PHYSIOLOGIC PROBLEMS IN PERIPHERAL VASCULAR DISEASE*

Hebbel E. Hoff, M.D.†

Houston, Texas

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INTRODUCTION

We have very little direct knowledge of the peripheral blood vessels, but the effects of their activity are of great concern, particularly when they are functioning improperly. Many of these difficulties arise from the fact that the peripheral vessels and the arterioles in particular have a double function to perform in the economy of the body.

In the first instance, the blood vessels serve as the nutrient channels of the parts they supply, and their obstruction results in malnourishment. Foisie (1) has stated that "The arteries are the supply lines. An ischemic limb resembles the inhabitants of a beleaguered town. With supplies diminished or cut off they can keep up normal appearances for a time, but soon they begin to starve. They feel cold, their faces are pale or blue, they become less active and as conditions grow worse they become apathetic, or complain loudly to those in authority. In the human limb there is absence of arterial pulsations, lowering of surface temperature, pallor or cyanosis, anesthesias and pain." Limbs that are not completely cut off from supply, but which are on short rations, may also show a variety of symptoms: "Malnutrition, which is the basic difficulty, results in degenerative changes of the musculoskeletal system primarily. Muscle atrophy, osteoporosis, limited and painful motion, flexion deformities and joint stiffness are the price of a prolonged arterial inadequacy. A rich blood supply is of primary importance for repair of injury and for maintaining good tone of the extremity pending return of function. Arterial spasm complicating injury throttles a blood supply that needs to be at its best."

There is much that is known and much to learn about the other function of blood vessels—as part of a hemodynamic system in which all the vessels participate in maintaining the central blood pressure by which peripheral blood flow is provided. Acting as part of the peripheral system, arterioles constitute a variable impediment to the outflow of blood from the arterial tree, and thus maintain a central head

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† From the Department of Physiology, Baylor University College of Medicine, Houston, Texas.
of pressure, which depends upon a combination of local tone and nervous and hormonal factors. Such a discussion would encompass the function of the peripheral vessel in the production of hypertension. The renin mechanism, in all probability, is a part of an emergency apparatus designed primarily to support peripheral arterial function in states of shock, and renin and what Shorr and Zweifach (2) call vaso-excitatory material may well be one and the same substance. The stimulating observation of Grollman (3) that hypertension develops in completely nephrectomized animals kept alive for long periods by careful nursing, diet, antibiotics and selective ion removal, renews our interest in the renal origin of hypertension, not in the sense of the renal origin of a hypertensive material, but in the sense of removal or inactivation of hypertensive agents produced elsewhere in the body.

At the opposite end is the problem of shock. Shorr, Zweifach, and Furchgott (2) demonstrated that a vasodepressor material was released by damaged muscle but was removed from the circulation by a normally functional liver and antagonized by vaso-excitatory material released by the kidney. From the peculiar physiology of the hepatic blood flow with its major supply from the portal system, it follows necessarily that when the gastrointestinal arterioles are excessively contracted, blood reaching the liver from the portal system is more than usually deoxygenated and liver oxygenation suffers. At a critical level of anoxia the liver not only ceases to inactivate the vasodepressor material, but begins to produce it. When the circulation is flooded with this material, peripheral vessels lose their tone and normal responsiveness to circulating hormones, fail to maintain a rapid blood flow through central channels and permit the blood to stagnate in side channels and be unavailable to the remainder of the circulatory system. The problem of participation of the nervous system in the production of shock is still not clear. The possibility remains that much the same changes in the peripheral circulation may be brought about by nervous mechanisms.

The series of problems concerned with the function of the peripheral vessel as a supply line are almost the reciprocal of those with which the arteriole must deal as part of the general peripheral resistance. By local dilatation an increasing amount of nourishment can be brought to its peripheral organ, but this entails a decrease in central blood pressure. It is only through constriction of the vessels which supply other organs in which there is less immediate demand for blood that an increased blood flow can be furnished to an organ which requires added nourishment. This principle is implicit in what is called the Lovén reflex, in which, by nervous mechanisms, relaxation of an artery leading to an active organ occurs, followed by a compensatory vasoconstriction in those which are inactive. This is the principle that Ray, Burch, and DeBakey (4, 5) have termed the principle of "hemometakinesia," or the "borrowing-lending" principle, and it underlies all of the circula-
tory readjustments in the constantly changing play of organ activity throughout the day, for there is insufficient blood to supply all organs if they were active at one time. Thus, as one organ becomes active, another must shut down, like the steamboat of Mark Twain with such a big whistle that the paddles had to stop when the whistle was blown. It is with the function of the peripheral vessels as supply lines to a peripheral structure that our interest lies in the present discussion.

The problem must largely be studied indirectly, inferring from alterations in the functions a vessel carries out that changes occur in the vessel. These alterations are changes in the color and temperature of a limb, by variations in the blood flow through a hand or an arm, by pallor and cyanosis, and by trophic changes. Fortunately, these changes can be studied as they occur in response to stimulation of the environmental changes of daily life. Perhaps the two most informative stimuli are thermal changes and mechanical trauma, for they encompass the entire range of normal and pathologic reactions.

**Reaction to Cold**

When the body and limbs of a normal subject are exposed to cold, blood flow through the digits becomes extremely slow, so slow that the arteries must be almost closed. Actually, closure is abnormal; it is, however, the characteristic feature of Raynaud’s disease and allied conditions. It is apparent that there is a gradual transition from the normal subject in whom closure never occurs to the patient who has severe disease in which the arteries are shut for long periods each day in cold weather. Many normal young people show the simplest form of Raynaud’s disease in recurrent but short attacks of symmetrical discoloration of fingers and sometimes of toes during exposure to cold. Lewis and Pickering (6, 7) questioned 60 young men and 62 young women in this regard and found that 25 per cent of the men and 30 per cent of the women noticed that one or more of their fingers occasionally became white or pale blue in color on exposure to cold, and that the fingers were numb to touch. Occasionally pain was present. Only the tip of the finger might be involved or the discoloration might spread over its entire length. Recovery was associated with reddening of the finger and tingling, and if not spontaneous, could be induced by warming or rubbing the part. The discoloration was always the result of exposure to cold, never of emotion. There were no instances of necrosis or other nutritional disturbance in the digits. Inquiry showed the onset to be at or before puberty in the majority of cases. Often this type of response was a family affection, and was found in lesser or more severe degree in other members of the same family. In more advanced cases, local nutritional changes were found along with spasm of the digital arteries, and in other groups this led to actual necrosis or gangrene of the fingertips.
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Raynaud attributed the disease which bears his name to a spasm of the peripheral vessels which results from excessive activity of the sympathetic vasoconstrictor fibers supplying them. Lewis, (8-13) on the other hand, offered evidence that the basic defect in the disease is a change in the responsiveness of the blood vessel itself to the stimulus of cold, and presented two main arguments in support of this view. First, he demonstrated that local cooling could induce a complete attack in a completely sympathectomized digit, and second, that, in a susceptible subject, generalized cooling of the body did not produce an attack in a finger which was kept warm while the body was cooled. In further support of this concept of a local fault, Lewis and Pickering (14) described 2 cases of Raynaud’s phenomenon arising from local injury. In the first case, a medical student, 23 years old, injured the proximal interphalangeal joint of the right ring finger when he hit a ball four years previously. The finger swelled and became painful at the site of the injury, and remained so for two to three months. Some months later he noticed that the two distal phalanges of this finger became waxy white in cold weather. Sensation in this finger became definitely impaired when it was white. When warmed the finger became red and sensation returned. This affection persisted for two winters and then disappeared. The second case was that of a shoemaker of 27 years who had noticed attacks of discoloration of his finger for half a year. At the time his trouble began he had been at this work for five and a half years; he used a machine for shaping the shoe and held the shoe in both hands against a rapidly revolving wheel. If the shoe was not held with considerable force against the wheel it vibrated rapidly, and the vibration was felt in hands and forearms. Later he worked on a lasting machine. The shoe was held in both hands while the machine tacked the upper part to the sole. The vibration was at the rate of about 120 per minute and was felt by both hands, but not uncomfortably. The man who preceded him on the first machine acquired the same difficulty. A worker of 60 who used the second machine was also affected. Attacks were never provoked by the vibration of the machine, but only by exposure to cold when he was not working. Exposure to cold air out of doors or immersion of the hands in cold water sufficed to produce an attack. The fingers became pale; pallor began at the tip of the finger and spread up as high as the proximal interphalangeal joint. Eventually the fingers became waxy in color and numb.

Raynaud’s phenomenon frequently develops in the hands of those who use rapidly vibrating pneumatic chisels to clean castings and in factory workers who mold shoes by means of pounding machines. It is evident that although the affection is the result of using these machines, the attacks are not provoked in this way. It is only when the hands become cold, and this is usually when no work is being done, that attacks are experienced. Allen, Barker and Hines (15) quoted
many such examples of Raynaud’s phenomenon, and called particular attention to those which developed from the use of pneumatic tools in drilling rock, breaking pavement, chipping stone and ramming sand. The rapid percussion of the pneumatic hammer does not initiate the attack but seems to sensitize the digital vessels so that Raynaud’s phenomenon occurs readily on exposure to cold. Attacks do not occur during work unless the tool is cold when it is in use. Consequently, riveters who use cold tools may be greatly annoyed by the occurrence of vasospastic change during work. Similar sensitization of blood vessels by percussion is seen in pianists and typists.

Lewis’s (8–13) conclusion that the basic disability in Raynaud’s disease is a local sensitization of the arterial wall to cold is not supported by all the available evidence. Simpson, Brown and Adson (16), who adhered to Raynaud’s original concept of the disease, have investigated a series of patients at an earlier stage, less complicated with anatomic changes, in whom adequate anesthetization of all sympathetic nerves supplying a finger completely abolished and prevented every manifestation of Raynaud’s disease in that finger, even under the most extreme conditions. Although the arteries became narrowed and the pulse was reduced when the sympathectomized digits were placed in cold water, the full occlusion characteristic of the Raynaud’s phenomenon did not occur. They also pointed out the importance of psychic precipitation of attacks and showed that after sympathectomy, psychic disturbances failed to have any effect. The presence of excess sweating in Raynaud’s phenomenon can hardly be explained on any other basis than excess sympathetic drive.

Hyndman and Wolkin (17, 18) have reviewed the arguments for and against local and reflex vasospasm and agreed with Lewis (8–13) for the following reasons:

1. Much of the indictment of the sympathetic system rests on the fact that sympathectomy benefits mild cases. The fact that it does not benefit patients with advanced disease has led some to admit that in these there is a degree of inherently abnormal vasoconstriction in response to cold. Marked benefit could not be expected after organic vascular change had taken place. However, if a local vasospastic disorder exists, the normally superimposed sympathetic influences in response to cold, emotion, and so forth, would enhance the abnormality and use up the narrow margin of reserve of the cutaneous vessels. Sympathectomy would be beneficial, and the degree of benefit would be contingent upon the severity of the disease and the magnitude of the vasoconstriction normally imposed upon the vessel. Obviously, sympathectomy would give the best subjective and objective results in mild cases, but the results would constitute palliation and not cure in the strict sense.

2. Hyndman and Wolkin (17, 18) have demonstrated that the in-
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herent capacity of the arteriole to respond to cold is tremendous. If, after unilateral cervicodorsal ganglionectomy, a nude patient is placed in a refrigerator at 0°C, and the temperature of the fingers is determined at intervals, the contribution of the "peripheral" and the "central" response can be distinguished quantitatively. After an hour in the refrigerator the temperature of the fingers may have dropped 10 or 18°C, and only 3 to 5 degrees of this can be accounted for by the sympathetic nerves.

(3) Hyndman and Wolkin (17, 18) have also observed that the effect of cooling the normal hand by local application of ice is a transient blanching followed by dilatation of the capillaries. A sympathectomized hand in the refrigerator will exhibit mild flushing, but nothing to compare with the flush of the normal hand. When the first patient was exposed in the refrigerator both hands presented islands of pallid skin and the distal two joints of all fingers were blanched. The only difference in the appearance of the two hands was one of degree. The sympathectomized hand was not quite as flushed in the non-blanched zone and was not quite as cyanotic as the other hand. Thus, sympathectomy abolished the aching, stinging pain ordinarily produced by cold, but altered the temperature and color changes only to a degree that was in keeping with what could be expected by eliminating a normal sympathetic influence for skin.

(4) Lewis (8–13) has shown that the effects of cooling or warming a single finger of a patient with Raynaud's disease are local, and that if this is a sympathetic reflex it does not obey the laws which characterize sympathetic reflexes.

Hyndman and Wolkin (17, 18) thus considered that the evidence favors the conclusion that Raynaud's disease is primarily a vascular and not a sympathetic disorder. Sympathectomy is beneficial objectively because it eliminates the vasomotor influence which is normally present in any case. It is beneficial subjectively because it abolishes the aching and stinging pain of vasoconstriction. This contention is based largely on the following major considerations: (1) As Lewis (8–13) has shown, the vascular spasm caused by cold water and its release in warm water are strictly local phenomena. (2) Hyndman and Wolkin (17, 18) have demonstrated that after preganglionic or postganglionic sympathectomy the hand still retains the local disorder objectively, that is, cold continues to cause the color change. This objective response is diminished in mild cases, but only to a degree that would be expected after elimination of the normal sympathetic vasomotor influence. (3) When a nude patient is taken into a refrigerator and kept there long enough to cause a fall in central temperature, and at the same time one of his hands is kept at room temperature, the latter does not show evidence of vascular spasm, either subjectively or ob-
jectively, even though the exposed hand reacts severely. One is justified in assuming that if the sympathetic system is responsible for the vascular spasm, the hand at room temperature under these circumstances would react somewhat like the other hand.

Pearse (19) took the broader view that, as evidence accumulates, it appears that both of these contentions are correct. The difference exists in the reaction of individual patients. Some have a vasomotor neurosis that is relieved by blocking the vasoconstrictor nerves. In others sympathetic denervation has only a slight effect and will neither prevent nor relieve attacks of vascular spasm in the extremity subjected to appropriate degrees of cold. In both, whether it is primary or secondary, there is hypersensitivity to cold. Pearse (19) concluded that the local abnormality causes an excessive reaction when any normal stimulus is applied, such as direct cold, emotion or vasomotor impulses. He found in a study of 4 patients with Raynaud's disease that, with hands kept warm, cooling the body will cause an attack of vaso-spasm, warming the body will relieve an attack, warming the body will not prevent an attack if the hands are exposed to cold, and the warming effect of food is inadequate to influence the vasospasm. It was concluded that regulation of body heat may have an influence on the vaso-spasm of Raynaud's disease. This constitutes further evidence that normal forms of stimulation may give rise to an exaggerated vascular response. It suggests that a local abnormality causes this excessive vaso-spastic reaction.

On the basis of a study of angiospastic syndromes in extremities, Morton and Scott (20) agreed that the essential abnormality in Raynaud's disease is the local hypersensitiveness of the peripheral smaller arteries to cold, as Lewis has emphasized, and that Raynaud's disease is not primarily the result of an abnormality in sympathetic innervation. Nevertheless, they pointed out that spasms provoked by cold except most severe cases are initiated or accentuated by vasoconstrictor gradient, and that the vasoconstrictor mechanism has an important role even if it is not a primary one, since the majority of attacks in all except the most severe cases are initiated or accentuated by vasoconstrictor stimuli under the ordinary living conditions of these patients. There are few cases of Raynaud's disease in which regional anesthesia has failed to produce some improvement in the circulation to the ischemic extremity, although in the more severe cases, the most distal part of the extremity might remain uninfluenced by it. The more or less extensive release afforded by surgical removal of vasoconstrictor influences also tends to bear out this opinion. As has been pointed out before, the frequent association of Raynaud's phenomenon with excessive sweating of the pallid digits points strongly to sympathetic over-activity and probably cannot be explained on the basis of a local arteriolar hypersensitivity to cold as the major factor.
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RECOVERY OF FUNCTION AFTER SYMPATECTOMY

The early and marked improvement in circulation to the extremities after sympathectomy, which gives, in many instances, promise of radical cure of the fundamental disability, is not always maintained with the passage of time. Although such instances of recovery of vasoconstriction have been used by some as arguments against Raynaud's original concept of sympathetic overactivity, they serve perhaps more usefully as a means of further investigation of the fundamental problem of vasomotor control. Recently Haxton (21) has reviewed the large numbers of patients treated by sympathectomy since 1931 in the neurovascular clinic at the Manchester Royal Infirmary, in an attempt to analyze the following questions: (1) What is the extent and completeness of sympathetic denervation shortly after the standard operation on the sympathetic chain? (2) What differences are found after the lapse of months and years? (3) How are these differences related to the postoperative lapse in Raynaud's disease? His results show quite clearly that the immediate result of sympathectomy in almost all circumstances is a complete disappearance of sympathetic activity. On the other hand, in study of the late results from one to fourteen years after sympathetic section of 46 upper extremities and 34 lower limbs, there was return of sympathetic control, as shown by vasomotor and sudomotor responsiveness, in all 15 cases of cervicothoracic ganglionectomy. Sweating returned in 7, normal electrical conductivity returned in 5, and electrical conductivity half or less than normal returned in 10. In 31 cases of thoracic section, signs of sympathetic activity returned in 31. Sweating was noticed in 11 cases and electrical conductivity returned to normal in 4, to half normal in 20 and to less than half normal in 7. Sympathetic activity returned in 31 of 38 cases of lumbar sympathectomy, sweating being noticed in 4 and return of normal electrical conductivity in 5. Some return of sympathetic activity could thus be demonstrated in all except 7 of the 38 lower limbs. This is particularly noteworthy in that the lower limbs usually have been regarded as immune to the return of sympathetic activity. Other criteria for the return of sympathetic activity were: (1) the response by flushing to procaine block of the peripheral nerve, (2) the return of reflex vasodilatation and sudomotor activity on heating the rest of the body, a response that is absent soon after sympathectomy, and (3) appropriate response to paravertebral block of the sympathetic chain.

What are possible causes of return of sympathetic activity? The first is that the operation has not yet been devised that completely denervates the part involved, particularly the upper extremity. Complete agreement has not yet been reached as to the best technic of sympathectomy or as to what constitutes complete denervation, particularly for the upper extremity. White (22) is of the opinion that the highest vasoconstrictor fibers to the upper extremity emerge in the
second thoracic nerve. Kuntz and his associates (23, 24) are just as firmly convinced that there are preganglionic components in the first thoracic nerve. Kirgis and Kuntz (25) have expressed the belief that in certain cases preganglionic fibers to the brachial plexus may be found which traverse a communicating ramus from the eighth cervical nerve. Unusual pathways to the upper extremities have been described by other observers, and it has been suggested that functional reorganization may occur, which permits sympathetic activity to take place through pathways which previously manifested no evidence of activity. Simmons and Sheehan (26), studying the connections of the sympathetic chain in dissections of 25 cadavers, observed that the thoraco-lumbar outflow leaves the spinal cord between the first thoracic and second lumbar segments, with occasional apparent contributions from the eighth cervical root. The uppermost origin of the major splanchnic trunk was usually from the sixth, but occasional variations in this level were found to extend from the fourth to the eighth thoracic roots. Skoog (27) has described the presence in 5 adults of intermediate sympathetic ganglia in the communicating rami to the cervical and the first thoracic spinal nerve which he considered to have possible significance in explaining relapse after sympathectomy in some cases. This depends on whether these ganglionic cells receive their preganglionic fibers from the sympathetic trunk or from the spinal nerves. On the assumption that the latter is true, it becomes obvious that sympathetic pathways may exist entirely within the spinal system which would not be severed by sympathectomy and could thus account for the early relapse after operation. On this basis, Skoog (27) believed that the intermediate short-term effect of sympathectomy can be considered comparable to a local shock effect brought about by severing several neurons, and that a small number of undamaged neurons would gradually assume the functions in a wide peripheral area.

There is also some question as to the extent of the procedures required for complete denervation of the lower extremity. It has generally been held that excision of the second and third lumbar ganglia is sufficient to provide complete denervation below the knee and that additional removal of the first lumbar ganglion almost completely denervates the entire extremity. A recent report by Ulmer and Mayfield (28) on the other hand, suggested that the eleventh and twelfth thoracic ganglia must also be removed.

Perhaps the most significant contribution to this problem has been made by Ray and Console (29) concerning residual sympathetic pathways after sympathectomy. They studied the results of 291 sympathectomies performed by various technics in 151 patients, using skin resistance as a means of estimating sympathetic activity. They were able to demonstrate consistent return of sympathetic activity in the twelfth thoracic to the third lumbar dermatomes following any of the commonly practiced operations, and even after complete resection
of the paravertebral ganglionic chain. Similar return of sympathetic activity was also observed in the face, the lower sacral dermatome, the axilla and the first and second thoracic dermatomes after presumably complete sympathectomies in these areas. Sympathetic activity could be interrupted by anterior rhizotomy, spinal anesthesia, the administration of tetraethylammonium chloride, procaine block or division of the lumbar nerve. These observations suggest that, following sympathectomy by any of the technics employed, regardless of the extent of the excision, residual sympathetic pathways exist which do not pass through any part of the paravertebral sympathetic chain. These pathways become manifest only after a process of readjustment, which may vary from three days to three months.

A second possibility is that after preganglionic section of the upper limb, the intact preganglionic fibers in the first thoracic white ramus communicans may form synapses with the cells in the cervicothoracic ganglia and so come to innervate the upper limbs. There is evidence of such a functional reorganization in cats following the operation (30). This theory, however, does not explain the recovery of sympathetic activity after cervicothoracic ganglionectomy or lumbar sympathectomy, in both of which operations the postganglionic fibers to the limb are isolated from all preganglionic fibers. The theory is dealt another blow by the fact that paravertebral block can abolish sympathetic activity without affecting the first thoracic sympathetic outflow.

Peripheral Reflex Centers.—Schwartz (31) demonstrated what appeared to be local sympathetic reflex activity in the forepaws of cats which was mediated by the cervical thoracic ganglion and its gray rami communicantes. This cannot be the explanation of the activity observed months or years after preganglionic section in man since it does not apply to ganglionectomy cases and does not explain the result of paravertebral block. Smithwick (32, 33) found evidence of ganglionic activity a few days after preganglionic section, and DeBakey (44) has confirmed his finding. It is a purely transient phenomenon and is probably the result of the stimulation of ganglionic cells by degenerating preganglionic fibers.

Investigators have long been intrigued with this idea that the sympathetic ganglia may constitute centers for integrated activity outside the central nervous system. Indeed, it is this concept that gave to the entire system the name of autonomic nervous system, for Bichat (34) believed that the ganglionic system was a system of independently operating nerve centers analogous to those in the spinal cord and brain. Tower and Richter (35), however, called attention to the fact that clear evidence, anatomic or physiologic, of a reflex arc in the ordinary sense contained within the sympathetic ganglia and postganglionic connections is wanting. The studies by Goltz and Ewald (36) of the activities possible to an animal in which considerable portions of its spinal cord are destroyed showed clearly that after the period of shock the blood
vessels recover tone, micturition and defecation take place regularly, and even the processes of parturition and suckling can be carried through. Characteristically, however, these functions seem to be imbued with less energy than in the intact animal. Tower and Richter (35) presented apparently conclusive evidence that a moderating influence is exerted on skin resistance by the intact postganglionic mechanism independent of the central nervous system. They showed that a real difference exists between animals in which preganglionic section has been performed and those in which postganglionic section has also been carried out for, in the group having preganglionic section only, the skin resistance never rises above 1½ million ohms, and after the twenty-fifth day is practically at a normal level. On the other hand, animals in which postganglionic sympathectomy has been performed show skin resistances as high as 5 million ohms on the twentieth day, and still as high as 2½ million ohms after the fortieth day.

Regeneration of the Divided Sympathetic Fibers.—According to Haxton (21), this is the only postulate which can explain the findings and is supported by a large mass of evidence from animal experiments testifying to the unusual power of regeneration possessed by the sympathetic fibers. It has been shown, for example, that fibers in the divided cervical sympathetic chain can find their way through interposed sternomastoid muscle to reconnect to the superior cervical ganglion cell.

In a recent review, Grimson (37) reported studies on dogs in which, months after sympathectomy, regenerating fibers could be found growing out from divided rami through the scar tissue to reconnect with the distal parts of the sympathetic chain. The bundles of regenerating fibers at first were thin, but in animals examined at longer intervals after operation they formed thick bands. This experimental evidence renders unlikely the theory that the return of sympathetic activity in man is the result of recovery of function of sympathetic fibers left bruised but undivided by the operation. The following clinical evidence is put forward in favor of regeneration: (1) There is a period of complete absence of sympathetic activity for three to eighteen or more months after operation, followed by a gradual return in nearly every case. (2) The period of freedom is longer in cases of ganglionectomy, in which the returning fibers have a much greater distance to cover than in the cases of preganglionic section. (3) Horner’s syndrome diminishes in ganglionectomy cases when sympathetic activity returns to the upper part. (4) Paravertebral block produces complete sympathetic paralysis in the hand without any sensory or motor disturbance. Therefore, the sudomotor and vasomotor constrictor fibers come from the sympathetic chain. This test also shows that the fibers come from below the first thoracic segment, probably from the lower divided end which is the main supply to the upper limb.
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There is no reason to suppose that the return of sympathetic activity in the lower limb does not result from the similar regeneration of divided lumbar chain, although it seems fantastic that the fibers can bridge the gap of 2 or more inches left after lumbar sympathectomy and presumably filled with scar tissue. It is indeed unfortunate that nature should have arranged that the sympathetic fibers which we wish to sever permanently should almost invariably regenerate, while, despite all the surgeon’s art, divided sensory and motor fibers regenerate very imperfectly as a rule. Further evidence of the regenerative ability of the sympathetic chain is afforded by animal experiments, particularly those of Tower and Richter (35) and Kirgis and Ohler (38). The latter investigators found that within a period of four months after extirpation of the cervicothoracic and second and third thoracic ganglions regenerating unmyelinated and myelinated axons ascend from the cut end of the thoracic sympathetic trunk to join similar fibers from the upper thoracic segment and establish functional connections with the cervical sympathetic ganglions as well as connections with the upper thoracic and lower cervical spinal nerves. These observations, like those of Haxton (21), direct attention to the importance of the central cut end of the thoracic sympathetic trunk, and particularly the preganglionic components, as the site from which the fibers grow back. Tower and Richter (35) also emphasized that postganglionic fibers fail to regenerate and that the major connections that develop anew are from preganglionic regeneration. (5) Although regeneration undoubtedly does occur, in most cases recovery of vasomotor tone takes place before regeneration might be expected on the basis of these studies. It seems clear that another important consideration which may affect both the early and late results of sympathectomy is the intrinsic capacity of the smooth muscles of blood vessels to restore and maintain an independent tone. There is sound experimental evidence of this functional property of denervated smooth muscle, but in man its precise role in diminishing the vasodilating effect of sympathectomy has not been fully defined and requires further investigation.

One of the most acceptable explanations for the discrepancy observed in late results following sympathectomy for involvement of the upper and the lower extremities was advanced by Freeman, Smithwick and White (39, 40) and Ascroft (41). These investigators called attention to the fact that, following the customary procedure of cervicothoracic ganglionectomy for the upper extremity, degeneration of the postganglionic neurons occurred, resulting in hypersensitization of the denervated vessels to circulating epinephrine. On the other hand, the conventional lumbar sympathetic ganglionectomy, which is actually a preganglionic neurrectomy, permits the postganglionic fibers of the vessels of the foot and lower legs to remain intact, and there is no postoperative degeneration. On the strength of this observation, both Telford (42) and Smithwick (32, 33) described technics of sympathetic
denervation of the upper extremity by which the postganglionic fibers are kept intact.

The controversy which has since developed as to the relative merits of preganglionic and postganglionic sympathectomy provides good evidence that this explanation has not been entirely satisfactory and the problem of postsympathectomy return of vasoconstrictor tone has not been solved completely. In his recent extensive review of this phase of the subject Grimson (37) agreed with the conclusion of Fatherree, Adson and Allen (43) that the unsatisfactory results have not been materially solved by the operations on the principle of technic of preganglionic sympathectomy. These observations conform with the experience of DeBakey and Ochsner (44).

The reasoning involved in the hypothesis of Freeman, Smithwick and White (39) is based on an observation of Meltzer and Meltzer (45, 46). While studying the circulation of the rabbit's ear after unilateral resection of the sympathetic chain or the superior cervical ganglion, they observed that the constriction of the blood vessels produced by intravenous administration of epinephrine began later, developed more slowly and lasted longer in a denervated than in the intact ear. They described an essential difference between division of the cervical sympathetic chain, or preganglionic sympathectomy, and excision of the superior cervical ganglion in rabbits and cats. Epinephrine given subcutaneously had no effect on the normal pupil or upon the pupil denervated by preganglionic sympathectomy, but it produced maximal dilatation of the pupil denervated by ganglionectomy. Elliott (47) extended these studies to include the smooth muscle of blood vessels and noted that the increased irritability persisted for at least ten months. He also noted that some degree of increased irritability followed preganglionic sympathectomy. He stated, "This, then, is true for all muscle thrown into contraction by adrenaline, that after decentralization (that is, degenerative section of the preganglionic sympathetic nerves) and still more clearly after denervation (degenerative section of the postganglionic sympathetic nerves), they contract in the presence of adrenaline alike with greater irritability and persistence." These studies are of the same nature as those which demonstrate the increased susceptibility of skeletal muscle to acetylcholine after degeneration of their motor nerves, and the phenomenon has been expressed as a law of degeneration by Cannon and Rosenblueth (48), who stated that following degeneration of its nerve a tissue becomes hypersensitive to the hormone by which its nerve normally influences it.

In animal experiments, however, maximal sensitization develops within the first few days after nerve section and reaches its peak in from eight days to two weeks, declining thereafter. It is certain also that in man, as in the animals studied by Elliott (47), preganglionic sympathectomy also sensitizes the blood vessels to circulating epinephrine, and the difference in the degree of sensitization caused by the two
types of denervation is not great. Thus Fatherree, Adson and Allen (43) pointed out that the vasoconstrictor effect produced by epinephrine, as indicated by the decrease in cutaneous temperature, was increased both by preganglionic and by postganglionic operations. Postganglionic section did not increase the magnitude of the vasomotor response to intravenous injection of epinephrine significantly more than did preganglionic section. They remark that, "We do not interpret these results as an indication that there is no difference in the magnitude of the vasoconstrictor effects of epinephrine following preganglionic and postganglionic sections, but the results suggest that this is true. Certainly if such a difference exists in man, it is small and much less obvious than in the monkey, and probably of little clinical significance." Simmons and Sheehan (26) studied 2 patients who had undergone preganglionic section of the sympathetic nerves of one extremity and postganglionic section of the other extremity. They found that when epinephrine was administered intravenously the decrease in cutaneous temperature was greater on the side of the postganglionic section. They pointed out, however, that the difference was not very great.

(To be Continued in the November 1952 Issue)

PROGRAM

1952 ANNUAL MEETING

THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

THE BELLEVUE-STRATFORD, PHILADELPHIA, PENNSYLVANIA

November 11-14, 1952

Tuesday, November 11, 1952

MORNING: GENERAL SCIENTIFIC SESSION:

Pituitary-Adrenal Response to Surgical Trauma and Anesthesia—Vincent Traina, M.D., Donald C. Muir, M.D., and Charles L. Burstein, M.D.

The Anesthesiologist and Therapeutic Nerve Block: Technician or Physician—Leroy D. Vandal, M.D., and James E. Eckenhoff, M.D.

The Pathology of the Respiratory System and Its Relation to Anesthesia—Raymond W. Burnap, M.D.

Carbon-Dioxide Accumulation in Various Surgical Positions—Frederick H. Van Bergen, M.D., Joseph J. Buckley, M.D., Allen B. Dobkin, M.D., E. B. Brown, Ph.D., Fletcher A. Miller, M.D., and Richard L. Vareo, M.D.

Recent Trends in Anesthesia in the British Isles with Special Reference to Induced Hypotension—J. W. Magill, M.D.

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