindividual differences in susceptibility to environmental factors is the best example. The role of smoking in VWF subjects is another. Nicotine, like cold, has a constrictory effect on blood vessels. The peripheral blood flow of heavy smokers therefore tends to be smaller than that of non-smokers, which results in lower skin temperatures in their fingers and toes in a cool environment. Investigations of vibration-exposed subjects, who are also smokers, have found that these have a higher white finger prevalence than non-smokers, while other studies have failed to do so. Observations of this kind in cross-sectional studies do not justify the conclusion that nicotine took part in the development of the disorder, only that it may enhance the present symptoms. As a matter of fact, no epidemiologic investigations have so far been able to demonstrate that heavy smoking

habits in the past have been more pronounced in VWF patients.

Several studies demonstrate a correlation between the occurrence or severity of white fingers and age. They have, however, failed to separate, in a statistically unequivocal way, this confounder from exposure duration and from individual effect modifiers, and results from longitudinal investigations that could settle this question have not been reported.

## A MODEL FOR THE PATHOPHYSIOLOGY OF VWF

Multifactorial etiology and pathogenesis of acquired vasospasm in the finger skin of persons using hand-held vibrating tools has been discussed[37] on the basis of physiological considerations. It was proposed that the level of sympathetic activity may rise during a prolonged exposure to environmental stressors with a vasoconstrictive effect. This proposition may now be expanded to regard both the development of true white fingers and conditions without Raynaud's phenomenon but with an abnormally strong vasoconstriction in toes as well as in fingers.

Incorporating current knowledge of local pathophysiological mechanisms, as discussed above, the pathogenic scenario might be suggested to be as follows (Fig. 2).

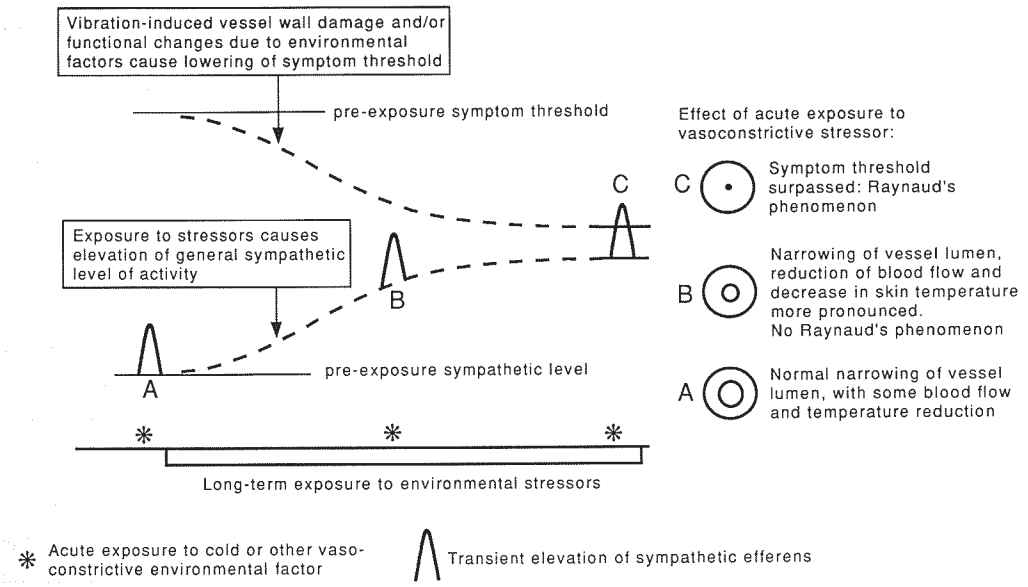


Fig. 2. A model for the occurrence of abnormally strong vasoconstriction and Raynaud's phenomenon in workers using hand-held vibrating tools.

I. In a normal individual without habitual exposure to environmental (and generally vasoconstrictive) stressors, acute cold stimulation causes a transient rise of the sympathetic efferens to the skin vessels, but the symptom threshold (with respect to Raynaud's phenomenon) is not surpassed (A).

II. In workers using hand-held vibrating tools an *elevation of the general level of sympathetic activity* may take place due to influence from physical and psychological stressors which cause repeated acute rises in sympathetic efferens. The relative role of vibration and other stressors

has not been quantified.

III. During this prolonged exposure to environmental stressors, *the symptom threshold is lowered.* This may be due to either or both of the following processes:

(1) mechanical vibration-induced damage causing endothelial injury or changes in receptor functions

(2) changes in blood flow caused by other environmental factors or by processes secondary to endothelial damage (for instance, platelet aggregation and increased viscosity).

In this period, a similar cold stimulation (B) leads to a more pronounced vasoconstriction (interpreted as a sign of "cold hypersensitivity"). Persons with constitutional Raynaud also behave in this way, since their level of sympathetic activity is more or less chronically raised and/or their threshold, for some reason, is lowered.

IV. A combination of the two trends (sympathetic elevation and threshold lowering) eventually causes the normal cold-induced raise in sympathetic efferens (C), now starting from a higher platform, to surpass the lowered symptom threshold, and Raynaud's phenomenon occurs.

The potential effect of elevated sympathetic activity level is the same as that of a lowering of the symptom threshold: as soon as the gap between the two curves becomes sufficiently narrow, Raynaud's phenomenon may appear in response to cold stimulation. The model presented here does not distinguish between these alternatives, which may also operate in conjunction. Both alternatives have been demonstrated, but neither has been ruled out.

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