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Raynaud's Disease: Neurogenic or Local Fault?

A Critical Review of the Evidence

by

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Summary

This review of Raynaud's disease, which examines the clinical and experimental literature of the last century, focuses on the physio-anatomical mechanisms that underlie the etiology of the disorder. A second purpose of this paper is to advocate the adoption of terminology and diagnostic criteria that are logically derived from a pathophysiological understanding of the disease etiology.

The name of Maurice Raynaud has been loosely and broadly applied to a variety of pathological conditions of the peripheral vasculature and such indiscriminate usage has produced a conflicting and almost uninterpretable literature for the unwary reader. This review distinguishes two nosological entities which, while presenting some overlap in symptoms, reflect quite different etiologies and prospects for treatment. The term Raynaud's disease, as historically conceptualized, describes a primary vasospastic disorder that is functional in nature and which is probably due to an aberration in nervous control of the peripheral vasculature. The term Raynaud's phenomenon, or as the author prefers, the term secondary digital ischemia, refers to episodes

of peripheral circulatory insufficiency clearly secondary to an identifiable organic disease.

While the etiology of secondary digital ischemia is readily evident from identification of the underlying organic pathology, two opposing theories have been advanced to explain Raynaud's disease. The neurogenic theory, originally introduced by Raynaud himself, posits a hyperactive sympathetic control of the peripheral circulation as the necessary and sufficient condition for the manifestation of clinical symptoms. An alternate hypothesis, proposed by Lewis, postulates that Raynaud's disease results from a vaguely defined "local fault", thus implying that the peripheral vessels are themselves pathologically involved in some unspecified way that is independent of the nervous regulation.

Lewis's forceful argumentation has led to uncritical acceptance of his reasoning and conclusions by a growing number of investigators. The local fault theory has gained preeminence and widespread support which, however, appear unjustified when the evidence is carefully examined. Lewis has never provided an adequate definition of the local fault, and, in spite of the interest that his concept has generated over the last 45 years, the precise nature of this local abnormality is yet to be identified. All possible local mechanisms,

which might be considered as the physiological counterpart of Lewis's local fault, are reviewed in this paper. None of them appears as a likely candidate since the contribution of these local factors to the control of the peripheral circulation is either negligible or ultimately subordinate to a powerful neurogenic regulation.

The evidence that is generally regarded as conclusively supportive of the local fault hypothesis is based on the impressive collection of clinical observations and experimental data gathered by Lewis on a number of patients with "Raynaud's disease". Lewis's reasoning, however, is vitiated by a fundamental diagnostic ambiguity which must be recognized at the basis of his faulty case selection, and which is so pervasive as to be by itself sufficient to invalidate his conclusions. In fact Lewis's patients were not examples of Raynaud's disease, but rather cases of digital ischemia secondary to a variety of organic vascular diseases.

A second source of evidence claimed by Lewis in favor of the local fault notion comes from his studies of the peripheral vascular reactions following local cooling and heating, ulnar nerve anesthesia, and sympathectomy. These experiments are carefully examined.

Erroneous assumptions, faulty methodology, and unwarranted conclusions vitiate Lewis's arguments, none of which stands the test of a careful scrutiny. Indeed many of his findings clearly favor the neurogenic theory against the local fault hypothesis.

In contrast, the neurogenic theory is found to be consistent with the physiological and clinical data reviewed in this paper. From the physiological evidence surveyed it is concluded that the peripheral blood vessels are chiefly under nervous control, and that only a breakdown of this precise neural coordination of vascular activity can plausibly account for the symptoms observed in Raynaud's disease.

The experimental and clinical validation of the neurogenic theory rests on numerous unequivocal findings, all of which converge in supporting the notion that the vascular symptoms in Raynaud's disease are the result of an overactive sympathetic innervation. Among the most convincing arguments are the occurrence of vasospastic phenomena in normal individuals, the prominent influence exerted by emotional stimuli on the peripheral circulation, the existence of individual differences in autonomic reactivity, the frequently encountered association of vasospasm with other indicators of sympathetic hypertonus, the conspicuous effects of

neurohumoral agents on the peripheral circulation, and the reported effectiveness of antiadrenergic pharmacological intervention in the management of Raynaud's disease.

It is concluded that the local fault theory of Raynaud's disease should be abandoned in favor of the neurogenic hypothesis.

Finally some important diagnostic issues are considered. As a necessary condition for the diagnosis of Raynaud's disease it is suggested that even very limited nutritional lesions be absent. A revision of the almost universally adopted Allen and Brown's diagnostic criteria is proposed.

Some Reflections Relevant to Biofeedback Research

The resurgence of interest in the study of psychosomatic diseases may be in large part attributed to the introduction of biofeedback as a strategy for investigating the ability to acquire control over autonomic functions in general and over symptomatic manifestations in particular.

Clinical biofeedback research has addressed its efforts to several empirical questions. These include the efficacy of autonomic conditioning in reducing symptoms and the contribution toward symptom relief of factors extraneous to operant control of the autonomic nervous system, such as cognitive mediation, placebo and skeletal muscle effects. However, investigators have expressed little interest in the pathophysiological mechanisms underlying the etiology of the disease under study.

This may be partly explained by the derivation of biofeedback from the operant conditioning tradition. The Skinnerian approach typically, and purposedly, ignores the physiological basis of behavior. While this attitude is justifiable when the response of interest is a bar-press or a key-peck, it is instead incompatible

with the study of visceral events especially in a clinical setting.

The therapeutic use of biofeedback procedures, as it is true for any other treatment modality, requires a committment to proper diagnosis which cannot be met without an adequate understanding of the etiology and physiological basis of the pathological process to be modified. Such knowledge should certainly lead to the more intelligent research designs necessary to clarify issues and advance the field. Moreover, the absence of such understanding has produced and will continue to generate research that is misleading and often counterproductive. Of what contribution is a study that unsuccessfully applies biofeedback techniques to relieve symptoms of hypertensive patients when it is unknown to the investigator that in part of the sample the elevated blood pressure is secondary to a faulty electrolyte regulation? Of what value are negative findings in the study of Raynaud's patients if the "cold hands" of most of the clinical cases are secondary to an unrecognized organic vascular disease?

This paper, which reviews the etiology of Raynaud's disease by examining a prodigious literature spanning over 100 years of investigations, will hopefully lay the groundwork for thoughtful researcn on the treatment of this fairly common psychosomatic disorder.

RAYNAUD'S DISEASE

Historical Background

Raynaud's Original Thesis

In 1862 Maurice Raynaud published his doctoral thesis entitled De l'Asphyxie Locale et de la Gangrène Symétrique des Extrémitiés. The primary objective of his work was clearly defined:

> I propose to demonstrate that there exists a variety of dry gangrene affecting the extremities which it is impossible to explain by a vascular obliteration--a variety characterised especially by a remarkable tendency to symmetry, so that it always affects similar parts, the two upper or lower limbs, or the four at the same time; further, in certain cases, the nose and the ears; and I hope to prove that this kind of gangreme has its cause in a vice of innervation of the capillary vessels which it remains for me to define. (pp. 7-8)

The review of 20 cases previously reported in the medical literature, and the study of 5 additional cases observed during his own clinical work allowed Raynaud to conclude that he was describing a new nosological entity affecting primarily the extremities, and presenting "local syncope," "local asphyxia," and "symmetrical gangrene" as three evolutive forms or stages of the same underlying pathological process.

Local syncope is the mildest form and is characterized by attacks of "dead fingers" precipitated by cold or by emotional upset. One or more fingers become suddenly blanched, cold, and anesthetic. The cutaneous sensitivity is markedly reduced and no bleeding is observed when the affected finger is pricked, indicating a temporary but complete interruption of blood flow to the part. The white-dead color characteristically spreads from the tip to the base of the finger. No pain is usually experienced during this phase which is of variable duration, and which is often followed by the asphyctic stage.

During the phase of local asphyxia a livid cyanotic color substitutes the pallor previously described and, starting at the tip of the finger, extends more proximally. Pain may be present, swelling of the fingers is sometimes observed, and the persisting numbness may seriously interfere with the normal use of the digits. Termination of this phase is often characterized by the gradual spread of bright red patches which slowly advance from the base to the tip of the fingers, and it is typically accompanied by a "pins and needles" sensation, burning, and tingling. Finally the digits warm up and the normal pink color returns to the skin.

In the more severe cases, according to Raynaud, the phase of symmetrical gangrene is observed. The

ever increasing frequency and duration of the ischemic crises result in thickening and hardening of the skin, and very small ulcerations may develop at the fingertips. These limited necrotic areas are extremely painful and heal very slowly, leaving small depressed scars, "which are, so to speak, the stigmata left after the malady" (p. 103). Impairment of the local nutrition affects also the state of the nails which stop growing, become deformed, thin and fragile, and may fall off altogether. Periods of remission and cicatrization alternate with the recurrence of ulcerations. The necrotic area may rapidly get larger and a dry superficial gangrene may spread to a good portion of the finger. The loss of tissue results in shortening and narrowing of the digit, and, at times, in the spontaneous or induced amputation of the whole terminal phalanx.

All the distinctive elements which today are attributed to this malady, such as its predilection for young females, the characteristic color changes in the fingers, the importance of psychological, constitutional, and hereditary factors, were clearly spelled out in Raynaud's account. His outstanding and most original contribution, however, has been to individuate a vascular disorder essentially functional in nature, as it occurs in the absence of organic arterial occlusion, and which is determined by spastic closure of the small

peripheral vessels consequent to "a fault of vasomotor innervation" (Raynaud, 1874, p. 154). These conceptually unequivocal definitional criteria constitute the essence of Raynaud's work, although the French physician often failed to rigorously adhere to them in his case selection as well as by placing undue emphasis on the process of symmetrical gangrene.

The Origin of a Historical Confusion

The inclusion of symmetrical gangrene as an integral component of the disorder Raynaud was describing generated a tremendous confusion in the literature which persists to this day. Raynaud attempted to clarify the issue when, in a second essay published in 1874 with the title Nouvelles Recherches sur la Nature et le Traitement de l'Asphyxie Locale des Extrémitiés, he wrote:

> Perhaps I may now be allowed to criticise the name which I gave to this disease. I have found many defects in it. First, there is always a real inconvenience in giving two distinct names to one and the same object. Local asphyxia and symmetrical gangrene are not two distinct maladies, but two degrees of one and the same malady. Of these two degrees, the second is often absent, which prevents our being able to adopt it as the basis of a precise nomenclature. (p. 153)

Neither Raynaud's explicitly stated position, nor the removal of the term symmetrical gangrene from the title of his second essay were able to prevent a massive flow into the literature of reports which, under the

name of "Raynaud's disease," described cases which did not present the characteristic signs specified by Raynaud, but comprised instead a variety of circulatory disorders where the vasomotor phenomena were often associated with organic vascular diseases.

As early as 1901 Hutchinson deplored that "many of the cases which have been quoted as examples of Raynaud's disease are, however, complicated or even primarily induced by organic disease of the skin (scleroderma), the blood vessels or the heart" (quoted by Allen, Barker, & Hines, 1962, p. 126). Hutchinson realized that what Raynaud had described was not an autonomous nosological entity, that is a disease, but rather a symptom complex present in many different conditions. He therefore suggested that "it would be well indeed if we could cease to use the term Raynaud's disease and speak rather of Raynaud's phenomenon" (quoted by Allen et al., 1962, p. 126).

But the matter was far from being settled and the chaotic state of affairs, which still pervaded the literature, is probably best exemplified in the position taken by Monahan (1926), who advocated the "further extension of the term Raynaud's disease to include all gangrenes, moist or dry, symmetrical or asymmetrical, deep or superficial, which gave evidence of being due to defective vasomotor influence" (p. 347).

Following Hutchinson's suggestion, Lewis and Pickering (1934) preferred to abandon the term Raynaud's disease and to maintain the designation Raynaud's phenomenon to indicate a clinical manifestation associated with numerous unrelated conditions. It will be shown later in this paper, however, that even Sir Thomas Lewis's classic work, which remains a necessary point of reference for anyone interested in the vasospastic disorders, was basically vitiated by a pervasive and ubiquitous diagnostic and terminological confusion, well reflected in the description of his clinical cases.

Allen and Brown (1932a) should be credited with the first systematic, and partly successful, attempt to bring some order to this situation. They critically reviewed all 31 cases described by Raynaud in his two essays, and concluded that only 5 of them could be accepted as fulfilling the requirements that Raynaud himself had spelled out. They also surveyed 25 randomly selected cases of "Raynaud's disease" reported in the German, English, and American literature, and determined that none of them satisfied Raynaud's criteria. In all these cases the vasomotor phenomena were secondary to a great variety of diseases. On the other hand, the direct study of 150 additional cases convinced Allen and Brown that the vasospastic symptoms can occur in a primary form, that is in the absence of any underlying

organic disorder, and they proposed that to this condition only should the term Raynaud's disease be applied. Allen and Brown also provided stringent criteria, very similar to the ones Raynaud laid down, which could assist in making the diagnosis of Raynaud's disease.

Hunt (1936) accepted the distinction between Raynaud's disease and Raynaud's phenomenon and recommended that the use of the term Raynaud's disease be carefully restricted "to one, and one only, of the ten or more conditions in which Raynaud's phenomenon occurs" (p. 402). In his review paper Hunt came to the conclusion that only one of Raynaud's 31 patients, and only 30 of 500 cases reported in the English and American literature, were true examples of Raynaud's disease. "No small wonder," he noted, "that a student has such difficulty in understanding what is meant by the term, and why some physicians wish to abolish it altogether!" (p. 400).

To fully recognize the merit of the present paper Hunt's observation should be kept in mind, especially since his comment seems to apply more to today's than to the 1936 student. As a matter of fact, in the subsequent 40 years, hundreds of articles have been published which have added even more to the existing confusion. While there is almost universal agreement today about the existence and nosological autonomy of a primary vasospastic condition, distinguishable from a collection

of vasomotor symptoms secondary to a number of well-known disorders, consistent use of terminology is still an unfulfilled ideal.

Although most investigators preface their papers with a clear statement regarding their use of terminology, the remarkable lack of consensus among authors is not as disturbing as the obvious inconsistencies found within the same paper, where frequently the writer "forgets" the terminological rules he had spelled out in the previous page. Moreover, to the old terms Raynaud's disease and Raynaud's phenomenon new ones have been added, such as "Raynaud's syndrome," "Raynaud's attack," Raynaud's spasm," "digital ischemia," and others, all of which are often used interchangeably, so that the unwilling reader is burdened with the onerous task of deciphering a cryptogram.

The obvious conclusion to be derived from the foregoing analysis is that a rigid control over terminological usage is very much needed if communication within the field is to be improved and ambiguity minimized. It is generally recognized that few other clinical entities have been the object of greater controversy than the one Raynaud described more than a century ago. The necessity of eliminating terminological confusion, then, appears ever more urgent when one considers the lack of agreement already existing regarding such

fundamental issues as diagnosis, etiology, and treatment.

Proposed Definition and Terminology

In the present paper the term Raynaud's disease will be used to indicate a primary peripheral vascular disorder characterized by intermittent episodes of spasmodic constriction in the small arteries and arterioles of the extremities, resulting in a transient marked reduction, or complete cessation, of blood flow to the part. This abnormal reaction is usually precipitated by exposure to cold or emotional stress, and it manifests itself in characteristic color changes of the skin of the extremities. These symptoms occur bilaterally and, as a rule, symmetrically. The disease shows a distinct preference for females in their second or third decade of life.

On the other hand the term "secondary digital ischemia" will denote all those vasospastic manifestations, clinically similar to those occurring in Raynaud's disease, but which are secondary to a variety of conditions usually having a recognizable organic etiology.

ANATOMY AND PHYSIOLOGY OF THE PERIPHERAL CIRCULATION

Since the pathological mechanism in Raynaud's disease is identified as an abnormal constriction of the peripheral blood vessels, and since the controversy regarding the etiology of this condition reflects a basic disagreement about the nature of the physio-anatomical derangement responsible for the spasmodic vascular contraction, the anatomical basis and physiological control of the peripheral circulation must be considered first.

Anatomical Overview

An exhaustive anatomical account of the peripheral circulation is obviously beyond the scope of this paper and the interested reader is referred to the work of Barker (1966, chap. 2) and Kvale (1946), or to a standard textbook of anatomy. Here only a few selected aspects, relevant to the subject of the present essay, will be reviewed.

It is customary to divide the vascular structures carrying blood to the periphery and returning it to the heart into: arteries, arterioles, capillaries, venules, and veins. These vessels are differentiated not only with regard to their size or caliber, but also in terms of their function: distribution of blood by the arteries, resistance and regulation of flow by the arterioles, nutrition of tissues by the capillaries,

collection and storage of blood by venules and veins. Admittedly this is an oversimplification as, in reality, differences among vessels are not so clear-cut and the transition from one type to the next is much more gradual than implied above. Nevertheless the distinction is useful from a descriptive point of view, and it is certainly consistent with the marked structural differences found among vascular units.

Except for the capillaries, the wall of all blood vessels is composed of three distinct layers: an innermost lining of endothelial cells, the intima; a middle layer of muscular and elastic tissue, the media; and an external sheath of connective tissue, the adventitia. The thickness of the wall and the proportion of a given tissue relative to the others are determined, to a great extent, by the size and function of the vessel. The media of major arteries contains very few smooth muscle fibers but has a large amount of elastic tissue, which gives these vessels considerable resilience and capacity to absorb and propagate changes in pressure associated with the systolic and diastolic phases of the cardiac cycle. As these large arteries branch out into smaller ones the ratio of muscular to elastic tissue gradually increases to reach a maximum in the arterioles, whose thick media contains almost exclusively muscle fibers and very little elastic tissue,

while the external adventitia is much reduced in size. This heavy muscular coat in the arteriolar wall has a rich sympathetic innervation and it allows active control of the vessel's caliber. Muscular contraction leads to reduction of the luminal space, that is to vasoconstriction, while relaxation of the smooth muscle results in expansion of the lumen, i.e., vasodilation. This ability of the arterioles to impede or facilitate blood flow plays a major role in the control of the peripheral circulation and in regulating perfusion of tissues according to their needs.

The capillaries are smaller branches of the arteriolar distribution, averaging about 8 microns in diameter. These microscopic structures, connecting the arterial to the venous system, have a thin wall composed of a single endothelial layer. Although various types of capillaries, differing in size, function, and structure, have been described (De Langen, 1961), here it will suffice to say that, in general, these vessels lack contractile muscular elements and serve the vital function of supplying the tissue with nutrients and oxygen while removing its metabolic products.

The three distinct layers described above are found again in the thin wall of the venules which have a variable amount of muscular tissue. They collect the blood from the capillary network and drain it into the

veins which then return it to the heart. Compared to arteries, veins have usually a larger lumen and a much thinner wall. As the veins get larger and larger the amount of smooth muscle fibers decreases, while the proportion of elastic and connective tissue progressively increases. Veins of medium and large size are provided with valves which efficiently preclude retrograde flow of blood.

In addition to the vessels described so far, the arterio-venous anastomoses should also be mentioned, especially since they are primarily found in the skin of the extremities. These structures connect the arterioles directly to the venules, bypassing the nutritive capillary network. Their thick muscular coat, abundantly supplied with sympathetic fibers, allows them to dilate widely or to constrict completely. The arteriovenous anastomoses are particularly numerous in the palms of the hands, in the soles of the feet, and in the region of the nail bed. When fully dilated they can greatly increase the cutaneous circulation by shunting an extraordinary amount of blood to the acral areas; conversely their constriction results in a considerable reduction of blood flowing to those areas.

Physiology of the Peripheral Circulation

Thermoregulation

The skin of the extremities is subject to larger circulatory fluctuations than any other area of the body. This is particularly true for the skin of the digits, where the arterio-venous anastomoses are most abundant, and where, according to Wilkins, Doupe, and Newman (1938), blood flow can be increased from .2 ml to 120 ml/min./100 ml of tissue; a six-hundredfold change. This remarkable range of flow rate through the skin of the extremities cannot be explained in terms of nutritional or metabolic requirements, but rather plays a prominent role in the thermoregulatory process.

In spite of large variations in environmental temperature, the core temperature of the body is maintained essentially constant by precise homeostatic mechanisms of heat conservation and heat dissipation. Of all other parts of the body the extremities, and especially the digits, are best suited for this vital thermoregulatory function. Constituting about 65% of the total body surface, the limbs provide a large area through which heat can be eliminated by conduction, convection, radiation, and evaporation. Furthermore, dilation and constriction of the cutaneous vessels, particularly of the arterio-venous shunts, can powerfully alter the circulation to the skin in response to

changes in environmental temperature, thus regulating the amount of heat dissipated or conserved.

When the body is exposed to a warm environment the peripheral vessels and the arterio-venous anastomoses dilate widely, allowing a large quantity of blood to the surface of the extremities; heat is quickly lost, and the blood is then returned by the dilated superficial veins, where more cooling takes place. Conversely, in a cold environment, constriction of the peripheral vessels reduces the cutaneous circulation to a minimum and prevents dispersion of heat by diverting the arterial blood into the deep venous plexus. As blood is returned through the venae comitantes it is further warmed by the adjacent arterial flow, the so-called countercurrent heat exchange system.

This accurate thermoregulatory mechanism is largely under the control of the sympathetic nervous system. It was previously noted that the contractile muscular elements in the walls of the precapillary resistance vessels and of the arterio-venous shunts receive a rich supply of sympathetic fibers. At any given time the particular pattern of neural discharge determines the relative state of contraction or relaxation of the smooth muscles, and it accounts, therefore, for the compensatory fluctuations occurring in the peripheral circulation when changes in the external temperature threaten

to disrupt the internal thermal equilibrium.

Nervous Control of the Peripheral Circulation

No attempt will be made here to provide a comprehensive survey of the anatomy, peripheral distribution, and supraspinal control of the sympathetic nervous system. Such information can be found in Abramson (1974, chap. 10); White, Smithwick, and Simeone (1952, chap. 3); Winsor (1959, chap. 1).

More relevant to this paper is the regulation of the vessels' caliber carried out at the peripheral level by the activity of the sympathetic fibers innervating the vascular smooth muscle. This activity is centrally integrated at the medullary, diencephalic and cortical levels. In particular, motor and premotor areas, as well as hypothalamic and medullary centers, have been shown to be implicated in the coordination of autonomically mediated vascular responses. These issues have been competently reviewed by Folkow (1955, 1956), and by Bard (1963).

Sympathetic vasomotor tone. The peripheral circulation is under the control of the sympathetic division of the autonomic nervous system, whose function is primarily vasoconstriction. The postganglionic axons are adrenergic unmyelinated C fibers which can produce maximal constriction in the innervated vessels firing at a rate no greater than 10 impulses/sec, although

their upper limit of discharge rate is in the order of 100 impules/sec (Celander & Folkow, 1953a; Folkow, 1956). "Vasoconstrictor" or "vasomotor tone" is the basal level of activity exhibited under normal resting conditions by these fibers which, firing at a frequency of 1 or 2 impulses/sec, maintain the peripheral elements of the vascular tree in a constant state of tonic contraction. This arrangement eliminates the need for an active vasodilator mechanism since maximal relaxation of the blood vessels can be obtained by inhibiting the tonic nervous discharge ("release of vasomotor tone"). Being centrally integrated, sympathetic activity can be increased or decreased to provide a wide range of control of the vascular caliber needed to meet the organism's thermoregulatory requirements. Central inhibition of vasoconstrictor impulses can be very simply and effectively induced, for example, by warming the body; a procedure known as "indirect" or "reflex vasodilatation" which will be discussed later in more detail.

The parsimonious regulatory mechanism just described, however, is not equally found in all sympathetically innervated vessels, and some anatomical distinctions are necessary. In general it predominates in the cutaneous and distal portions of the limbs, like hands and feet, where sympathetic innervation, and therefore vasomotor tone, is most powerful, and where arterio-venous

anastomoses are most abundant. On the other hand, in more proximal cutaneous areas, like arms and legs, as well as in skeletal muscles, an additional active vasodilator mechanism is present.

Sympathetic vasodilator fibers to hands and feet. The question of whether sympathetic vasodilator fibers exist is not only of interest to the physiologist but also to the clinician, since it has important implications in the treatment of peripheral vascular disorders, including the vasospastic ones.

Lewis and Pickering (1931) first presented evidence for the presence of sympathetic vasodilator fibers in the hands of patients with "Raynaud's disease." Their findings were later confirmed by Fatherree and Allen (1938). Both studies, however, failed to demonstrate the existence of such fibers in the extremities of normal individuals. These results are quite puzzling, as the difference in innervation between normal people and patients with Raynaud's disease escapes any reasonable physio-anatomical explanation. The discrepancy, however, becomes less enigmatic if one considers the possibility that the vasomotor phenomena exhibited by those patients were the result not of a primary vasospastic disorder but rather of organic arterial occlusion, which would easily explain the reported failure of the vessels to dilate after nerve block.

It was noted earlier, and it will be later considered in much greater detail, that Lewis' erroneous conception of what should be included under the diagnostic category of Raynaud's disease has often undermined the applicability of his conclusions to the primary vasospastic condition. Two cases of "Raynaud's disease" were observed by Lewis and Pickering in their 1931 study. The first case had been already described in a previous paper (Lewis, 1929), where the patient was included in the "severer group," her fingertips being affected by dry gangrene with considerable loss of substance. Description of the second case is very scanty, but pain and impaired flexion of the fingers is noted.

In these two doubtful cases of Raynaud's disease Lewis and Pickering found that ulnar nerve block failed to raise the skin temperature of the cooled little finger, and that vasodilatation in response to body heating appeared with considerable delay in the anesthetized area. They inferred that blocking of the sympathetic vasodilator fibers in the ulnar nerve was responsible for the finding. This conclusion, however, does not seem warranted and the observed results are those expected from discrete structural damage to the digital vessels. The same findings might have been obtained even without blocking the nerve, since impairment of

the local circulation was most probably due to vascular occlusion, and not to interruption of alleged vasodilator impulses. It is well known (Goetz, 1956a) that in cases of organic arterial disease reflex vasodilatation is much delayed when compared to the normal reaction, the magnitude of the delay being dependent upon the degree of vascular obliteration.

The study by Fatherree and Allen (1938) is subject to the same criticism. Here information relative to the diagnostic selection of the six cases presented is completely lacking. Absolutely nothing is said about the first three patients, whose age and sex are not even reported. The remaining three are described as cases of "moderately severe Raynaud's disease," two of them exhibiting sclerodermatous changes in both upper and lower extremities, and the third having "moderately severe rheumatoid arthritis involving the joints of all four extremities" (p. 1025). The existence of sympathetic vasodilator fibers innervating the cutaneous peripheral vessels in these patients is just as likely as the diagnosis of Raynaud's disease given to them.

Many subsequent investigators have conclusively demonstrated the absence of a sympathetic vasodilator mechanism directly increasing blood flow in the distal regions, not only in cases of Raynaud's disease (Gaskell, 1956; Sarnoff & Simeone, 1947), but also in

normals (Arnott & Macfie, 1948; Gaskell, 1956; Roddie, Shepherd, & Whelan, 1957a; Sarnoff & Simeone, 1947; Warren, Walter, Romano, & Stead, 1942). These studies have been reviewed by Barcroft (1960), whose paper should be consulted.

There is now overwhelming evidence that in man nervous control of the cutaneous blood flow through the distal portions of the limbs is mediated exclusively by the sympathetic vasoconstrictor innervation of the vascular smooth muscle, and that in those acral areas vasodilatation is a passive phenomenon determined solely by the release of vasoconstrictor tone.

Active vasodilatation in proximal portions of the limbs. (a) Sympathetic vasodilator fibers. It was pointed out earlier that in the more proximal regions of the limbs the density of arterio-venous anastomoses is greatly reduced and vasomotor tone is much less powerful. Early reports seemed to authorize the conclusion that the vessels of these cutaneous areas were indeed supplied with sympathetic vasodilator fibers. The hypothesis was originally advanced by Grant and Holling (1938) who observed that heating the body drastically increased blood flow to the skin of the forearm. Interruption of the sympathetic outflow to this region, either by sympathectomy or by blocking the nerve with procaine, clearly prevented reflex vasodilatation,

which was instead fully preserved in the normally innervated forearm.

Adopting basically the same experimental paradigm, subsequent researchers (Doupe, Cullen, & Macaulay, 1943; Edholm, Fox, & Macpherson, 1956; Roddie, Shepherd, & Whelan, 1957b) corroborated Grant and Holling's suggestion, and again pointed out the necessary contribution of sympathetic vasodilator nerves in regulating the cutaneous circulation through the forearm. Later Blair, Glover, & Roddie (1960) extended the findings relative to the forearm to include upper arm, calf, and thigh.

Roddie, Shepherd, and Whelan (1957c) identified two stages in forearm vasodilatation produced by warming the body. A small initial increase in blood flow, observed only when the subject was kept in a relatively cool environment prior to body heating, appeared unaffected by intra-arterial atropine and it was, therefore, attributed to release of adrenergic vasoconstrictor tone. As body heating continued, the experimenters noted a second and much larger increase in forearm blood flow which usually coincided with the onset of sweating. This major vasodilatation was considered to be an active process mediated by cholinergic fibers, since injection of atropine prevented its occurrence. But the interesting finding was that the inhibitory action of atropine was only temporary. Although both

sweating and response to injected acetylcholine were completely abolished, thus demonstrating a lasting effect of atropine which was further secured by additional infusions, after an interval of about 20 minutes vasodilatation in response to body heating resumed in atropinized forearm. Furthermore, if atropine was administered at the height of reflex vasodilatation no reduction in forearm blood flow was observed even temporarily.

Among other equally plausible explanations Roddie and his collaborators acknowledged the possibility that metabolic activity of the sweat glands, and not necessarily the presence of vasodilator nerves, could have accounted for the reported findings. It is quite evident that if the increase in forearm blood flow were mediated by sympathetic cholinergic fibers, administration of atropine should have completely prevented the observed vasodilatation.

(b) Bradykinin. The prominent role of sweat gland activity in regulating the forearm cutaneous circulation in humans was convincingly demonstrated by Fox and Hilton (1956, 1957, 1958). They showed that the activited sweat glands liberate a proteolytic enzyme into the surrounding tissue fluids, where proteins are broken down to form bradykinin, a polypeptide with remarkable vasodilator properties. Moreover they

determined that with body heating the amount of bradykinin in the subcutaneous tissue of the forearm increased up to five times above the prewarming level. The observed vasodilatation was therefore attributed to the increased bradykinin content coincident with the onset of sweating.

The relationship between bradykinin and vasodilatation, mentioned here with reference to the sweat glands, had already been noted by Hilton and Lewis (1955, 1956, 1957) with respect to the cat's submandibular salivary gland. These investigators established that, upon stimulation of the chorda tympani, release of the bradykinin-forming enzyme was greatly enhanced, and they ascribed the local vasodilatation, accompanying the salivary secretion, to the conspicuous increase in bradykinin formation.

Both the salivary and the eccrine sweat glands are innervated by sympathetic secretomotor fibers which are cholinergic and are, therefore, inactivated by atropine. It is interesting to note, however, that although atropine abolishes both sweating and salivary output, the vasodilatation associated with those secretions is only delayed, or, at most, reduced, but not suppresed (Barcroft, 1914; Doupe et al., 1943; Fox & Hilton, 1958; Hilton & Lewis, 1955; Roddie et al., 1957c). This apparent incongruity has been explained by Barcroft

(1914), who demonstrated that stimulation of the chorda tympani failed to induce secretion in the atropinized salivary gland, which, nevertheless, continued to show a heightened metabolic activity, as judged by the gland's oxygen consumption. Barcroft dismissed the possibility of special vasodilator fibers and concluded instead that the resulting increase in blood flow, which he referred to as "functional dilatation," was due to the products of the gland's metabolic activity. His interpretation was confirmed by Hilton and Lewis (1955), and was extended to the case of the sweat glands by Fox and Hilton (1958).

While the hypothesis linking vasodilatation to the action of bradykinin seemed established on very solid evidence, the observed temporal succession of the two events did not appear to fit the idea of a causal relationship. Several researchers (Fox & Hilton, 1958; Hellon & Lind, 1956; Senay, Christensen, & Hertzman, 1960; Senay & Hertzman, 1960) have reported an erratic, or at least inconsistent, temporal sequence between the onset of sweating and forearm vasodilatation, whereas the bradykinin hypothesis would require that sweating precede the increase in blood flow. Love and Shanks (1960), however, have pointed out that the results of those studies were basically vitiated by the failure to distinguish between passive dilatation, brought about

in the forearm skin by release of vasomotor tone upon body heating, from the active vasodilatation phase mediated by bradykinin. The required temporal succession should be expected only in the second case, after the initial passive dilatation is concluded. Love and Shanks were able to identify experimentally the transition point between passive and active vasodilatation by comparing, before and after body heating, the blood flow in the nerve-blocked and in the atropinized forearm with that obtained in the normal forearm. They found that in all eight cases studied the onset of sweating always preceded the appearance of active dilatation.

In summary, there is presently substantial agreement about the existence of an active vasodilator mechanism in the more proximal portions of the limbs. The bulk of the evidence would suggest the identification of this mechanism with the local and direct action of bradykinin on the cutaneous blood vessels. The sympathetic nervous system is believed to contribute only indirectly by way of sudomotor fibers innervating the sweat glands, and not, as previously assumed, by virtue of special vasodilator fibers directly supplying the muscular coat of the vascular wall.

The evidence reviewed here against the existence of sympathetic vasodilator nerves to the skin vessels

is consistent with the reports of some authoritative Scandinavian researchers (Folkow, 1955, 1960; Uvnäs, 1954, 1960) who have pointed out that the peripheral distribution of cholinergic vasodilator fibers is limited to the skeletal muscles and, perhaps, to the coronary vessels.

Reflex and indirect vasodilatation. As noted earlier, in the distal parts of the limbs a powerful vasoconstrictor tone is maintained by the adrenergic innervation of the resistance vessels and of the numerous arterio-venous anastomoses. The most effective way, if not the only one, of inducing cutaneous vasodilatation in those apical regions is therefore to inhibit the tonic vasomotor discharge. This can be accomplished by several procedures such as reflex vasodilatation, blocking the peripheral nerves or the sympathetic ganglia with a local anesthetic, general anesthesia, oral ingestion of alcohol, even intentional production of fever by administration of typhoid vaccine or other substances, and, of course, the most radical of all, sympathectomy. Most of these techniques, which can be very useful both diagnostically and therapeutically, have been adequately reviewed already (Abramson, 1956, 1974, chap. 4; Goetz, 1956a; Winsor, 1959, chap. 9).

Here the mechanism of reflex or indirect vasodilatation deserves to be described in some detail, since

it offers some very valuable applications in the diagnosis of peripheral vascular disorders and, particularly, in the differentiation of primary vasospastic conditions from organic vascular diseases.

The technique is based on the simple principle that a marked cutaneous vasodilatation is readily obtained in the extremities by warming another part of the body (Gibbon & Landis, 1932). Many variations of the basic procedure have been adopted with respect to the body area being heated, and different sources of heat have been used (Kerslake & Cooper, 1950). The easiest and probably the most effective method seems to be the one described by Goetz (1956a), to whom the reader is referred for technical details and for helpful suggestions relative to the proper diagnostic interpretation of the technique.

The local increase in blood flow through the extremities following body heating has been attributed to the return of warm blood from the heated area of the body to the general circulation, the rise in temperature of the returning blood acting as a stimulus at the hypothalamic level to inhibit vasoconstrictor impulses (Bader & Macht, 1948; Gibbon & Landis, 1932; Pickering, 1932; Pickering & Hess, 1933). In support of this notion Pickering (1932), and Gibbon and Landis (1932) have shown that when blood return is prevented by

occluding the arterial and venous flow the vasodilator response is suspended until the circulation is restored. Their findings and interpretations have been conclusively confirmed (Goetz & Ames, 1949).

Kerslake and Cooper (1950), on the other hand, reported that heating the trunk or legs with a radiant heat cradle produced a prompt, although small, vasodilatation in the hand within 10 to 15 seconds, a latency much too short for the response to be explainable in terms of warm blood return. In addition they found that when the legs were heated and the return of warm blood was prevented by arresting the circulation, the immediate increase in hand blood flow was fully preserved. In view of these results the reflexive nature of the response was proposed.

According to Richards (1970) the term "reflex vasodilatation" should then be reserved only for this initial and almost instantaneous response, while "indirect vasodilatation" should indicate the much larger increase in blood flow ensuing with a latency varying between 10 and 30 minutes, and resulting from the return of warm blood to the hypothalamic temperature-regulating center, where inhibition of vasoconstrictor tone is initiated.

Gibbon and Landis (1932) suggested that organic arterial occlusion can be ruled out when skin temperature

reaches a level of 32°C within 30 minutes of body heating. This widely accepted criterion was taken by Goetz (1956a) as the "normal vasodilatation level" against which to compare the cutaneous temperature recorded for any given case.

Patients with a functional vasospastic disorder like Raynaud's disease typically exhibit, under normal conditions, a very low skin temperature, as a result of an abnormally high vasoconstrictor tone. The blood flow in their extremities, however, reaches normal, or nearly normal, values within half an hour of indirect body heating, thus demonstrating a complete release of vasomotor tone. Failure of the cutaneous vessels to dilate normally after warming the body, on the other hand, indicates organic vascular disease, and the degree of circulatory impairment, according to Goetz, can be estimated by the difference between the temperature registered and the normal vasodilatation level.

A more explicit interpretation of skin temperature deviations from the criterion has been proposed by Holling (1972) who considers the state of the circulation to be "normal" if the skin temperature recorded in the extremities following body heating reaches values of 32°C or above, "reduced but adequate" between 28° and 32°C, "intermediate" between 25° and 28°C, and "very seriously reduced" below 25°C.

Both Goetz and Holling have cautioned against the injudicious diagnostic use of skin temperature as a measure of blood flow which may result in a large number of false negatives; in particular mild cases of organic vascular occlusion might show full peripheral vasodilatation, as measured by skin temperature, and will therefore be missed. This happens because at relatively high rates of flow the relationship between skin temperature and blood flow breaks down; thus while the temperature may rise to the maximum level, the blood flow could be as little as 25% of the maximum (Burton, 1948; Cooper, Cross, Greenfield, Hamilton, & Scarborough, 1949; Felder, Russ, Montgomery, & Horwitz, 1954; Fetcher, Hall, & Shaub, 1949; Goetz, 1946; Sheard, 1944). The problem can be obviated by employing a more direct measure of blood flow such as plethysmography, which can be used alone or in conjunction with skin temperature.

Axon reflex and dorsal root vasodilatation. This discussion of the nervous control of the peripheral circulation cannot be concluded without at least a brief mention of a mechanism capable of producing a local cutaneous vasodilatation mediated not by the sympathetic but by the somatic sensory system.

The neural arrangement is that of an axon reflex involving afferent sensory nerves, almost certainly pain-conducting unmyelinated C fibers having their cell

bodies in the dorsal root ganglia. These ascending pain fibers, before entering the cord, give out peripheral branches which innervate the smooth muscles of the small cutaneous blood vessels.

When the sensory nerve endings distributed to the skin are stimulated, nerve impulses propagate both in a centripetal (dromic) direction, and centrifugally (antidromically) along the sensory branches to the contractile vascular elements. The vasodilatation resulting from the antidromic excitation is not centrally controlled but it is dependent exclusively on the integrity of the peripheral mixed nerves. To this local increase in blood flow has been attributed the appearance of the "flare reaction," one component of the "triple response" observed following mechanical trauma to the skin.

Clearly the axon reflex mechanism plays a rather limited part in the regulation of the peripheral circulation, and its function is primarily one of local protection of the cutaneous tissues against noxious stimuli. Further details on the physio-anatomical basis, neurochemical mediation, and functional significance of this dorsal root vasodilatation can be found in Folkow (1956) and in Bard (1968).

The protective role of the sensory axon reflex was believed by Lewis (1930, 1931) to be at the basis of the "cold vasodilatation" phenomenon, characterized by

alternating cycles of vasoconstriction and vasodilatation (Lewis's "hunting reaction"), and occurring when the digits are exposed for some time to temperatures lower than 10°C. Greenfield, Shepherd, and Whelan (1951) challenged Lewis's notion attributing cold vasodilatation to a local axon reflex, as they found that, although reduced, the reaction was still present following section and degeneration of the somatic sensory fibers.

Shepherd and Thompson (1953), on the other hand, presented persuasive evidence in support of Lewis's view by demonstrating that return of sensation after peripheral nerve section was accompanied by a parallel recovery of the cold vasodilatation response which had been lost in the injured fingers. Moreover, the degree of recovery of the reaction to cold was proportional to the degree of recovery of sensation. Shepherd and Thompson concluded that the return of the cold vasodilatation response was facilitated by regeneration of the somatic sensory fibers, that is by reinstitution of the axon reflex circuit.

It should also be noted here that some authors (Magos & Okos, 1963; Marshall & Gregory, 1974) have proposed to identify the etiopathogenetic element in Raynaud's disease with an impaired cold vasodilatation response, which in patients suffering from that vascular

disorder was found to be reduced, delayed, or even absent. This suggestion, however, has received little support and stands in evident contrast with Thompson's (1959) conclusions. Furthermore, in this author's opinion, it seems possible to dismiss that hypothesis on purely clinical grounds, for attacks of Raynaud's disease are often observed at temperatures not rigid enough for the cold vasodilatation reaction to occur.

Before attempting to discuss the nature of the pathological mechanism responsible for Raynaud's disease, the various determinants of the normal peripheral ciru-lation must be clearly understood and their relative importance assessed.

The preceeding lengthy excursus, outlining the nervous regulation of the peripheral vascular activity in different cutaneous areas, has unequivocally indi-cated the extraordinary influence exerted by the sym-pathetic nervous system, especially in the more distal portions of the limbs. In addition to this powerful neurogenic control, however, other factors, particularly humoral and local, contribute to modify the state of the peripheral circulation and must, therefore, be considered.

Humoral Control of the Peripheral Circulation

Hormonal and chemical agents transported by the blood can actively change the vessel caliber by acting

directly on the vascular smooth muscle.

Although epinephrine and norepinephrine, the catecholamines released by the adrenal medulla, have received the greatest share of the researchers' attention, numerous other vasoactive substances have also been described. The powerful action of bradykinin, for example, has been considered earlier. The literature in this area is exceptionally rich, but the results are still rather inconclusive and it would be very difficult to summarize them concisely. Excellent reviews are already available (Folkow, 1956; Herxheimer, 1961; Shepherd, 1963; Vane, 1969; Whelan, 1967).

It is now recognized that the physiological response of the peripheral blood vessels to epinephrine and norepinephrine is determined by the type of adrenergic receptor acted upon by these hormones. Stimulation of alpha receptors produces vasoconstriction, while activation of beta receptors results in vasodilatation. Both epinephrine and norepinephrine constrict the cutaneous blood vessels which have predominantly, if not exclusively, alpha receptors. The vascular effects of the catecholamines will be further examined later in this paper, where they will be integrated in a detailed discussion of the neurogenic basis of vasospasm.

Local Control of the Peripheral Circulation

Nervous impulses and blood-borne chemicals exert a remote or extrinsic control over the peripheral circulation. It is now necessary to consider in some detail the role played by local or intrinsic factors, whose contribution to the regulation of the vascular caliber must be clarified if an accurate evaluation of the etiological theories proposed for Raynaud's disease is to be attained.

Autoregulation. The different factors which participate in the local control of the circulation share the important homeostatic function of maintaining a constant flow of blood in spite of marked variations in arterial perfusion pressure. This precise local adjustment, known as autoregulation of flow, takes place at the level of the resistance vessels, and insures adequate nutrition to vital organs like the brain and the heart. Metabolic, myogenic, and other hemodynamic mechanisms have been proposed to explain the phenomenon of autoregulation.

(a) Metabolic theory. In brief, the metabolic hypothesis suggests that a decrease in blood flow, consequent to a reduction in transmural pressure, leads to a proportional increase in the local concentration of metabolites which, having a vasodilator action, restore the circulatory equilibrium by relaxing the vascular

smooth muscle. Conversely, an increase in intraluminal pressure, and hence in blood flow, is compensated by a lowered concentration of the vasodilator metabolites, which are "washed away" or inactivated, and the normal flow values are thus restored.

Accumulation of vasoactive metabolites has been associated with the occurrence of reactive hyperemia, a vascular phenomenon observed after a period of local ischemia, which can be induced in the hand, for example, by inflating a cuff around the limb above systolic pressure. As soon as the circulation is restored there is a large increase in blood flow greatly exceeding the preischemic level, followed by a gradual return to the resting value. The phenomenon is visually conspicuous, as the skin assumes a bright red color which slowly fades away. Freeman (1935) showed that, within certain limits, the blood "repayment" is related to the blood flow "debt" determined by the duration of the circulatory arrest.

The local nature of this vascular reaction is unquestionable, for it occurs even after complete section of the sympathetic and somatic nerves. Although many substances have been proposed, attempts to identify the precise chemical nature of the vasodilator metabolites have, so far, failed.

(b) Myogenic theory. According to the myogenic

autoregulation hypothesis, originally introduced by Bayliss (1902), an imbalance in blood flow level is counteracted by the activity of the vascular smooth muscle stimulated by changes in wall tension. Thus, if transmural pressure is increased, either by an increase in intraluminal pressure or by a decrease in extraluminal pressure, the increased tension in the wall of the resistance vessels causes the smooth muscle to contract. On the other hand, a reduction in the normal level of transmural pressure is offset by relaxation of the smooth muscle.

The myogenic theory has received much experimental support from the work of Folkow (1949), who more recently has presented an interesting model where the metabolic and myogenic mechanisms are well integrated, the metabolic factors providing stability to an otherwise precarious regulatory system (Folkow, 1964a; Folkow & Neil, 1971).

The myogenic hypothesis rests on the necessary assumption that the smooth muscle of the resistance vessels has an inherent tonic contractility which can be increased or decreased, as the situation requires, to meet the need for an efficient regulation of flow. It is now clear that the postulated myogenic automaticity does indeed exist, at least in some vascular areas. This spontaneous activity of the smooth muscle, better

known as "basal vascular tone," is entirely local in origin, for it is fully preserved after the influence of nervous factors and of blood-borne vasoactive substances is completely removed.

It needs to be strongly emphasized here, however, that this basal tone is not equally present in the smooth muscle of all resistance vessels. It can be generally stated that in those vascular areas where sympathetic vasomotor tone is most powerful the basal tone is weakest, and vice versa. Conflicting reports as to whether autoregulation and intrinsic myogenic contractility are present in the limbs can probably be explained in terms of the failure to distinguish between regions where skin is the major component (fingers, toes, ears) and areas where skeletal muscle tissue predominates (arms, legs).

When the very distal portions of the limbs are considered, the most conspicuous, and perhaps exclusive factor controlling the circulation is neurogenic in origin. In animal preparations, where the limbs have been completely denervated, an almost maximal dilatation is observed in the apical regions, while a considerable tone, obviously local in nature, remains in the more proximal portions (Celander & Folkow, 1953b; Folkow, 1960, 1964b). In particular the arterio-venous anastomoses, most numerous in the distal areas, have a

thick coat of smooth muscle which shows a very intense neurogenic vasoconstrictor tone, but virtually no local basal tone.

This regional differentiation is in keeping with Bozler's (1948) notion postulating the existence of two types of smooth muscles performing different functions: the "visceral" or "single-unit" type which exhibits a basal tone, and the "multi-unit" type which lacks spontaneous myogenic activity and which responds largely to neurogenic influences. As previously noted, the great increase in blood flow, brought to the extremities by the opening of the arterio-venous anastomoses, by far exceeds the local nutritional requirements and rather serves a general thermoregulatory function which needs to be centrally coordinated. In this case it is necessary that the vascular smooth muscle be under nervous control and the multi-unit specialization is highly appropriate. Fulfillment of the local nutritional demands, on the other hand, becomes of paramount importance in the case of vital tissues. Here the intrinsic basal tone of the visceral smooth muscle type serves the precise and essential homeostatic function of maintaining a constantly adequate supply of nutrients.

The two situations described above represent two extremes of a continuum; extrinsic and intrinsic regulatory mechanisms are not necessarily mutually exclusive,

and, in some tissues, like the skeletal muscle, they show a more balanced interaction.

Local effect of cold on the circulation. As noted earlier, the marked reduction in hand blood flow following exposure to cold is largely a thermoregulatory response centrally coordinated and mediated peripherally by sympathetic vasoconstrictor fibers. Temperature changes, however, can also produce local vascular reactions independent of the sympathetic innervation, as demonstrated by the possibility of eliciting cold vasoconstriction in the sympathectomized extremities (Buchanan, Cranley, & Linton, 1952; Doupe, 1943; Freeman, 1935; Lewis, 1938a; Lewis & Landis, 1930).

Although hemodynamic, chemical and metabolic explanations have been proposed, the exact nature of this local response is not yet understood. Increased blood viscosity may partly account for the reduced blood flow at low temperatures (Edwards & Burton, 1960).

Whatever the mechanism underlying the direct effect of temperature changes on the blood vessels, it must be noted that a powerful central control, activated by a state of thermal imbalance, can facilitate or completely inhibit the action of the local factors, and will result, in the final analysis, as the chief determinant of vascular adjustments. This fundamental point has been too often overlooked, in spite of considerable evidence

accumulated in its support.

Spealman (1945) studied the vascular effects of the interaction between hand and environmental temperature and found that, regardless of the local temperature applied to the hand, hand blood flow increased as the body became warmer. After cooling the hands down to 15°C, a value which should produce maximal vasoconstriction since cold vasodilatation does not occur at this temperature, blood flow was 20 times larger at an ambient temperature of 32°C than at 16°C. Similar observations have been reported by Bader and Mead (1949) who pointed out that at an ambient temperature of 32°C local thermal variations have little effect on finger blood flow.

Rapaport, Fetcher, and Hall (1948) showed that, if the body was sufficiently heated, the bare hands and feet could be maintained comfortably warm even when exposed to temperatures as severe as -18°C and -34°C.

After exposing the rabbit's ear to the amazing temperature of -48°C, Miller (cited by Rapaport, Fetcher, Shaub, & Hall, 1949, p. 61) was able to keep it from freezing for two hours by supplying the animal's body with enough heat.

Rapaport, Fetcher, Shaub, and Hall (1949) again recorded hand skin temperatures above 21°C when the unprotected extremities of well-heated subjects were cooled to -18°C, -29°C, and -34°C. They concluded that

the local direct effect of cold on the blood vessels is subordinate to the autonomic control of the peripheral circulation, and also suggested that in order to prevent frostbite or to relieve vasospasm it is necessary to warm the whole body and not just the affected extremities. Analogous recommendations have been made by Burton and Edholm (1954) who have observed:

> The practical importance of the dependence of the local circulation on general body temperature is in clothing design. It was shown that, if the body is cooling, electrical heating for the hands alone is useless and may be dangerous: it is more important to supply heat to the body than to the extremities. (p. 140)

These findings are not very surprising when interpreted in light of the indirect vasodilatation principle discussed earlier. They clearly demonstrate that the local action of temperature is overridden by the general thermoregulatory requirements, so that it would be very difficult, for example, to induce vasodilatation in the locally heated extremity if the body is cold, and to elicit vasoconstriction by local cooling if the body is kept warm. Within a wide temperature range, the state of constriction or dilatation of the peripheral vessels will be determined, in each case, by the body's need to conserve or to dissipate heat, rather than by the direct effect of thermal stimuli on the blood vessels.

This general principle is not necessarily incompatible with the above-mentioned studies indicating

that after sympathectomy the peripheral vessels still constrict upon local cold stimulation.

In the first place, surgical denervation does not exclude definitely the possibility of a nervous mediation of the vasoconstrictor response to cold. As it will be clearly shown later, incomplete denervation as well as regeneration of the severed fibers are common enough to seriously limit the therapeutic efficacy of the operation. In such cases the persistence of neurogenic vasoconstriction has been unequivocally demonstrated.

Secondly, in this author's opinion, it may not be unreasonable to postulate that the local reactivity of the blood vessels to temperature might develop as a compensatory mechanism after the essential homeostatic function of vascular regulation, performed by the nervous system, is lost as a result of sympathectomy. Effective thermoregulation, of course, depends upon an intact supply of sympathetic vasoconstrictor fibers. Surgical removal of vasomotor tone would produce a permanent vasodilatation in the denervated extremities, which would continue to lose heat even when the cold organism may need to conserve it, and the vital thermoregulatory mechanism would thus be dangerously disrupted.

The intrinsic responsivity of the blood vessels to thermal stimuli, which sets in under these circumstances, is very adaptive as it preserves the body's ability to

maintain a fairly constant core temperature by dissipating and conserving heat as needed. Admittedly this type of thermoregulation, being exclusively local and not coordinated centrally, may prove rather precarious. In theory local heat could induce peripheral vasodilatation even though the cold body might need to conserve heat, and vice versa; these situations, however, would rarely occur in nature.

The question of whether the local sensitivity of the blood vessels to temperature changes is present already in the intact extremities, or whether it develops after sympathectomy is only marginally relevant to the subject of this paper and needs no further elaboration here.

The conclusion which must be stressed instead, in line with the physiological evidence presented above, is that local factors play but a neglegible role in the control of blood flow through the extremities, and that in the normally innervated limbs the nervous system constitutes the primary regulator of the peripheral circulation.

ETIOLOGY OF RAYNAUD'S DISEASE

About 10 years before Raynaud's original thesis was published Claude Bernard had discovered the existence of sympathetic vasoconstrictor nerves. Stimulated

by this work, Raynaud (1874) concluded his second thesis with the suggestion that "local asphyxia of the extremities ought to be considered as a neurosis characterised by enormous exaggeration of the excito-motor energy of the grey parts of the spinal cord which control the vasomotor innervation" (p. 182).

This clear formulation of the neurogenic theory remained virtually unchallenged until Sir Thomas Lewis (1929) published a detailed report with the results of a series of experiments indicating that not a vasomotor disturbance, but rather a "local fault" in the vessels themselves was to be considered as the primary pathological factor in the vascular disorder described by Raynaud.

Lewis's views have exerted an enormous influence and a growing number of investigators has accepted his conclusions. The enigma concerning the etiology of Raynaud's disease, however, is yet to be resolved, and the current literature is still basically divided between Raynaud's and Lewis's conflicting hypotheses.

In order to evaluate how serious a challenge the local fault alternative presents to the vasomotor theory, Lewis's contribution must be thoroughly reviewed. This is particularly urgent not only because, to this author's knowledge, no comprehensive critical appraisal of Lewis's ideas has been undertaken to this day, but also because

the validity of the local fault notion rests essentially on the accuracy of those ideas. Lewis's impressive work is still widely cited as incontrovertible evidence against the neurogenic hypothesis by numerous authors who have accepted, often uncritically, the authority of the British researcher, and who have added very little to what he had reported more than four decades ago.

It hardly needs to be noted that the polemic approach, which will be evident in the following pages, is directed not to a man, whose contribution to the physiological and clinical understanding of the peripheral vascular disorders has been invaluable, but rather to a theory which, although still popular, demonstrates many fallacies upon close scrutiny. This writer readily recognizes the unfairness of criticizing someone's ideas while availing himself of 45 years of accumulated knowledge and would see no point in doing so were it not for the tremendous influence which those ideas continue to have at this time.

The Local Fault Theory

Lewis's 1929 paper deserves to be examined in detail since it constitutes the most complete collection of experimental data on which the local fault hypothesis is based. Unless otherwise specified, reference to this work is implied throughout the present discussion of Lewis's views.

Lewis's Cases

Before considering the merit of Lewis's arguments, a general comment on the nine clinical cases used in the study is necessary. The first three cases are described as "severer" since they all "had experienced dry gangrene of the finger tips" (p. 12). By Lewis's own admission in that same paper, as well as elsewhere (Lewis, 1932, 1938a, 1938b, 1949), organic vascular disease must be assumed in the presence of such severe symptomatology.

An organic etiology of the vasospastic phenomena must be also suspected for the "intermediate cases" 4 and 5. Lewis recognized that case 4 "resembled cases of Group 1" (p. 12), i.e., the severer group. This 18-year-old lady experienced attacks not only during the cold weather with a frequency of about twice a day, but also in the summer months. She had a systolic blood pressure of 135, and her hands were cold and discolored even between attacks. Case 5 was a 64-year-old woman suffering from chronic rheumatoid arthritis, a condition often associated with digital ischemia. Early rheumatoid changes were observed in the metacarpophalangeal joints, and a necrotic lesion was present at the base of one nail. Her systolic blood pressure was 160.

Even in the "milder" cases (6, 7, 8, and 9) a

functional origin for the vascular disorder appears very unlikely. The very high frequency of occurrence of the attacks in this group as a whole, and especially in cases 6 and 7 who experienced them many times a day, together with the continued presence of vasospasm even during the warm season, suggest rather advanced conditions of considerable severity. Moreover, case 8 suffered from mitral stenosis and auricular fibrillation; conditions not rarely producing emboli to which digital ischemia is often secondary. Finally the conspicuous swelling of the hands, as well as the pulmonary fibrosis reported in case 9, strongly suggest the diagnosis of diffuse scleroderma.

It would seem safe to conclude that most, if not all, of Lewis's patients were not examples of Raynaud's disease, but were rather cases of digital ischemia secondary to organic vascular disorders. While Lewis acknowledged the existence of different "types of 'Raynaud's disease' and the need of distinguishing them" (p. 83), he has been unable to isolate the primary form, and what he described, in his own words, "is the form in which the digits become periodically pale or cyanotic and, in which, after several or many winters of repeated attacks, terminal portions of the digits may be lost by a process of slow dry gangrene" (p. 98).

It is now clear that the observations gathered by

Lewis were based on cases of organic disease associated with vasospastic phenomena; his conclusions, then, are totally unwarranted when applied to Raynaud's disease, which is a clinical entity by definition lacking an identifiable organic pathogenesis. This is a crucial point which by itself seems sufficient to entirely dismiss the local fault hypothesis. It should also be noted that those observations, which according to Lewis conclusively refuted the vasomotor theory, were conducted primarily, and sometimes exclusively, on the three most severe cases, for whom the organic etiology is unequivocal.

Some investigators (Allen & Brown, 1932b; Simpson, Brown, & Adson, 1930, 1931; White et al., 1952) had already noted that Lewis's cases were too advanced, but they failed to raise the decisive criticism that those patients were not at all cases of Raynaud's disease. To those early objections Lewis (1938a) replied that his cases "were no more severe than cases described by Raynaud himself and regarded by him as the immediate result of abnormal sympathetic tone; that the more severe cases are proving to have digital arterial disease is consistent with my views but not with his" (p. 335).

Lewis's protestations obviously elude the issue, which is not to determine whose cases were more severe, Raynaud's or Lewis's, but rather to recognize that

those cases of "digital arterial disease," just as the ones described by Raynaud, could not be considered as cases of Raynaud's disease. Adoption of the diagnostic requirements specified by Allen and Brown (1932a) would have led to the same conclusion. Those criteria were available to Lewis and it is rather surprising that he never referred to them.

It is now time to consider the validity of the arguments adduced by Lewis in the 1929 paper against the neurogenic theory of Raynaud's disease. The fundamental observations, which formed the experimental basis for his contention, were derived from the study of the peripheral circulation following local cooling and warming, ulnar nerve anesthesia, and sympathetic denervation.

Local Effect of Temperature on the Blood Vessels

Vasospasm as a result of local cooling. Lewis has reported that vasospastic attacks could be readily induced in his patients by locally cooling their hands. Moreover, blood flow to a single finger, or to a portion of a finger, could be interrupted by limited cooling of that part alone. He argued that if the vasoconstrictor response were mediated by the vasomotor nerves a more generalized reaction, rather than such a highly specific one, should have occurred.

It must be noted, however, that Lewis's finding (observation 16) of "a definite and rather precise

relation between the area cooled and the area in which the blood flow ceases" (p. 46), was immediately contradicted by his subsequent observations (17 - 21), where he found that if the fingers were kept warm and the rest of the hand was cooled, vasospasm still occurred in the warmed phalanges.

Furthermore, the alleged correspondence between area cooled and distribution of vasospasm, rather than evidence against the neurogenic theory, might well be taken as an additional proof that Lewis's patients were cases of organic vascular disease. To reverse an argument put forth by Lewis, it is to be expected that the normal vasoconstriction produced by a locally applied cold stimulus, or, for that matter, by generalized body cooling, would bring an organically diseased vessel, whose lumen is already reduced by intimal thickening, thrombus formation, etc., to a state of complete occlusion. Under these conditions the topographical distribution of vasospasm will lack the generalized appearance observed in functional cases, and will be determined not only by the size of the area cooled but also by the locus, extension, and severity of the lesion.

It will be clearly shown later that, if Lewis's local fault is equated with structural damage of the peripheral blood vessels, his conclusions are flawless. Interestingly, Lewis himself acknowledged that in his

milder cases local cooling often failed to produce the response pattern noted in the severer ones.

The observation that locally applied warm or cold stimuli produce an increase or decrease in cutaneous blood flow generally confined to the distal portions of the extremities has been frequently invoked by Lewis as irreconcilable with the neurogenic hypothesis. He argued that "reflex vasomotor impulses created by cold are known to be conveyed very widely" (p. 53), and cannot account for the rather specific and localized circulatory changes reported. The validity of his argumentation, nonetheless, vanishes when it is remembered that the arterio-venous anastomoses are most abundant in the apical regions of the limbs. Vasoconstrictor impulses affect maximally these specialized vascular structures which receive an exceptionally rich sympathetic innervation, and whose opening or closing can determine considerable variations in cutaneous blood flow.

The anatomical distribution of the arterio-venous shunts also provides an answer to another objection raised by Lewis, who claimed that the neurogenic theory could not explain the orderly and gradual involvement of the digits during an attack, which is generally characterized by a slow progression of vasospasm from the tips towards the more proximal parts. This is indeed

what should be expected from the distribution of the arterio-venous anastomoses, whose density decreases progressively in a distal to proximal direction (Grant & Bland, 1931; Wilkins et al., 1938).

A fundamental fallacy in Lewis's presentation is constituted by the assumption that he was testing the independent effect of local cooling on the peripheral circulation. Inspection of his report will reveal that the pertinent experiments, described in observations 16 to 21, were conducted at the following room temperatures: 19°C, 16°C, 16°C, 14.5°C, 15.3°C, 14.5°C, 13.5°C, 13-15°C, 13.7°C. When the body is exposed to these low environmental temperatures the vasomotor tone is heightened and, of course, peripheral vasoconstriction is to be expected. Cessation of blood flow, in other words, would have occurred at such low room temperatures even in the absence of local cooling.

This possibility could have been easily checked by inspecting the appearance of the untreated hand during those experiments in which only one hand, or part of it, was cooled. Unfortunately Lewis, usually very meticulous in describing his observations, in this case neglected to report about the state of the nontested hand. Absence of vasospasm in the hand left at room temperature would have obviously afforded considerable support to his thesis; his silence in this regard is therefore

at least puzzling. In the absence of direct evidence, the occurrence of vasospasm in the untreated hand must be postulated not only because it is indisputable that body cooling, by raising the vasomotor tone, has a powerful constrictor effect on the peripheral vascular bed, but also in view of the well-demonstrated phenomenon of reflex or indirect vasoconstriction, i.e., vasoconstriction in one hand as a result of cooling the other hand (Bader & Macht, 1948; Downey & Frewin, 1973; Lottenbach, 1966; Menzies, 1937; Pickering, 1932; Rai, Mathew, & Purkayastha, 1974). Indirect vasoconstriction, like indirect vasodilatation, is a centrally integrated event, mediated peripherally by sympathetic nerves.

Later in his paper, Lewis presented additional observations (31 - 33) on the vascular response to local cooling. As a result of these experiments, conducted at different room temperatures with the explicit objective of testing the effect of increasing or decreasing vasomotor tone, he had to recognize that, especially in the milder cases, body cooling is a very important factor, "spasm to obliteration occurring only at the lower room temperatures or being more quickly induced, more extensive, and longer lasting in these" (p. 81).

Certainly Lewis's ability to provoke vasospastic attacks "at will" in his patients simply by local cooling is in sharp contrast with the experience of many

frustrated clinicians unable to reproduce his success. The literature is rich with reports attesting the difficulty of inducing attacks of digital ischemia by local cooling and demonstrating the necessity of raising the vasomotor tone in order to produce vasospastic symptoms (Allen & Brown, 1932b; Burch & Phillips, 1963; Goetz, 1956b; Guntheroth, Morgan, Harbison, & Mullins, 1967; Hellstrom & Myhre, 1971; Morris, 1968; Shepherd, 1963, p. 279; Tsapogas, Kakkar, & Gleave, 1968, p. 78).

Relief of vasospasm by local heating. In support of his local fault hypothesis Lewis has also adduced the results of experiments on local heating. He found that vasospasm in the hand could be relieved and the circulation restored by locally warming the extremity. This occurred even in the presence of a high vasomotor tone, induced by low environmental temperatures. Moreover, spasm could be removed, or its occurrence prevented, only in the warmed hand and not in the other which was maintained at room temperature.

While these findings have been generally interpreted as strongly arguing against the neurogenic theory, in this author's opinion the evidence is not at all convincing. The demonstration that locally applied thermal stimuli, cold or heat, modify the state of the peripheral circulation, does not prove, in itself, that a local fault is the necessary etiological mechanism in

Raynaud's disease unless it could also be demonstrated that in cases with structurally normal digital vessels exposure of one extremity to a thermal stimulus brings about changes in blood flow which are confined exclusively to that part and are absent on the contralateral side.

The possibility of such validation, however, is denied by a firmly established physiological principle. It is known that locally heating one hand of a normal person will produce an increase in blood flow not only in the warmed hand but also in the other one. This indirect vasodilatation might be slightly delayed or reduced in magnitude, but it is still clearly observed in cases of Raynaud's disease, where the digital vessels are structurally normal; it will be appreciably impaired, instead, or it might even fail to occur within the specified temporal criterion in cases of organic arterial disease. Lewis's observation that cutaneous vasodilatation was present only in the heated hand and not in the contralateral one further strengthens the previously established conclusion about the diagnostic classification of his clinical cases.

Similar considerations apply to the study conducted by Hyndman and Wolkin (1942), who corroborated Lewis's findings after testing a case of digital ischemia clearly secondary to an arthritic disorder and

presenting abundant signs sufficient to exclude a diagnosis of Raynaud's disease (case 2 of their series).

It is apparent from this discussion that when the etiological element responsible for Raynaud's disease is investigated by studying cases of organic vascular disease, spurious evidence is easily obtained in favor of the local fault theory for the simple reason that in those cases a local fault does indeed exist, and can be conceived as marked reduction, or even total obliteration, of the vascular lumen resulting from structural changes within the vessels. The fallacy, then, lies in the generalization from these cases to functional ones, in which a local fault, as defined above, cannot be found.

The evidence reviewed earlier in this paper rather convincingly indicates that, although thermal stimuli can produce local effects on the blood vessels independently of the sympathetic innervation, those effects can be overcome by centrally integrated vasomotor reactions. In particular it was shown that, at least in normal individuals, the direct vasoconstricting action of intense cold stimuli can be counteracted and neutralized by keeping the body warm. It has been demonstrated that this central compensatory response also occurs in cases of Raynaud's disease, since vasospasm of the extremities can be relieved by warming the body (Gibbon

& Landis, 1932; Goetz, 1956a; Pearse, 1935). On the other hand, general body cooling can produce vasospastic attacks even in hands maintained very warm (Pearse, 1935; Simpson et al., 1930). Finally, in their study of the digital blood flow, Wilkins et al. (1938) determined that the vasodilatation induced in a finger by general body warming was larger than that resulting from locally heating the finger, the first method being almost as effective as the use of both methods combined.

All these findings are in evident conflict with Lewis's observations about the local effects of temperature, and reject his suggestion that a local cold stimulus could alone be sufficient to obliterate the lumen of structurally normal digital vessels.

Anesthetization of the Ulnar Nerve

Lewis has reported that cutting the sympathetic supply to the little finger by anesthetizing the ulnar nerve at the elbow did not prevent in that finger the occurrence of vasospasm, induced by local application of cold. In addition the nerve-blocking procedure virtually failed to relieve preexisting spasm in the little finger. He therefore concluded that vasomotor impulses could not be responsible for the observed circulatory arrest.

Simpson et al. (1930) repeated Lewis's anesthetization experiments on less severe cases, meeting Allen

and Brown's (1932a) requirements for a diagnosis of Raynaud's disease, and found that full vasodilatation, as witnessed by a cutaneous temperature of about 34°C, could be secured in the anesthetized region, where local application of cold failed to induce vasospastic manifestations. Similar results, documenting the remarkable vasodilator effects of vasomotor paralysis in every early uncomplicated case, were presented by White et al. (1952, p. 187), who explained Lewis's negative findings with his failure to anesthetize the median nerve in addition to the ulnar, the two nerves being often connected.

Warren and his associates (1942) demonstrated that blocking the sympathetic outflow produced a nearly maximal vasodilatation in the normal hands. Most indicative, however, are the findings reported by Mendlowitz and Naftchi (1959), who determined that indirect heating and blocking of the sympathetic ganglia brought about full peripheral vasodilatation only in cases of Raynaud's disease with structurally normal digital vessels, and not in patients with digital vascular obstruction.

The discrepancy between Lewis's observations and the results of the studies mentioned here can be readily interpreted in terms of a faulty diagnostic selection. It is again necessary to point out that the

anesthetization experiments were conducted by Lewis exclusively on cases 1 and 2, the most severe of his series, and for whom the diagnosis of Raynaud's disease is untenable. It is rather intuitive that in these cases release of vasoconstrictor tone by any of the available procedures--indirect vasodilatation, nerve block, sympathectomy--will not remove an organic interference to blood flow.

When considered in this context, Lewis's argument becomes equivalent to the paradoxical proposition that the way to test whether a causal relationship exists between vasomotor discharge and the vasospasm occurring in a condition, which, by definition, excludes the possibility of organic complications, is to study the vascular reactions of clearly diseased and obstructed vessels. Following this obviously false premise to its conclusion, it is then deduced that failure to restore a normal circulation upon removal of vasomotor tone proves that the primary factor in Raynaud's disease is a local fault and not a nervous derangement. Evident as it may appear, the tautologic and erroneous nature of this reasoning has remained essentially unchallenged for over 45 years.

Of course even in cases of organic arterial disease, if the vascular lumen is not completely occluded, release of vasoconstrictor tone should bring about some degree of cutaneous vasodilatation, the magnitude of

which will vary inversely with the extent of luminal obstruction. Indeed partial relaxation of the blood vessels in the anesthetized area was observed by Lewis, whose interpretation of the finding is consistent with a definition of the local fault as a structural abnormality of the digital vessels.

Sympathectomy of the Upper Extremities

Lewis has indicated that, as a necessary corollary of the neurogenic hypothesis, resection of the sympathetic supply to the digital blood vessels should bring about a complete and permanent relief of the vasospastic symptoms in the affected extremities. He argued that, while there is an immediate increase in cutaneous blood flow following the operation, the effects soon disappear and attacks can still be induced in the sympathectomized hand by local application of cold. Lewis maintained that the poor results of the surgical treatment, established by his review of clinical cases previously reported in the literature (Lewis, 1929), as well as by his personal observations (Lewis, 1938a; Lewis & Landis, 1930), once more indicated that in Raynaud's disease the primary fault lies in the blood vessels themselves, not in the nervous system.

The legitimacy of these conclusions rests upon the validity of two basic premises: first that therapeutic failures are not due to undetected organic vascular

disease since they are just as likely to occur in unequivocal cases of primary Raynaud's disease; and secondly that when failures do occur in the latter condition they are not attributable to technical difficulties such as incomplete denervation, regeneration of the severed fibers, or to postoperative complications. It will be shown here that both assumptions are false, and Lewis's inferences therefore unjustified.

Reasons for therapeutic failures following sympathectomy. (a) Faulty diagnostic selection. Even a cursory review of the cases presented by Lewis in support of his position will reveal that organic vascular disease was most probably responsible in those patients for the persisting circulatory impairment and the poor results of sympathetic denervation. In this regard the same considerations made earlier about the anesthetization experiments obviously apply here.

The value of sympathectomy, especially in relatively mild cases of Raynaud's disease, is well documented in the literature (Abramson, 1974, p. 236; Gifford, Hines, & Craig, 1958; Hines & Christensen, 1945; Johnston, Summerly, & Birnstingl, 1965; Kirtley, Riddell, Stoney, & Wright, 1967; Montorsi, 1974; Pickering, 1951; Simpson et al., 1930, 1931).

In their survey of 147 cases of uncomplicated Raynaud's disease Allen and Brown (1932b) reported excellent

results of sympathectomy in all but 17 of the operated patients. De Takats and Fowler (1962a, 1962b) indicated that, in their series, all eight denervations performed on patients with Rayanud's disease proved, without exception, very successful. Richards (1970, pp. 96-97) reviewed a number of previously published studies and found good results in about 50% of the 758 operations. The figure, however, is scarcely useful as the series was diagnostically mixed, including cases of both Raynaud's disease and secondary digital ischemia. Tsur, Adar, Bechor, Bogokowsky, and Mozes (1973) presented the results of 17 operations in 11 patients with Raynaud's disease and estimated a success rate of 88% when the therapeutic outcome was evaluated within two years of the surgery.

The value of sympathectomy, at least in cases of Raynaud's disease, is undeniable and was recognized even by Lewis (1949) who acknowledged that

> It has been shown beyond any doubt that sympathectomy greatly improves the circulation to the limbs in cases of Raynaud's disease. From the hands of mild cases it usually abolishes the attacks altogether. . . . more than enough effect remains fully to justify the operation in selected cases; both temporary and permanent results are often dramatic. From the simple standpoint of the vascular result the operation has everything to recommend it. (p. 79)

The widespread diagnostic confusion mentioned earlier in this paper, preventing a necessary

differentiation between a primary vasospastic disorder and digital ischemia secondary to other conditions, seems to account for a large number of therapeutic failures often reported following sympathetic denervation. It is readily evident that when organic changes supervene in the wall of the digital arteries prodigious results cannot be expected from the operation. This point has been emphasized by numerous investigators who have noted that sympathectomy is not indicated in cases of secondary digital ischemia (Allen & Brown, 1932b; Gifford, 1968; Gifford et al., 1958; Haxton, 1970; Lynn, Steiner, & Van Wyk, 1955; Peacock, 1969; Porter, Snider, Bardana, Rösch, & Eidemiller, 1975; Simpson et al., 1930; Spurling, Jelsma, & Rogers, 1932).

The diagnostic difficulty is particularly serious when digital ischemia is secondary to scleroderma, since the vasospastic symptoms alone may precede the full manifestation of the disease by several years (Fiessinger & Housset, 1975). According to de Takats and Fowler (1962a, 1962b) as many as 16 years may separate a diagnosed scleroderma from the early characteristic digital color changes which, occurring in isolation, often lead to the erroneous diagnosis of Raynaud's disease. De Takats and Fowler have pointed out that when these patients are operated the results are invariably unfavorable. In their series the group of collagen disease

exhibited the poorest response to sympathetic denervation; of the 14 operations performed none was successful. Therapeutic failures, they suggested, can be virtually eliminated by an accurate case selection aimed at excluding cases of unrecognized collagen disease from the surgical treatment. Their conclusions have been more recently substantiated (Gifford, 1971; Richards, 1970, p. 97; Tsur et al., 1973).

Although, on purely theoretical grounds, sympathectomy is chiefly indicated for cases of Raynaud's disease, these patients, presenting only relatively mild symptoms, actually constitute the smallest fraction of the operated population. Because of its radical nature the surgical approach is more often adopted in cases with longstanding and incapacitating symptoms, for whom all other treatment modalities have failed, and whose severe nutritional disturbances suggest the presence of organic vascular changes (Abramson, 1974, p. 236; Hines & Christensen, 1945; Gifford, 1971). While these selective criteria are reasonable, they may entail a high failure rate which should not be construed as evidence against the neurogenic theory.

It is known that sympathectomy may prove quite helpful in cases of nonprogressive occlusive arterial disease (Abramson, 1974, pp. 411-415; de Takats & Fowler, 1962a, 1962b; Jepson, 1951; Johnston et al., 1965).

This is to be expected since denervation relaxes the smooth muscle and causes a substantial increase in vascular caliber which, in many cases, might be sufficient to relieve the circulatory impairment and to reestablish an adequate nutritional flow. As noted with respect to the nerve-blocking procedure, however, the magnitude of the vasodilatation and the degree of clinical improvement depend on the severity of the obstruction and also on the adequacy of the collateral circulation. Under these circumstances postoperative failures should be explained on the basis of the local pathology and pose no difficulty to the neurogenic theory of Raynaud's disease.

In addition to the presence of undetected organic vascular disease, other important factors limiting the successful use of upper limb sympathectomy must be considered.

It is generally agreed that within five years of the operation vasomotor control of the digital vessels is reestablished in most cases (Birnstingl, 1968, 1971; Strandness, 1969, p. 276). It seems possible to distinguish an early recurrence of sympathetic activity, which in a matter of a few weeks reaches values close to the preoperative level (Barcroft, 1952; Barcroft & Walker, 1949), and a late return, which in the majority of cases can be demonstrated both clinically and by

means of appropriate tests about two years after surgery (Birnstingl, 1971; Haxton, 1970; Richards, 1970; 1972, p. 96). While the former can be attributed to incomplete denervation and to postoperative sensitization of the blood vessels to circulating catecholamines, the latter type of relapses is most likely due to regeneration of the sympathetic fibers.

(b) Incomplete denervation. In the upper extremities incomplete denervation is not a rare event (Abramson, 1956; 1974, pp. 409-410; Raynaud & Raynaud, 1967; Strandness, 1969, p. 276; White et al., 1952, pp. 196-197). There is still considerable disagreement not only about the range of thoracic segments from which the preganglionic fibers leave the cord, but also regarding at what level of the sympathetic chain synaptic connections occur between pre and postganglionic fibers. Anatomical variations and the development of alternative sympathetic pathways by way of a secondary vasomotor system (Spurling et al., 1932) or intermediate sympathetic ganglia (Boyd, 1957) have been proposed to explain the residual vasomotor activity sometimes demonstrable shortly after surgery.

(c) Sensitization of the denervated vessels to catecholamines. Freeman (1935) indicated that even when a complete denervation is achieved, body cooling could still produce a marked reduction in blood flow not only

in the normally innervated hand but also in the sympathectomized one. In keeping with earlier reports (Freeman, Smithwick, & White, 1934; Smithwick, Freeman, & White, 1934) he presented evidence that the returned vasoconstriction in the operated extremities was due to a heightened sensitivity of the peripheral vessels to adrenal secretion.

There is now nearly universal agreement that in the denervated vascular smooth muscle hypersensitivity to epinephrine and norepinephrine does indeed develop in the early postoperative period. The phenomenon can be demonstrated both after pre and postganglionic sections, although some investigators (Haxton, 1970; White et al., 1952, p. 189) have maintained that it is less evident following preganglionic procedures.

The sensitization to circulating catecholamines, which constrict the cutaneous vessels by acting on the alpha receptors of the vascular smooth muscle, has been linked with the degenerative process in the severed fibers (Shepherd, 1963, p. 82).

(d) Regeneration of sympathetic fibers. Another postoperative complication precluding lasting clinical gains is regeneration of the cut fibers. Vasomotor control returns, with time, no matter how extensive the excision and regardless of the surgical technique adopted. Haxton (1970), however, has shown that nervous

connections are reestablished sooner after preganglionic sympathectomy than following cervicothoracic ganglionectomy. White et al. (1952, pp. 200-201) found that not even a second or a third operation, intended to sever again the regrown fibers, could avert the occurrence of further regeneration. They concluded that "in some cases it seems almost impossible to prevent regeneration of vasoconstrictor fibers" (p. 201).

Murray and Thompson (1957) have proposed collateral axonal sprouting as an alternative explanation for the regained vasomotor activity after smypathectomy. The phenomenon, occurring in all nervous tissue, is a response of neighboring intact fibers which give off thin branches in the presence of adjacent degenerating nerve fibers. The eliciting stimulus for the sprouting is probably a chemical agent released by the degenerating axons.

Haxton (1970), on the other hand, has presented strong evidence that the basic factor responsible for clinical relapses is regeneration of the excised sympathetic fibers themselves, which slowly grow back to reestablish functional connection with the denervated effector organ.

Return of sympathetic activity and local fault. The various mechanisms by which vasomotor tone is reinstated are not mutually exclusive and may occur in

any combination, thus explaining the different degrees and time intervals characterizing the recovery of vasoconstrictor activity in the denervated upper extremities.

It should be abundantly clear from this review that there is no need to postulate, as Lewis did, a postoperative persistence of the local fault to account for therapeutic failures, since well-founded and certainly more plausible explanations are available both for the early and late relapses observed clinically.

In this regard it should be noted that from Lewis's viewpoint it is conceptually difficult to understand why, although "in the period directly following operation, the effects of the treatment were striking. . . . The full vasodilatation seen on the day after operation is not maintained . . . the decline occurring gradually over a period of about a week" (Lewis, 1938a, pp. 333, 335). Since a local fault is not in the least affected by sympathectomy and no time interval needs to elapse before its return, it should continue to produce its pathological effects immediately after the operation just as it did before, thus it cannot account for the symptomatic relief seen right after surgery nor for the gradual deterioration which follows.

While recognizing that a prompt clinical improvement invariably follows sympathetic denervation, as well as nerve block, Lewis (1929; 1932; 1938a; 1949,

p. 79) minimized the implicit threat presented to his views by arguing that such finding was not incompatible with the local fault notion and it was indeed to be expected since those procedures remove a normal vasoconstrictor tone, which is only one determinant of the state of the peripheral circulation. Simply interrupting the sympathetic outflow to the digital vessels, he maintained, cannot produce complete and lasting results because it leaves unaltered the local component which is at fault and which, in the final analysis, makes the difference between normal individuals and patients with Raynaud's disease.

This rather convenient reasoning, however, still fails to account, as Freeman (1935) cogently pointed out, for the wearing off of the beneficial results achieved by sympathectomy. The question of why vasoconstriction gradually returns, with time, in the denervated extremity remains unanswered unless recurrence of sympathetic activity, by any of the mechanisms outlined above, is assumed.

One final point to consider, and one that is most difficult to explain by Lewis's concept, is the undisputed finding that vasospastic symptoms in the lower extremities are completely and permanently relieved by lumbar sympathectomy (Gifford et al., 1958; Hyndman & Wolkin, 1942; Lewis, 1949, pp. 79-80; Peacock, 1960b,

1969; Richards, 1970, p. 95; Simpson et al., 1930, 1931; Spurling et al., 1932). It is not readily apparent why the local fault should disappear postoperatively from the lower limbs while it is so obstinate in the upper extremities. Neither can it be assumed that two different mechanisms, a neurogenic disorder and a local fault respectively, operate in the two cases.

The dissimilar therapeutic results are rather due to the minimal technical difficulties presented by lumbar sympathectomy. No ambiguity exists regarding the anatomical distribution of vasomotor fibers to the feet and complete denervation is therefore easier to achieve (Abramson, 1956; Atlas, 1956). Moreover postoperative sensitization to vasoconstrictor substances is a much less frequent complication in the lower extremities (Abramson, 1956). It can be seen that, when total and lasting removal of the pathological element, i.e., an exaggerated vasoconstrictor tone, is made possible, excellent clinical results are obtained.

Nature of the Local Fault

Is the local fault just a theoretical construct? If not, what is its physio-anatomical nature? How does it come about? These legitimate questions present themselves most insistently to the reader's attention after a review of Lewis's work. Unfortunately Lewis dedicated very little space in his writings to clarify a concept

which after all was the basic tenet of his challenge to the traditional neurogenic theory of Raynaud's disease. Moreover, whatever information he did provide is so unclear that still today it is not possible to give a simple answer to the above questions.

Although in the current literature abundant references to Lewis's local fault can be found, attempts to define the term, or even to speculate as to its meaning, have been significantly lacking. It is indeed the amgibuity of Lewis's position that has made it advisable to devote a good portion of this paper to a review of the physiology of the peripheral circulation and of the basic mechanisms controlling it, in the attempt to exhaustively consider all those factors which might be identified with the local fault.

It is interesting to note that in his 1929 extensive report Lewis presented with great detail the experimental evidence he had gathered against the vasomotor theory and in support of the conclusion that the circulatory aberration needed to be local, but he spent no more than half a page to discuss what the nature of this local fault might be. There he simply suggested that it consists of "an abnormality of the digital arteries . . . [which] displays itself in hypersensitivity of these vessels to relatively low temperatures" (p. 90). He tentatively implicated the vessel wall but refused

to analyze further the essence of this local abnormality. No less amgiguous is the summary section of the same paper, where it is stated that the pathological element is not nervous in origin but rather "is a direct reaction and due to a peculiar condition of the vessel wall locally" (p. 98).

Later Lewis (1932) expanded his initial formulation of the local fault to make it more adherent to the patient population he had been studying. "It is here to be pointed out," he wrote, "that the local fault may be theoretically of either one of two kinds. It may be due to structural change in the arteries involved, or it may be due to these vessels reacting more powerfully to such a local stimulus as cold" (p. 137). The important implications of this explicit equivalence of organic vascular disease with the local fault have been repeatedly pointed out earlier in this paper and need no further comment here.

This dual conception of the local fault was retained in Lewis's subsequent work (Lewis, 1938a, 1938b, 1949), but with a shift in emphasis which reflected a sharpened awareness on his part of the diagnostic heterogeneity present among the clinical cases he had been describing.

As a result of a well-controlled study, Lewis (1938b) finally provided a lucid differentiation between primary and secondary vasospastic disorders. Post mortem

comparison of the digital arteries of warm-handed individuals with those of people who had suffered vasospastic symptoms, permitted Lewis to divide the latter group into two categories: cases of "intermittent spasm with local nutritional changes" (p. 302), for whom post mortem examination revealed obstructive disease of the digital arteries, which "may be regarded as constituting what I have previously termed the 'local fault'" (p. 306); and "cases of intermittent spasm of the digital arteries, exemplified by the mildest form of so-called 'Raynaud's disease'" (p. 310). In this second group no nutritional changes were present, no structural disease was discovered, and the vasospastic attacks were attributed by Lewis to "over-action of the muscular wall" (p. 310).

Lewis's insightful distinction brings to mind a similar one enunciated years later by Jepson (1951), and even more explicitly by Mendlowitz and Naftchi (1959), who found that patients with digital ischemia fell in two groups: one with digital vascular obstruction and normal vasomotor tone, and a second group with no organic obstruction but with a heightened vasomotor tone. Mendlowitz and Naftchi pointed out that vasospastic attacks could, therefore, be produced either by organic vascular obliteration or by an exaggerated neurogenic vasoconstrictor activity.

It would seem that Lewis's position, as it transpires from his late writings, was not very distant from those conclusions. It is particularly significant that the second type of local fault, which he had previously defined as a hypersensitivity of the blood vessels to cold, began to lose much of its original emphasis. Although Lewis (1938a) continued to maintain that vasospastic attacks "are due primarily to a local fault; this may consist," he added, "of occlusive structural disease, or it may not. In the latter case the digital vessels appear to present increased susceptibility to cold, the reason for which still remains obscure" (p. 336).

Finally, in the second edition of a posthumously published book on the peripheral vascular disorders it is possible to read that "where, as in the milder cases, no unusual [intimal] thickening can be discovered after death, it is certain that abnormally high tone must develop in the artery to close it" (Lewis, 1949, p. 72). If the diagnosis of Raynaud's disease is restricted only to those uncomplicated cases, as it should be, Lewis's conclusions are tantamount to an endorsement of the neurogenic position.

It is quite evident that when Lewis's thinking is followed in its evolution, the local fault concept becomes more and more synonimous with organic vascular

disease, which is to be expected as most of Lewis's patients carried that diagnosis. Naturally, to determine that a structural abnormality of the vessels is a local fault is a demonstration of the obvious: If blood flow is obstructed by a clot, or if the vascular lumen is reduced by intimal proliferation or by other structural changes, there is little doubt that the fault is local.

When the local fault is defined as structural disease Lewis's findings, although trivial, are indisputable, but cannot be generalized to a condition like Raynaud's disease where such structural abnormalities do not exist. When this latter entity is considered, it is sufficiently clear that Lewis has been unable to provide convincing evidence for an etiological mechanism consistent with his local fault hypothesis. It is indeed for these cases of Raynaud's disease that the neurogenic theory can offer a sensible pathogenetic explanation, the evidence for which will be examined in the next section.

The Neurogenic Theory

It is generally recognized that the most forceful arguments against the concept of a nervous causation of Raynaud's disease were those advanced by Lewis and thoroughly examined in the preceeding pages. In the course of this paper the validity of Lewis's objections

has been strongly questioned and the determinant role of the vasomotor nerves has been, as a consequence, implicitly recognized. More direct evidence in favor of the neurogenic hypothesis, however, is available and will be presented here.

Vasospastic Phenomena in Normal People

Nervous mechanisms exert such a powerful vasoconstrictor influence on the vascular bed that the peripheral circulation can be brought to complete arrest even in normal individuals (Fox, 1968; Greenfield & Shepherd, 1950; Magos & Okos, 1963; Mufson, 1944). Contrary to Lewis's (1949, pp. 63, 70) claim, Hunt (1936) showed, as a result of experiments conducted on himself, that total cessation of cutaneous blood flow can be produced in the extremities of normal people when the body temperature is sufficiently lowered; a finding which is incompatible with Lewis's belief that a local fault is required for complete circulatory arrest to occur.

If such a degree of neurogenic peripheral vasoconstriction can be induced in normals who have no local fault, it seems much more parsimonious to assume that the same nervous factor, abnormally exaggerated this time, operates in patients with Raynaud's disease, rather than invoke in the latter case a new independent mechanism, i.e., a local fault.

It should also be mentioned, incidentally, that

the characteristic bilaterality and symmetry of the vasospastic manifestations, pointed out for the first time by Raynaud and now universally accepted as necessary criteria to make a diagnosis of Raynaud's disease, remain rather difficult to explain unless a neural origin is recognized.

Association of Vasospasm with Neurological Disorders

The occurrence of vasomotor symptoms in a variety of neurological conditions has been traditionally interpreted as confirming the neurogenic basis of vasospasm. While in many of these cases the peripheral circulatory insufficiency can still be considered as a sign of the underlying nervous derangement, in several other instances alternative explanations have been proposed.

In the neurovascular compression syndromes, for example, the vasomotor concomitants seem best explained by the formation of digital emboli and not, as previously thought, by irritation of the sympathetic nerve (McGrath & Penny, 1974). Similarly, in all those neurological disorders resulting from a lesion of the motor neuron the reduced blood flow observed in the paralyzed limb is most likely due to prolonged immobility and disuse of the part (Shepherd, 1963, pp. 340-342).

Vascular Effects of Emotional Stimuli

A very powerful line of evidence in favor of the neurogenic theory of Raynaud's disease is represented

by the abundantly demonstrated notion that emotional states, and especially anxiety, exert a profound influence on a variety of vegetative functions. It is well-known that cold is not the only stimulus eliciting a peripheral vasoconstrictor response, and the prominent role of emotional stress in the precipitation of the vasospastic crises occurring in Raynaud's disease has been clearly documented (Craig, 1944; Grace and Graham, 1952; Mittelmann & Wolff, 1939; Neumann, Lhamon, & Cohn, 1944; Peacock, 1958a). The importance of psychogenic factors in Raynaud's disease has been so unequivocally established that both psychotherapy (Ingvarsson, 1952; Millet, 1956; Millet, Lief, & Mittelmann, 1953) and sedatives or tranquilizers (Raynaud & Raynaud, 1967) have been recommended as valuable therapeutic approaches. Some authors (Graham, 1955, 1972; Mufson, 1944) have also attempted to identify the precise nature of the emotional experience underlying the circulatory disorder.

Peripheral vasoconstriction in response to emotional stimuli is a normal reaction mediated by the sympathetic nerves, but it is so exaggerated in cases of Raynaud's disease that it may precipitate an attack even in a warm environment. It is certainly not easy to explain these reflex vascular phenomena on the basis of a local fault.

Raynaud's Disease: Exaggeration of a Normal Reaction to Vasoconstricting Stimuli

The intensity and duration of the circulatory response to cold and emotional stress vary considerably among individuals and show a tremendous range, at one end of which is the person with a reduced vasomotor tone, warm and dry extremities, while at the other extreme of the continuum is the patient with Raynaud's disease exhibiting clammy hands and feet and a marked vascular reactivity to vasoconstricting stimuli (Abramson, 1974, p. 214; Edwards, Ottinger, & Ruberti, 1959; Halpern, Kuhn, Shaftel, Samuels, Shaftel, Selman, & Birch, 1960; Holling, 1972, pp. 140, 145; Marshall & Gregory, 1974; Naide & Sayen, 1946).

Consistent with this view are those studies suggesting an abnormally longer temperature recovery time following cold exposure in cases of Raynaud's disease (Charles & Carmick, 1970; Edwards et al., 1959; Halpern et al., 1960; Porter et al., 1975).

Peacock's (1959a, 1959b, 1960a) findings are also interpretable in this context. He has shown that not only in cases of secondary digital ischemia with nutritional changes but also in patients with Raynaud's disease the peripheral blood flow, measured under normal resting conditions and in a neutral thermal environment, is much lower than in normal controls. Similar findings

have been reported by Goetz (1956b) and by Willerson, Thompson, Hookman, Herdt, & Decker (1970). As Willerson and his collaborators (1970) have cogently pointed out, a considerable reduction in hand blood flow under normal conditions may indicate either the presence of organic vascular disease or it might be the result of a heightened vasomotor tone. The second alternative seems to apply to cases of Raynaud's disease, as Peacock (1958b) demonstrated that in these patients a normal circulation could be reestablished following removal of sympathetic vasoconstrictor tone by body heating.

The results of all these studies are in keeping with the notion that in Raynaud's disease neurogenic vasospasm is the clinical manifestation of a high tonic level of sympathetic discharge which determines an exaggerated vascular response to all vasoconstricting stimuli, especially cold and emotional stress.

Individual Differences in Autonomic Reactivity and Sympathetic Dominance

The idea that the intensity of sympathetic vasoconstrictor tone may so vary in different people that in some might be heightened enough to be pathological, is more than just a convenient notion offered by the proponents of the neurogenic theory of Raynaud's disease. The general concept of individual differences in autonomic reactivity is not only a basic assumption

in psychosomatic medicine, but is so well established that sound psychophysiological research cannot avoid taking it into account (Lykken, 1968, 1975).

Particularly relevant to this discussion is Wenger's concept of "autonomic balance," which he has studied with admirable tenacity for many years. He has provided two excellent reviews of this work (Wenger, 1966; Wenger & Cullen, 1972), the latter of which exhaustively covers a period of 30 years. Already Eppinger and Hess (1917) had proposed that many pathological conditions, classified today under the psychosomatic disorders, might be the result of an imbalance between the antagonistic functions of the sympathetic and parasympathetic divisions of the autonomic nervous system. After studying the physiological responses of many individuals and their reactions to various drugs they concluded that people show different degrees of dominance of one autonomic branch over the other, that is, different degrees of autonomic imbalance. To account for these differences Eppinger and Hess introduced the concepts of sympathicotonia and vagotonia, denoting a state of hyperactivity of the sympathetic and parasympathetic systems respectively.

In order to test this intriguing notion Wenger recorded several physiological responses on the basis of which "scores of autonomic balance" could be assigned

to each individual; low scores indicating sympathetic dominance and high scores parasympathetic dominance. Marked differences in autonomic reactivity were found in children and in adults, males and females. Such differences were in general normally distributed around a mean value which was taken as an expression of autonomic balance.

Although other mixed patterns were later discovered by Wenger, it is of interest here to note that the pattern of sympathetic dominance occurred with the highest frequency both among psychoneurotic patients and in a group of normal students experiencing high levels of pre-examination anxiety, and who exhibited instead a pattern of autonomic balance one month before or after the examination. Wenger (1972) concluded that "these results provide further support for the belief that SNS activity is particularly prominent in anxiety and fear" (p. 566).

The implications of these findings for psychosomatic medicine and the related issue of autonomic response specificity exceed the scope of this paper, and the reader is referred to Graham's (1972) comprehensive review.

Association of Vasospasm with Other Clinical Indicators of Sympathetic Hypertonus

The hypothesis which postulates a state of

sympathetic hyperactivity as the primary etiological factor in Raynaud's disease seems further supported by the occurrence in those patients of other signs of a heightened sympathetic discharge and by a frequent association of the circulatory impairment with a variety of other psychosomatic disturbances.

The combination of hyperhidrosis with vasospastic symptoms in Raynaud's disease is of particular interest since it points directly to an hyperactive state of the sympathetic nerves which carry both vasomotor and sudomotor fibers to the same skin area (Abramson, 1974, p. 218; Richards, 1970, p. 92; Simpson et al., 1930; White et al., 1952, pp. 180, 189).

The association of Raynaud's disease with hypertension and migraine is also significant and it has led some authors to hypothesize the presence of a common causal element such as a generalized increase in peripheral vascular resistance (Allen et al., 1972, p. 186; Blain, Coller, & Carver, 1951; Langeron & Croccel, 1960, pp. 89-91; McGrath & Penny, 1974; Montorsi, 1974; Mendlowitz, 1954, p. 97). In many respects the controversy regarding the etiology of Raynaud's disease appears to parallel the dispute about the mechanism of essential hypertension, a closely related condition where the neurogenic element is now recognized to be more than just a myth (De Quattro & Miura, 1973).

Furthermore the occurrence in patients with Raynaud's disease of other functional symptoms, such as tachycardia, dysmenorrhea, insomnia, diffuse aches, and a variety of gastro-intestinal disturbances, suggests in these people a high level of anxiety and emotional instability which parallels the lability of their vasomotor system (Allen & Brown, 1932b; de Takats & Fowler, 1962a, 1962b; Gifford & Hines, 1957; Goetz, 1956b; Hines & Christensen, 1945; Mufson, 1944).

This clustering of functional symptoms has suggested the possibility of identifying in patients with Raynaud's disease a particular psychological make-up or personality structure. Altschule (1953) has abundantly documented the effects of psychogenic factors on the peripheral circulation and has also pointed out the high incidence of cold moist hands, indicating an exaggerated vasomotor activity, among neurotic patients, and especially in cases of hysteria (see also Millet et al., 1953; Peet & Kahn, 1936).

The frequency with which these psychophysiological characteristics are found in cases of Raynaud's disease would actually be much higher than that reported in the literature if one could eliminate not only the diagnostic confusion between primary and secondary vasospastic disorders, but also the physician's unwillingness or lack of sophistication in exploring the psychological basis

of physical symptoms, as well as the patient's reluctance to expose sensitive areas of his emotional life.

It seems worthwhile mentioning that the present interest in the genetic basis of psychological traits and physiological response patterns is in keeping with the long-recognized importance of hereditary factors as contributors to the development of a vasomotor instability (Gifford & Hines, 1957; Goetz, 1956b; Guntheroth et al., 1967; Langeron & Croccel, 1960; Peacock, 1958a, 1969). The familial tendency underlying vulnerability to vasospasm had been so repeatedly noted that Hunt (1936) described "hereditary cold fingers" as a separate nosological entity. This condition, however, is now regarded as a mild form of Raynaud's disease, differing from it not in the nature of the primary pathological process but merely in degree (Wade, 1965).

Neurochemical Basis of Sympathetic Hypertonus

Neuropharmacological investigations on the vascular effects of chemical agents, particularly sympathomimetic like the catecholamines and sympatholytic, which facilitate or inhibit respectively adrenergic transmission, have further elucidated the determinant role played by the sympathetic nervous system in the control of the peripheral circulation, and have offered reasonable suggestions as to the nature of the neural derangement underlying the primary vasospastic disorders. The

results of those studies can be, therefore, adequately integrated into the neurogenic theory of Raynaud's disease.

The catecholamine hypothesis. It is presently believed that the level of catecholamines in the urine or plasma gives a good estimate of sympathetic activity (Gunn, Wolf, Block, & Person, 1972). Some reports have recently appeared indicating increased catecholamine levels in the blood of patients with essential hypertension (De Quattro & Chan, 1972; Engelman & Portnoy, 1970; Louis, Doyle, & Anavekar, 1973).

Peacock (1959b) measured the concentration of epinephrine and norepinephrine in the venous blood collected at the wrist in cases of Raynaud's disease and in normal controls. He found higher levels of circulating catecholamines in the patient group both under warm resting conditions and especially during cold-induced reflex vasoconstriction. Most remarkable was the increase in the norepinephrine fraction which appeared to parallel the clinical severity of the disease.

Peacock suggested a causal relationship between this increased production of epinephrine and norepinephrine and the heightened vasomotor tone indicated in patients with Raynaud's disease by lower than normal hand blood flow values. He tentatively attributed the elevated concentrations of vasoconstrictor substances

to an impaired monoamine oxidase function, which is necessary for the metabolic destruction of the circulating amines. In support of this interpretation he showed that no monoamine oxidase could be detected in the digital arteries obtained from the amputated finger of a patient with digital ischemia most probably secondary to organic disease, while a normal monoamine oxidase activity was present in the digital arteries taken from fingers amputated for nonvascular reasons.

This suggestion was corroborated by Halpern and his associates (1960) who studied the intensity and duration of the vasospastic response to a cold stimulus in patients with Raynaud's disease following intravenous injection of iproniazid, a monoamine oxidase inhibitor. Administration of the drug before the cold stress produced much more severe and prolonged attacks of digital vasospasm, which the investigators ascribed to inhibition of the metabolic oxidation of the vasoactive amines with a consequent increase in their local concentration.

The validity of Peacock's conclusions has been challenged, and the possibility has been suggested that the higher concentrations found in cases of Raynaud's disease could have been an artifactual result of the reduced blood flow which Peacock had found in these parients (Birnstingl, 1971; Burch & Phillips, 1963;

Kontos & Wasserman, 1969).

Kontos and Wasserman (1969) replicated Peacock's study and reported no statistically significant differences in the arterial or venous catecholamine levels in patients with Raynaud's disease as compared to normal controls. Their results have been emphatically interpreted as decisively rejecting Peacock's catecholamine hypothesis (Birnstingl, 1971; McGrath & Penny, 1974; Sapira, Rodnan, Scheib, Klaniecki, & Rizk, 1972). Such conclusions, however, will appear to be at least overstated upon careful inspection of Kontos and Wasserman's findings.

While in the method section of their paper they indicated that 11 cases of Raynaud's disease and 6 normal volunteers were studied, data on the amine levels are presented only for 9 patients and 5 controls, and nothing is said about the 3 excluded subjects. With a sample size as small as they used a test of significance is not very meaningful, and the practice of subjecting to statistical analysis data derived from such exiguous samples is highly objectionable. When Kontos and Wasserman's results are interpreted with these considerations in mind they seem to support, rather than refute, Peacock's thesis. Although the differences fail to reach statistical significance, both venous and arterial concentrations of epinephrine and norepinephrine

were consistently from two to three times higher in the Raynaud's group than in controls.

Another factor which may have contributed to produce lower catecholamine concentrations than Peacock had reported is the fact that in Kontos and Wasserman's study as many as 5 patients had ulcerations of one or more fingers and thus, by the authors' own admission, there remains the possibility of "structural changes in the blood vessels of the hand which are known to occur in patients with this disorder, especially when they have ulcerations" (p. 265). In these cases there is no reason to expect an abnormally high level of neurohumors since the vasospastic phenomena can be explained on an organic basis.

Analogous considerations apply to a study by Sapira et al. (1972), who were also unable to find any significant increase in catecholamine concentrations either in the venous blood or in the urine of patients with digital ischemia secondary to scleroderma. Of the several criticisms which Sapira and coworkers have moved to Peacock's hypothesis only one seems legitimate. While the details of their argumentation will not be reproduced here, it suffices to say that they have presented convincing evidence that a deficiency in monoamine oxidase activity cannot account for a rise in catecholamine levels. It would be erroneous, however,

to infer from their findings a total invalidity of Peacock's neurochemical hypothesis. The suggestion of a monoamine oxidase deficiency was introduced only as a speculative explanation by Peacock and was not a necessary assumption in his formulation.

Other interpretations, still compatible with Peacock's findings, are available, the simplest being, of course, the idea that an abnormally high discharge rate of the sympathetic nerves in response to cold or emotional stimuli might result in overproduction of catecholamines and especially of norepinephrine, which happens to be the neurotransmitter released by the postganglionic nerve endings at the neuroeffector junction. This concept is particularly appealing since it would also explain those personality characteristics and psychophysiological response patterns attributed to patients with Raynaud's disease and discussed earlier in this paper.

Therapeutic value and mechanism of action of antiadrenergic agents. When the contribution of pharmacological treatment approaches to the control of vasospastic crises is considered, it is quite evident that the most promising possibilities are offered by those drugs which are known to inhibit adrenergic activity; a conclusion certainly congruent with the neurogenic theory of Raynaud's disease and with its neurochemical

correlates outlined above.

Methyldopa (Varadi & Lawrence, 1969), guanethidine (Kontos & Wasserman, 1969; Porter et al., 1975), and especially reserpine (Gifford, 1971; Peacock, 1960b; Romeo, Whalen, & Tindall, 1970; Tindall, Whalen, & Burton, 1974) have proved to be of considerable therapeutic value in the treatment of Raynaud's disease or secondary digital ischemia.

Willerson et al. (1970), and Willerson and Decker (1971) have confirmed the excellent results of intra-arterial reserpine and have in addition pointed out that the poor response to the drug shown by some patients was probably attributable to the presence of substantial organic vascular disease which precluded the potential benefit of reducing the neurogenic influence. Brachial arteriography supported this suggestion by revealing unequivocal signs of organic occlusion in 2 of the 3 nonresponders.

While the great majority of the investigators seems to agree that the beneficial effects of reserpine are primarily due to its catecholamine-depleting action, some authors (Sapira et al., 1972) have indicated that just as important might be depletion of endogenous serotonin, which is liberated as a result of blood platelets destruction during vasoconstriction (Cécile, Bertram, & Bonte, 1968; Montorsi, 1974).

The relative contribution of serotonin and of the sympathetic amines epinephrine and norepinephrine to the pathophysiology of the vasospastic conditions has been carefully studied by Halpern and his collaborators (1960). These researchers investigated the vascular effects of serotonin not only by injecting the drug directly into the brachial artery of patients with Raynaud's disease and secondary digital ischemia and of normal controls, but also by observing the response to UML-491 (1-methyl-D-lysergic acid butanolamide), a powerful serotonin antagonist, and to iproniazid, a monoamine oxidase inhibitor which prevents the metabolic destruction of serotonin and of other vasoactive amines. Stellate ganglion block and intravenous injection of Hydergine, an ergot alkaloid with a potent sympatholytic action, permitted them to study the role played by the sympathetic nervous system and its interaction with serotonin.

Intraarterial infusion of serotonin evoked the expected marked peripheral vasoconstriction and produced, even in normal subjects, a conspicuous vasospastic symptomatology. However, a paradoxical vasodilatation after administration of the drug was also observed. Halpern and his colleagues concluded that serotonin has a dual action which is dependent upon the relative state of contraction or relaxation of the vascular bed; in other

words, the drug constricts vessels that are already dilated and dilates constricted ones, the nature of the response being therefore primarily determined by the intensity of the sympathetic vasomotor tone.

This antagonistic relation between serotonin and the sympathetic amines, according to the authors, serves the important homeostatic function of correcting eventual deviations from a state of vascular balance. In this sense serotonin is considered as a "buffering system" which exerts a modulating influence on the vasoconstricting action of endogenous epinephrine and norepinephrine. Disruption of this equilibrium, aggravated by a monoamine oxidase deficiency, has been proposed by Halpern and coworkers as the basic mechanism responsible for the vascular changes occurring in Raynaud's disease.

In his comprehensive review of the antihypertensive drugs, Frohlich (1974) has clearly indicated that sympathetic activity can be pharmacologically inhibited at different neural levels, so that it is possible to distinguish: (a) drugs with a central effect, acting on hypothalamic or brain stem centers; (b) ganglion blocking agents, which prevent transmission of the nerve impulse to the postganglionic neuron; (c) postganglionic sympathetic inhibitors, which hinder effective neuromuscular synaptic transmission and which include drugs interfering with the byosynthesis of norepinephrine or

with its reuptake, catecholamine depletors, false neurotransmitters; and finally (d) alpha receptor blocking agents which compete with norepinephrine for the receptor sites.

Whatever the precise mechanism of action of the drugs previously mentioned, there is no question that their ability to inhibit sympathetic activity, regardless of the neural level at which that inhibition takes place, is at the very basis of their therapeutic value in the management of Raynaud's disease. This point has been stressed quite clearly by Porter who has observed that "whatever the stimulus for vasospasm . . . the final common pathway appears to be through the sympathetic neuromuscular synaptic end plate. Any drug which alters end plate transmission appears to result in clinical benefit in these patients" (Porter et al., 1975, p. 22).

If pharmacological inhibition of sympathetic discharge relieves vasospastic symptoms, administration of a sympathetic stimulant should be expected to produce the opposite effects, namely reduction in blood flow and peripheral circulatory insufficiency. This does indeed happen and the physician is usually cautioned against such possibility when he prescribes sympathomimetic drugs which have found therapeutic applications in numerous conditions such as hypotension, asthma,

nasal congestion, and various allergic disorders.

Sympathetic Hypertonus and Critical Closing Pressure

In order to clearly understand how an exaggerated vasomotor tone can bring the peripheral vessels to a state of complete closure, which is clinically evidenced in the vasospastic crises occurring in Raynaud's disease, the concept of "critical closing pressure" must be briefly discussed.

From Laplace's law, which expresses the physical equilibrium in elastic tubes, Burton (1951) predicted that if the transmural pressure, that is the pressure difference across the wall of a vessel, falls below a given critical value, the vessel will close completely and blood flow will cease. The transmural pressure can be reduced either by a decrease in intraluminal pressure or by an increase in active wall tension as determined by the tone of the smooth muscle, which in turn depends primarily upon the sympathetic innervation. The second factor naturally plays a predominant role in closing the very muscular resistance vessels.

Organic vascular occlusion and Raynaud's disease can be probably considered as the most evident clinical examples of those two physiological ways of reaching critical closing pressure values. In cases of embolic or thrombotic events in the artery, for instance, the intravascular pressure distal to the occlusion is

dramatically reduced to the point that even a normal degree of vasoconstrictor tone can bring the transmural pressure to the critical value for closure. Alternatively, when no structural changes are present in the blood vessels, as in Raynaud's disease, an abnormally exaggerated sympathetic tone can so alter the pressure difference across the wall as to make complete vascular closure possible.

Certainly other hemodynamic factors and rheological properties of the blood, such as its viscosity, can modify the transmural pressure, and other local stimuli may contribute to determine the degree of tension in the vascular smooth muscle. All these influences interact in an agonist or antagonist direction with the neurogenic element, and may therefore potentiate or mitigate the vascular effects of an increased vasomotor tone, thus introducing some degree of variability in the clinical manifestations observed.

The anatomical, physiological, and pharmacological evidence reviewed in this paper, however, consistently indicates that, when the peripheral circulation is considered, the nervous control is of paramount importance, justifying the conclusion that in Raynaud's disease a state of sympathetic overactivity is the necessary and often sufficient condition for the occurrence of the vasospastic crises.

DIAGNOSTIC CONSIDERATIONS

Numerous detailed accounts of general procedures and special techniques which may assist in the diagnosis of the peripheral vascular disorders, and particularly in differentiating Raynaud's disease from digital ischemia secondary to various organic conditions, are easily available (Abramson, 1974, chap. 2-5; Chucker, Fowler, & Hurley, 1974; Gauthier, Gauthier, & Texier, 1973; Holling, 1972, chap. 2; Richards, 1970, chap. 4). Here only a few comments appear indicated with particular regard to some controversial diagnostic issues relevant to the specific topic of this paper.

The Diagnostic Significance of Nutritional Lesions

It is generally admitted that the presence of trophic changes in the digits is a strong indicator of organic vascular occlusion, since it implies a local ischemia so severe and prolonged that even the minimal nutritional requirements of digital tissue cannot be satisfied. Healed or unhealed necroses, paronychial infections, subungual ulcerations, thickening of the skin with atrophy of the pulp (sclerodactylia), deformed and brittle finger nails are some of the trophic disturbances thought to be invariably associated with considerable organic changes in the blood vessels, such as intimal thickening, fibrosis of the media, and

thrombosis (Birnstingl, 1968, 1971; Peacock, 1959a, 1969).

If these nutritional complications imply structural damage, and if the very definition of Raynaud's disease excludes the possibility of organic changes in the peripheral vessels, simple logic should lead to the necessary deduction that trophic disturbances must be absent in Raynaud's disease; a conclusion explicitly reached by several investigators (Birnstingl, 1971; Gifford, 1971; Lottenbach, 1971; Montorsi, 1974).

Interestingly, however, many researchers, while acknowledging the organic implications of an impaired nutrition, continue to routinely accept patients exhibiting tropic complications as cases of Raynaud's disease. At the root of these inconsistencies there is probably not only Raynaud's original emphasis on symmetrical gangrene, but also the allowance for limited skin necrosis in Allen and Brown's (1932a) requisites for a diagnosis of Raynaud's disease. Their criteria have been universally endorsed and are still widely used, although they are in urgent need of revision. It is rather evident that, unless the presence of trophic changes is regarded as incompatible with a diagnosis of Raynaud's disease, the conceptual contradiction of attributing the pathology of this condition to organic structural abnormalities will be circularly perpetuated. Considerable

experimental evidence is available to support such conclusion.

Spurling et al. (1932) reported that histopathological examination of the digital arteries in one of their patients revealed substantial structural damage. Those fingers were amputated because of gangrene, and it should not be surprising to find that extended necrosis and organic disease of the digital vessels occur together. These results, however, have been often cited as evidence for the claim that structural changes might be present in cases of Raynaud's disease, clearly illustrating the danger of circularity mentioned above and the fallacy of generalizing from complicated to uncomplicated cases, as noted by Peacock (1958b).

Lewis and Pickering (1933) conducted extensive observations on a variety of vascular conditions with or without associated gangrene, and concluded that "it is a mistake ever to regard gangrene as the result of an uncomplicated spasmodic affection. . . . There is increasing evidence in the group of cases as a whole that when gangrene occurs, a structural change such as thrombosis has happened and permanently plugs the vessel" (p. 363). Lewis and Pickering recognized as manifestations of those organic changes not only the obvious extensive gangrene, but "also the minute necrotic foci which form on the fingers of cases that are primarily

spasmodic" (p. 364). Allen (1937) studied by arteriography the digital vessels of 22 patients with uncomplicated Raynaud's disease, and found evidence of organic obstruction only in 2 cases. The presence of structural changes in those two patients simply indicates the difficulty of accurate clinical diagnosis, and does not imply, as many have instead suggested, that organic complications may be of etiological importance in Raynaud's disease.

In a study previously mentioned, Lewis (1938b) examined the histological appearance of the digital arteries obtained post mortem from 6 patients with Raynaud's disease and from 18 warm-handed individuals who served as controls. No evidence of organic changes could be established in 3 cases of mild Raynaud's disease uncomplicated by nutritional lesions, but in the other 3 patients, who exhibited scars and ulcers at the fingertips, intimal thickening and thrombotic formation were demonstrated.

The validity of using the presence of nutritional disturbances as an indicator of structural damage has been confirmed by Lynn et al. (1955), who found a nearly perfect correlation between occurrence of trophic lesions and the existence of organic vascular disease independently determined by arteriography. On the basis of the radiological findings Lynn and his associates

ascertained that 16 of their 23 patients appeared to have anatomically normal digital arteries, while the remaining 7 showed evidence of organic obliteration. In all 7 cases of the latter group trophic changes were present, and in 15 of the 16 patients with structurally normal vessels no sign of nutritional complications could be found. The authors, therefore, suggested that two different and essentially independent conditions were likely to be responsible for the clinical manifestations in the two groups of patients.

Peacock (1958b) called attention to the technical difficulties presented by arteriography which may produce misleading results, especially when a control group is not included. He consequently measured hand blood flow by venous occlusion plethysmography in patients with Raynaud's disease and in normal controls, and adopted a reduced capacity of the peripheral vessels to dilate as a more reliable indicator of organic vascular disease. The patients were divided into a group "without disability" presenting mild symptoms and no trophic complications, and a group "with disability" characterized by severer symptoms and nutritional problems of unspecified incidence.

For all 8 patients in the first group blood flow reached the normal level suggesting absence of organic obstruction. Several of the 22 patients in the second

group showed an impaired vasodilator response indicative of organic arterial occlusion. In this group the presence of circulatory impairment as well as its degree were estimated on the basis of the blood flow measures, so that the vessels were considered to be (a) unobstructed, (b) moderately obstructed, and (c) severely obstructed. The number of patients falling in each subgroup was not provided. When this plethysmographic estimate of the severity of the vascular obliteration was compared with a clinical indicator of organicity, constituted by the presence of trophic complications, a good correspondence was found, the incidence of nutritional lesion being 0%, 33%, and 71% respectively for the three subgroups defined on the basis of the hand blood flow values.

More recently arteriography has been used by Porter et al. (1975) in order to evaluate the clinical response to quanethidine in 25 patients, 20 with secondary digital ischemia and 5 with Raynaud's disease. They found arteriographic evidence of vasospasm in all of them, however organic arterial occlusion was absent in all 5 cases of Raynaud's disease, while it was present in 18 of the 20 patients with secondary digital ischemia. Interestingly, the 2 cases of the latter group, for whom no structural changes could be demonstrated, suffered from neurovascular compression syndromes.

While it is sufficiently clear from the foregoing discussion that the presence of nutritional complications invariably indicates considerable structural damage to the digital arteries, it should be equally evident that the absence of these trophic lesions does not guarantee that the vessels are anatomically normal, and subclinical degrees of organic obstruction are still possible (Peacock, 1958b, 1959b). Lack of nutritional complications is, therefore, a necessary but not sufficient condition for a diagnosis of Raynaud's disease, and the possibility of structural damage must be ruled out by adopting other independent methods of testing for organicity, such as arteriography or assessing the capacity of the vessels to dilate normally.

Functional Vasospasms and Organic Changes: Dichotomy or Continuum

Having stressed throughout this paper the need to distinguish Raynaud's disease from secondary digital ischemia, a logical question to ask is whether the recurrence of transient functional vasospastic crises, which individually considered are unable to injure the tissue, can gradually lead to permanent structural changes in the digital vessels and, consequently, to the nutritional complications described previously.

Some investigators (Gifford & Hines, 1957; Hines & Christensen, 1945; Lynn et al., 1955; Peacock, 1958b;

Pickering, 1951) have denied such possibility and have observed that in many cases attacks of digital spasm keep reoccurring for numerous years without resulting in organic damage to the arteries or in trophic changes of the digits. The great majority of the authors, however, agrees that Raynaud's disease can, with time, evolve into organic complications (Goetz, 1956b; Holling, 1972, p. 140; Mufson, 1944; Simpson et al., 1930; Spurling et al., 1932; Tsapogas et al., 1968, pp. 78-81; White et al., 1952, pp. 179, 182, 184).

Although no definitive evidence is available for the idea that repeated vascular spasm can induce structural changes in the vascular bed, the notion is sensible and it is certainly consistent with a fundamental postulate in psychosomatic medicine and with the concept of "psychogenic organic disorders." Alexander (1950) pointed out that "these disorders develop in two phases: first the functional disturbance of a vegetative organ is caused by a chronic emotional disturbance; and second, the chronic functional disturbance gradually leads to tissue changes, and to an irreversible organic disease" (p. 44).

The prognosis in Raynaud's disease is generally considered to be good, even though in a number of cases a progressive deterioration is observed. Gifford (1958, 1963) indicated that about 30% of the patients progress

to the point of developing nutritional lesions. Similar figures had been reported by Blain et al. (1951) in a follow-up study of 100 patients with Raynaud's disease covering a period of 11 to 55 years. They established that in 69% of the cases the condition remained more or less stationary, in 6% definite progression of the symptoms with an increased frequency and severity of the attacks was found, and finally in 25% of the patients the deterioration was so severe that sympathectomy was required.

It has been suggested (Burch & Phillips, 1963; Mendlowitz, 1954) that, once structural changes occur in the progressive group, a vicious cycle is installed and the symptoms are self-perpetuated. In these patients a heightened vasomotor tone and a luminal reduction, resulting from the superimposed structural damage, act synergistically to maintain a low transmural pressure. As the critical closing pressure value is reached more and more often, the vasospastic episodes become more and more frequent, and further vascular damage is produced.

Although little is known about the factors which determine the transition from a functional vasomotor disorder to an organic disease, it is reasonable to assume that intensity, duration, and frequency of the vasospastic episodes are of extreme importance, thus justifying the emphasis given to preventive measures in

the treatment approach (Raynaud & Raynaud, 1967).

It seems possible to conclude that for about one third of the patients with a diagnosis of Raynaud's disease, the condition will run an unfavorable course. While the concept of an evolution from functional to organic is generally accepted, no decisive evidence has been presented in its support. In particular, it remains difficult to determine whether the structural changes are the result of repeated functional vasospastic attacks, or whether instead those vasomotor crises were the forerunners and early manifestations of an underlying, but yet undetected, organic process. In either case, if terminological and diagnostic confusion is to be avoided, it is necessary that, once the presence of organic changes is recognized, the diagnosis of Raynaud's disease be discontinued.

CONCLUSIONS AND RECOMMENDATIONS

If Raynaud's disease needs to be retained as an autonomous nosological entity, as this author believes, it must be carefully differentiated, both terminologically and diagnostically, from a number of organic vascular conditions which may present clinically with similar symptoms of digital ischemia.

Terminological Revision

In spite of numerous appeals for a more precise nomenclature and a more rigorous diagnostic screening which at regular intervals have appeared in the literature since Hutchinson (1901) first tried to introduce some order in this matter, the situation is still very chaotic today. Changes in the existing nomenclature, proposed in the attempt to eliminate unnecessary confusion, have met scarce success.

This author shall try again by suggesting here that the term "Raynaud's disease" be retained to designate a functional vasospastic disorder of the extremities which is primarily determined by a neurogenic fault, definable as an abnormally heightened tonic sympathetic discharge. It is proposed, in addition, that the term "Raynaud's phenomenon" be abandoned in favor of "digital ischemia," or similar alternative expressions, indicating attacks of peripheral circulatory insufficiency and digital discoloration resulting from a known organic vascular disorder. "Raynaud's phenomenon secondary to thromboangiitis obliterans," for example, would be changed to "digital ischemia secondary to thromboangiitis obliterans." Similarly, in those instances when Raynaud's disease progresses severely to the point of structural damage and luminal obstruction, the diagnosis should be substituted with that of

"digital ischemia secondary to organic vascular occlusion," with the possibility of further specifying the nature of the occlusion as embolic, thrombotic, and so forth.

On the one hand this new nomenclature, by keeping the association between the name of Maurice Raynaud and functional vasospasm, would still pay tribute to the French physician who was the first not only in pointing out that attacks of digital ischemia, or "local asphyxia" as he called it, can occur in the absence of organic vascular disease, but also in proposing a vasomotor derangement as the underlying etiological mechanism. On the other hand the nomenclature suggested here would eliminate such confusing terms as "Raynaud's phenomenon" and "Raynaud's syndrome," which have been used by different investigators, and often by the same one in different occasions, to refer to different nosological entities.

The indiscriminate use of terminology, and the even more disturbing looseness in diagnostic selection, have greatly retarded progress in the understanding of the vasospastic disorders, and are still evident today in most of the published reports, thus making uninterpretable, or at least inconclusive, the results of otherwise well formulated and methodologically sound experiments.

Diagnostic Revision

It is the failure to accurately distinguish Raynaud's disease from other peripheral vascular disorders which is largely responsible for the widespread acceptance of Lewis's local fault as the most adequate explicative hypothesis of Raynaud's disease; a contention which is completely devoid of fundament, as this paper has hopefully made clear. The fallacy of the experimental paradigm adopted to prove the validity of the local fault notion is readily apparent once the fundamental diagnostic ambiguity on which it rests is recognized. Unless cases of organic vascular disease are excluded from a study seeking to investigate the etiological mechanism in Reynaud's disease, the demonstration that a local fault, i.e., structural damage, is present in the vessels of those organic patients will inevitably lead to the false conclusion that a local fault is responsible for Raynaud's disease.

There is no excuse today for continuing to confuse vascular conditions which only have in common some exterior symptoms but certainly not the etiology, prognosis, or indications for treatment.

Undoubtedly one reason for the persisting confusion is the lack of adequately updated criteria for a diagnosis of Raynaud's disease. Allen and Brown (1932a, 1932b) had proposed that a diagnosis of Raynaud's

disease should satisfy the following requirements: (a) intermittent attacks of discoloration in the extremities precipitated by cold or emotional stress; (b) symmetrical or, at least, bilateral involvement; (c) absence of any other condition, such as organic arterial occlusion, to which those attacks might be secondary; (d) trophic changes, when present, limited largely to the skin; and (e) a history of symptoms of at least two years. These criteria have had a tremendous clarificatory impact at a time when, in almost every case of gangrene, the diagnosis of Raynaud's disease was entertained; however, a revision of the last two criteria seems necessary, since they have still allowed the possibility of erroneous diagnosis.

All too often adherence to Allen and Brown's requirements has permitted a diagnosis of Raynaud's disease even in the presence of nutritional complications, which, as noted earlier, are invariably indicative of organic vascular disease. This author proposes, therefore, that the fourth criterion be so modified: (d) absence of past or present evidence of any trophic change. The rationale for this substitution is sufficiently evident from the preceeding discussion on the nutritional lesions and needs no further elaboration here.

Furthermore, available follow-up data clearly

suggest that the requirement of two years, during which the symptoms must be present before a diagnosis of Raynaud's disease can be made, is definitely insufficient. Allen and Brown (1932b) have themselves pointed out that in those cases progressing to scleroderma, arthritis, or gangrene, the underlying organic disease develops from 1 to 15 years after the onset of symptoms. Blain et al. (1951) reported that, of the patients who showed severe clinical deterioration, only in 40% were the complications evident after 4 years, in 64% after 7 years, and in 92% after as much as 15 years.

Even Gifford and Hines (1957), convinced supporters of Allen and Brown's diagnostic criteria, admitted that the time interval between the onset of vasospastic symptoms and the manifestation of rheumatoid arthritis was from 4 to 14 years, while it took up to 26 years for acrosclerosis to be discovered. Finally, de Takats and Fowler (1962a, 1962b) cautioned that a period of 16 years may separate the first evidence of vasospasm from the appearance of scleroderma.

From these studies it can be concluded that, in almost all cases, a latent period of about 15 years is sufficient for the underlying organic process, when present, to become evident. It would certainly be at least impractical, however, to suggest, as an alternative to the 2-year criterion proposed by Allen and

Brown, that a diagnosis of Raynaud's disease should be made only if, after 15 years, no organic involvement is observed. It is more reasonable to recommend, instead, that the 2-year requirement be dropped and that Raynaud's disease be diagnosed on the basis of the other four criteria listed earlier, which include the first three of Allen and Brown and the fourth criterion modified as suggested above.

After the diagnosis is made the evolution of the condition should be carefully monitored in order to recognize the signs of an underlying organic process, realizing that the longer the time during which the functional picture remains uncomplicated, the more confidence can be placed in the accuracy of the diagnosis. In this regard, the practice of specifying, in published papers, the number of years elapsed in each case since the onset of symptoms is strongly encouraged.

Finally, a diligent search for other independent signs of sympathetic hyperactivity may be of considerable assistance in diagnosing functional vasospasm. A very promising area for further research is offered by the frequent association of Raynaud's disease with other functional disorders, which has justified the tentative assumption that a common psychophysiological make-up might be at the root of the aberrant sympathetic response pattern. A systematic attempt to test this

interesting notion should include a thorough psychological assessment, as well as the measure of other psychophysiological response modalities besides hand blood flow. Although the available preliminary indications would certainly warrant such an effort, this line of research has been conspicuously neglected.

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