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On the Mechanism of Spastic Vascular Disease.*

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Two opposing views exist as to the mechanism of spastic disease of blood vessels. Some regard it as an expression of dysfunction of the vaso-motor nerve supply to the vessels. Chief support for this conception is found in the symmetrical nature of the lesion and the paroxysms which characterize it. Others, especially Lewis and his coworkers, regard it as a local fault not primarily associated with abnormal innervation. This local defect as studied in Raynaud's disease of extremities expresses itself in an abnormal response to cold, in the spatial order of development and disappearance of the vascular constriction, and in the failure of local anesthetization of the nerve supply to prevent or release completely an attack. Our own observations on these aspects of the disease lead us to support the contention of Lewis and others.

Evidence is herein presented that the fault is a local one, and represents not a hyperfunction of a sympathetic innervation, but a change in the blood vessels, namely that they respond to epinephrine in a manner similar to tissues deprived of their sympathetic nerve supply (paradoxical response) while the nerve supply can be demonstrated to be functional.

The evidence is derived from the study of 3 patients with vascular abnormalities of the upper extremities, 2 cases of Raynaud's disease and one case of acro-asphyxia. The first 2 were subjected to the following tests: (1) 1 cc. or less (graded doses) of epinephrine hydrochloride (1-1000) was given hypodermically and the effect on the diseased and control extremities noted. An attack was invariably induced in the diseased extremities. Then the effect of intravenous glucose or of a meal rich in carbohydrate was noted. (2) Ten to 15 units of insulin were administered to produce a physiological secretion of epinephrine. The effect on the diseased and control extremities was noted and again the effect of carbohydrate on the attack determined.

Case I. Male, age 37 with well advanced Raynaud's disease of fingers of both hands, the tip of one finger was gangrenous. Doses

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of epinephrine, 0.2 cc. to 1 cc., hypodermically administered produced violent attacks with cyanosis, blanching, and pain. Attacks were relieved in 5 minutes by intravenous glucose. Fifteen units of insulin produced a severe attack in 50 minutes. The blood sugar dropped from 70 to 33 mg. %. Intravenous glucose quickly relieved attack. No effect occurred in vessels of feet or of other parts not obviously abnormal during either of the tests.

Case II. Male with well developed Raynaud's disease of upper extremities, gangrene of tips of 3 fingers on each hand. Response to epinephrine and insulin similar to that in Case I. Cyanosis after insulin extended almost to shoulders. The blood sugar dropped from 54 mg. % to 27 mg. %.

Case III. Male with definitely established attacks of hypoglycemia in which blood sugar dropped to 14 mg. %. During each attack patient's fingers blanched and caused him to experience burning pain. Removal of ¾ of the pancreas with relief from attacks of hypoglycemia also resulted in relief from attacks of white fingers.

These 3 cases demonstrated a local hypersensitiveness of the blood vessels to circulating epinephrine. There was normal or increased sweating and no loss of pilomotor function in the diseased extremities. No operation on sympathetic nerves had been carried out in any of these patients. Previously such hypersensitiveness to epinephrine on the part of smooth musculature has been noted following denervation. Investigation as to the nature of changes in tissues responding paradoxically to epinephrine is, therefore, being continued, particularly from the point of view of nervous function.

That the nerve supply to blood vessels was functional in these cases was demonstrated as follows: Anesthesia of the nerves of the arm in Case I resulted in definite dilatation of the vessels and cooling curves taken in a water-jacketed plethysmograph indicated greater constriction (faster cooling) in the hand normally than after anesthetization. Case II developed pain in all the fingers of one hand in a plethysmograph when the air was 21°C., although a thermometer between 2 fingers gangrenous at their tips read 34°C. This occurred within 5 minutes after cooling started, the air in the room being 32°C., and the initial temperature between the fingers 33.5°C. Reflex constrictions resulting in pain, therefore, occurred before significant cooling. Dipping the elbow of either arm in water at 6°C. resulted in pain in the fingers within 2 minutes homolaterally, but not contralaterally (local reflexes) with no measurable change in temperature of the palm or fingers. This pain persisted for 10 minutes with the arm in the air at 32°C., with cyanosis. The

patient was put in a cold room at 6°C. with both arms bundled to the shoulder in 3 inches of cotton batting. Pains occurred while the temperature between the fingers was still rising (initial T. 33.5° C., pain at 34°C., intense pain at 33.8°C.) and on coming out of the cold room the pain stopped in 4 minutes with no detectable change of temperature in the fingers of the wrapped hand (33.8°C.). The pain was obviously due to reflex spastic constrictions or circulating epinephrine and not to changes in temperature of the fingers. The alternative to the defect being a local one in the arteries would seem to be to suppose a hyperfunction of the nervous supply to these parts. This would not explain a paradoxical reaction to epinephrine.

These conditions could be explained by inferring a local (paradoxical) reaction to epinephrine or similarly acting body substances, but without the loss of nervous function which is the one known cause of such a condition. But the local reaction (spasm, pain) is not due only to circulating epinephrine; it can be called forth reflexly and also by local cooling of the anesthetized parts. That is, the affected parts go into spasm due to all the stimuli that would normally cause mild constriction, and pain and gangrene result secondarily from arterial spasm rather than from cold.

These findings may be applied to a better understanding of spastic vascular disease, such as Raynaud's disease of the extremities or certain cases of angina pectoris, etc., where external and internal alterations in environment are known to result in an increase in circulating constricting agents and also to produce 'attacks'. They cast doubt on the soundness of conception of surgical procedures in which the sympathetic nerve supply to blood vessels is interrupted. Procedures involving the removal of post-ganglionic neurones would tend especially to exaggerate to maximum degree an already existing fault. Procedures resulting in the interruption of pre-ganglionic neurones would exaggerate the fault to a lesser degree because the fully developed paradoxical response to epinephrine occurs only after removal of post-ganglionic neurones. Such procedures, while resulting in hyperaemia and in the relief of pain, may do so only temporarily until the aggravation of the condition due to denervation leaves the remedy more embarrassing than the original disease.

Uncomplicated arteriosclerosis to the extent of producing gangrene of the extremities does not involve anything resembling the paradoxical epinephrine reaction.