SUMMARY. The pathogenetic theories and treatment of Raynaud's phenomenon are reviewed. In primary Raynaud's disease, most evidence supports a local defect at the digital artery level, with vasoconstriction or vasospasm of the digital arteries inducing the color changes. Normal sympathetic activity, low transmural arterial distending forces, and serotonin may be associated factors in the production of vasospastic attacks. In Raynaud's phenomenon, persistent vasoconstriction, thickened vessel walls, increased blood viscosity, and low digital artery blood pressure distal to obstructions may lead to vasospastic attacks with normal sympathetic nerve stimuli. Since the underlying cause of primary Raynaud's disease is unknown, treatment involves the use of agents to reduce sympathetic nerve activity or to prevent vascular smooth muscle contraction. Most patients will respond to conservative measures, but if they fail nifedipine is the drug of choice and alleviates the syndrome in about two thirds of patients. Reserpine and guanethidine may be as effective, but well-controlled studies have not been performed. The beneficial response to prazosin is moderate and dissipates with time. Side effects with these drugs prevent their use in many patients. Diltiazem and nitroglycerin ointments are of questionable value. Ketanserin, a serotonin S2-receptor antagonist, which has been shown to decrease the frequency of vasospastic attacks, and parenteral prostacyclin are among the new promising therapies.

KEY WORDS. Raynaud's phenomenon, vasospasm, alpha2 adrenoceptor, serotonin, ketanserin, nifedipine

The diagnostic sign of Raynaud's phenomenon is a demarcated blanching or cyanosis of one or more digits on exposure to cold and sometimes emotional stimuli. The blanching is evidently due to vasospasm or closure of the digital arteries. The cyanosis occurs due to a very slow blood flow caused by vasoconstricted arteries, which allows desaturation of the oxyhemoglobin. One or both color changes may occur during the vasospastic attacks. The thumbs are often spared; one reason may be that their blood supply arises directly from a branch of the radial artery. Following the vasospastic attack, the vessels open widely to compensate for the period of ischemia, and the digits often become red with the reactive hyperemia. Despite many years of investigation, the cause of the digital artery vasospasm remains unknown. The digital circulation is very reactive in the control of body and digital temperature via the sympathetic nervous system and primarily the alpha2 adrenoceptors [1]. As will be discussed, the fault in iodiopathic or primary Raynaud's disease may be at this level. Raynaud's phenomenon occurs only in cutaneous areas containing arteriovenous anastomoses, but a defect in the reactivity of these structures has not been demonstrated [2]. Since the underlying cause of the disease is unknown, treatment is nonspecific. Agents that interfere with sympathetic or serotonin vasoconstriction by blocking the appropriate receptors, or drugs that interfere with calcium-dependent vascular smooth muscle contraction, have been used with some success.

Pathogenesis

Although the mechanism of vasospasm can be surmised in many of the secondary forms of Raynaud's phenomenon, the basic abnormality in primary (idiopathic) Raynaud's disease remains unknown. Most evidence favors the existence of a pathophysiologic fault at the level of the digital arteries. Support for this theory is derived from Lewis' experiments demonstrating that vasospastic attacks could be induced in fingers with acute sympathetic nerve blockade. Halpern and coworkers [3] were also able to produce attacks in limbs during sympathetic ganglionic blockade. Lewis' demonstration in 1929 that attacks could be induced by proximal cooling of the finger with the distal finger warm, and that the disappearance of attacks occurred only when the finger was warmed proximally and not distally [4], implicates an abnormality at the digital artery and not at the arteriolar
level. Some evidence points to the defect being in the alpha adrenoceptors. Keenan and Porter [5] found an increase in the alpha2 adrenoceptors of platelets in patients with primary Raynaud’s disease compared with control subjects and patients with secondary Raynaud’s phenomenon. The same group also reported increased binding capacity and affinity of alpha2 adrenoceptors of platelets only in patients with the primary disease [6]. Since the alpha2 adrenoceptors are most important in the digital vasoconstriction elicited by reflex sympathetic stimulation [1], the local fault theory with an alpha2 adrenoceptor abnormality appears quite logical but not proven.

The fact that vasospastic attacks cannot be reliably reproduced in most patients with primary Raynaud’s disease by local cold indicates that other mechanisms may be involved. Overactivity of the sympathetic nervous system has been extensively investigated. Arguments for an increased activity of the sympathetic nerves include normal hand or finger blood flows in patients during warming [7] or after alpha adrenoceptor blockade [2], exaggerated vasoconstrictor response to postural changes [8], and induction of attacks by emotional upsets. The strongest evidence against this theory is the failure of Fagius and Blumberg [9] to find a hypersensitivity of the digital blood vessels to sympathetic bursts of activity or an increase in sympathetic outflow by microelectrode recordings of skin sympathetic nerve activity in patients with primary Raynaud’s disease. Also, Downey and Frewin [10] did not measure an increased reflex sympathetic vasoconstriction by local cooling of one hand while measuring blood flows in the opposite hand or an increased sensitivity to cold in the cooled hands of patients compared with normal subjects. Catecholamine levels have been reported as normal in these patients in the most recent studies [11, 12]. However, normal sympathetic vasoconstrictor activity may be a concomitant factor in producing vasospastic attacks.

Patients often complain that their vasospastic attacks are induced by cold plus pressure. Attacks occur grasping a steering wheel on cold mornings, holding cold drinks, or shoveling snow. Cohen and Coffman [13] found that patients with primary Raynaud’s disease had decreased brachial artery, finger systolic, and fingertip perfusion pressures compared with normal subjects. Digital nerve blockade induced an increase in finger perfusion pressure and blood flow in both normal subjects and patients, suggesting a similar amount of sympathetic-nerve-mediated vasoconstriction of small fingertip resistance vessels. A low finger blood pressure would be accompanied by a similarly low transmural arterial distending force, and therefore external pressure could be a precipitating factor in inducing vasospastic attacks. Furthermore, since digital systolic pressure has been shown to decrease at cool temperatures in patients with primary Raynaud’s disease [14], external pressure could be a major factor in the closure of digital arteries.

Serotonin or 5-hydroxytryptamine (5HT) has been implicated in vasoconstriction or vasospasm in some vascular beds. We have been able to show that intraarterial 5HT causes a dose-related decrease in finger blood flow that is blocked by the 5HT2 receptor antagonist, ketanserin [15]. During reflex sympathetic vasoconstriction induced by body cooling, ketanserin significantly increases finger blood flow. Ketanserin was shown to have no effect on the digital vasoconstriction caused by intraarterial phenylephrine, clonidine, or angiotensin, indicating the specificity of the response and that alpha2 and alpha1 adrenoceptors were not involved. Therefore, vasoconstriction of the finger caused by body cooling may be partially mediated by a serotonergic mechanism. Halpern and coworkers [3] found that methysergide, a serotonin inhibitor, reduced the intensity and duration of the response of their patients with primary Raynaud’s disease to immersion of the hands in cold water, although blanching still occurred. In several small clinical studies, ketanserin has been reported to benefit or to have no effect in patients with Raynaud’s phenomenon, although in the largest study the frequency of vasospastic attacks was significantly reduced [16]. The problem with implicating serotonin as a primary mechanism of the idiopathic disease is that intraarterial infusions of 5HT produce a reddish hand without blanching [15] and acute administration of ketanserin does not prevent cold-induced vasoconstriction, although it alleviates vasoconstriction once it occurs [17]. Therefore, serotonin from platelets or serotonergic nerves may be an associated factor but not the main determinant of vasospastic attacks in the primary disease.

Blood viscosity has been studied extensively as a cause of vasospastic attacks. The studies are conflicting and, at present, blood or plasma viscosity abnormalities cannot be considered of importance in primary Raynaud’s disease [18]. Similarly, platelet factors, thromboxane A2, beta thromboglobulin, factor 4, and metabolites of vasodilatory prostaglandins have been measured in patients and variable results reported. Treatment studies with platelet, prostaglandin, and thromboxane A2 inhibitors such as acetylsalicylic acid, dipyriramole [19], dazoxiben [20], and indomethacin [21] have shown no beneficial effect.