 Quadrilateral Peripheral Vascular Disease
in the Young Adult

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This is a report of seven cases of chronic occlusive arterial disease of the extremities of young adults that initially involved the smaller primary arteries of all four limbs. There were consistent pathologic findings, distinctive arteriograms, and constant clinical features in these cases. The disease process presenting in these patients is easily distinguished from common arteriosclerotic disease.

During the period of observation, cases of quadrilateral vascular disease were excluded from this series when they were instances of obvious ordinary arteriosclerosis. Some other cases were excluded because the disease was not quadrilateral although the other findings were typical of the disease to be described.

Case Reports

Case 1. (E.L.S.)

At age 24 this man was discharged from the army because of superficial phlebitis of both legs, which had continued intermittently during the subsequent 13 years of observation. At age 34 palpable and tender nodules appeared in several veins of the left forearm. Six months later arterial insufficiency of this hand was noted and the left ulnar and right radial pulse were no longer palpable. Electrocardiogram and blood cholesterol were normal. An arteriogram of the left arm showed normal subclavian and brachial arteries; the radial and ulnar arteries were occluded at their origin. The distal radial artery and the radial side of the palmar arch filled via collateral vessels from the dilated anterior interosseous artery (fig. 1). An arteriogram of the other arm showed occlusion of the right radial artery at its origin with a thread-like, tortuous recanalization but there were few symptoms. Biopsy of the left radial artery near its origin showed obliteration of the lumen by cellular fibrous tissue that was infiltrated by inflammatory cells. Slit-like vascular spaces were present in this intraluminal tissue. Multinucleated inflammatory giant cells were present as well as rare neutrophils and many round cells. Minimal inflammatory reaction was present in the vessel wall and in the adjacent connective tissue where it was concentrated about small vascular channels. Cervical sympathectomy did not cause anhidrosis of the hand and he was readmitted 6 months later because of a painful ischemic ulcer of the left index finger. An anterior transthoracic sympathectomy (D1-D5) was then performed and the pain was relieved and the finger healed. There has been no disability of the upper extremities since then.

Two years later, at age 37, he was readmitted because of intermittent claudication of both feet, an ischemic ulcer of the left fourth toe and recurrent superficial phlebitis of the legs. The left posterior tibial pulse was weak, and the left dorsalis pedis pulse was absent; all other pulses in the legs were normal. Arteriograms of the left leg (fig. 2) showed occlusions of the posterior tibial and peroneal arteries. The proximal anterior tibial artery was normal. A right femoral arteriogram (fig. 3) showed slight irregularity of the wall of the proximal posterior tibial artery but abrupt and complete occlusion distally. The right femoral, popliteal, and anterior tibial arteries were normal throughout. Biopsy of the calf over a tender area of palpable thickening showed an organizing thrombus in a rather large vein. An inflammatory infiltrate, composed primarily of chronic inflammatory cells, was present in the wall of the vein. There were also dilated capillaries in the wall of the vein and scattered neutrophil polymorphonuclear leukocytes. These changes distorted the wall somewhat but no necrosis was evident. A cuff of chronic inflammatory cells was noted about many of the small vessels in the adjacent soft tissue. Bilateral lumbar sympathectomies removed 13 and 17 cm. of ganglionated nerve. The ulcer of the toe healed. Two years later, at age 39, new areas of superficial phlebitis appeared in the left leg after the patient resumed smoking. An ischemic ulcer then appeared on the left great toe, which was subsequently amputated. An arteriogram of this extremity showed a new occlusion of the anterior tibial artery in its distal third. The tolbutamide and steroid-tolbutamide tolerance tests were normal.

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Figure 1

Arteriogram of left arm (E.L.S.). The radial and ulnar arteries are occluded at origins; distal vessels are filled via collateral channels of the anterior interosseous artery.

Case 2. (W.L.N.)

At age 21 this seaman developed ischemic ulcers of the right thumb and index finger and intermittent claudication of the feet. After dorsal and lumbar sympathectomies he was improved and discharged from the navy.

Two years later he was hospitalized for recurrent ischemic ulcers of the right index finger and a new ulcer of the right great toe. A right femoral arteriogram (fig. 4) was normal except for occlusion of the anterior tibial artery beginning at the midcalf, and occlusion of the posterior tibial artery at the ankle with minimal recanalization. Gangrene of the toe progressed and, when transmetatarsal amputation failed, amputation was performed below the knee. An arteriogram of the amputated leg confirmed the previous findings. Nine sections from the amputation specimen were available for review. A rather small muscular artery and accompanying vein were present in several of them. The lumen of the artery was obliterated by rather loose-appearing fibrous tissue containing many thin-walled vascular spaces, hemosiderin-laden macrophages, and scattered round cells. Vasa vasora were prominent in the media. A small eccentric nonocclusive mural thrombus was present in one small vein. The patient was killed in an automobile accident 3 years later. Autopsy was not performed.

Case 3. (J.L.S.)

This young veteran first noted intermittent claudication of his feet, and coldness and pain of his fingers at age 27. Gangrene of the right great toe developed 1 year later; lumbar sympathectomies were performed. Three years later, at age 30, he was hospitalized for an ischemic ulcer of the right index finger. The right radial pulse and all pedal pulses were absent. Following a right dorsal sympathectomy the ulcer healed and the pain disappeared.

A subclavian arteriogram showed normal arteries except for a block of the entire ulnar artery with a few sites of recanalization. A few months later he was readmitted for superficial thrombophlebitis of the left lower leg.

One and one-half years later, at age 32, a painful ulcer appeared on the right great toe. This recurred 1 year later, and amputation was ultimately necessary below the knee. No pulses were palpable in the left leg below the common femoral artery at this time. An aortogram showed a block of the left superficial femoral artery, and a right femoral arteriogram showed occlusion of the anterior tibial artery. The Allen test indicated that there was poor arterial flow in the ulnar side of the left hand, and both ulnar pulses and the right radial pulse were absent.

Two years later, at age 36, a painful ulcer appeared on the left great toe, which subsequently necessitated amputation of this digit. A right femoral arteriogram showed a block of the entire superficial femoral and popliteal arteries with a paucity of collateral vessels.

Case 4. (E.L.H.)

At age 22 this infantryman had frostbite of all four extremities with discoloration, pain, and swelling. Other members of his company were not similarly affected under the same combat conditions.

Three years later the distal phalanx of the right index finger was amputated because of nonhealing, ischemic ulceration and pain. Simultaneous with appearance of the ulcer, he noted intermittent superficial thrombophlebitis of the right forearm. Right dorsal sympathectomy (D1-D3) and bilateral lumbar sympathectomy were performed.

Four years later, at age 29, he was re-hospitalized for swelling of the ankles and pain in both hands and forearms. The symptoms were relieved when he stopped smoking, and he has not smoked since. Examination showed trophic changes of the fingers and feet with atrophy, hair loss, and slight pigmentation. The right ulnar and left radial pulses were normal. Other pulses at the wrist were weak and the Allen sign indicated poor arterial flow in the area supplied by the diminished pulses. The dorsalis pedis pulses were absent and the posterior tibial pulses were barely palpable. Electrocardiogram and blood cholesterol were normal.

Arteriograms of both legs showed occlusions of the left superficial femoral, the terminal segment of the left profunda femoris, and parts of

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the anterior and posterior tibial arteries. Arteriography of the left arm (fig. 5) showed occlusion of an otherwise normal ulnar artery at the palmar arch and occlusion of the proximal radial artery. The palmar arch fills via collateral vessels from the anterior interosseous artery to the distal radial artery.

A left thoracolumbar sympathectomy was done and 4 cm. of the ganglionated chain from D11 to L1 were removed, following which he slowly improved although anhidrosis was noted only on the posterior thigh and below the knee. His blood cholesterol, electrocardiogram, fasting blood sugar, and tolbutamide-steroid tolerance tests were all normal. Recently he has had saphenous phlebitis in the right thigh.

Case 5. (T.K.)

This 30-year-old white man was hospitalized in January 1958, with gangrene of the tip of the left fifth finger. He had been well until he developed superficial thrombophlebitis of the left leg at age 28. One year later he noted bilateral calf claudication upon walking one to two blocks, recurrent superficial thrombophlebitis in both legs, and persistent pain and swelling in the left fifth toe. The patient smoked two to three packages of cigarettes daily since the age of 20.

On admission the four pedal pulses were absent, but all proximal pulses were present and there were signs of advanced arterial insufficiency of the feet and hands. Allen’s sign was present bilaterally and there was superficial gangrene of the left little finger. Bilateral lumbar sympathectomies were done after preliminary sympathetic nerve block revealed a circulatory reserve.

The pain and swelling of the left fifth toe disappeared and he was well except for recurrent superficial thrombophlebitis of both legs. The pa-
tient continued to smoke. One and one-half years later he again developed intractable pain in the left fifth toe and an arteriogram was made. Shortly thereafter ulceration and osteomyelitis of this toe necessitated amputation. Upon microscopic examination the acute inflammatory process in the toe was found to extend from the surface ulceration into the underlying tissues so that the small digital arteries were ensheathed in inflammatory tissue. Organized thrombi filled the lumina of the vessels in the sections. The medial layer of the vessels was free from inflammatory changes. A left femoral arteriogram was made.

The patient was admitted 1 month later with progressive gangrene of the left large toe, which finally necessitated infracondylar amputation. Dissection of the specimen revealed that the major vessels of the leg were free from arteriosclerotic lesions and were widely patent. The major vessels of the foot, however, were grossly thickened and the lumen of the dorsalis pedis artery was obliterated by golden-yellow tissue.

Loose cellular fibrous tissue filled the lumens of many of the small arteries. This tissue was quite vascular, and small collections of hemosiderin-laden macrophages were present in it, which were thought to be recanalized, organized thrombi. No changes were noted in the media of the vessels except for an apparent slight increase in vascularity, these vascular channels being of the same magnitude as the channels in the intraluminal tissue. No inflammatory process was recognized in these affected arteries but small nodular accumulations of chronic inflammatory cells were seen as cuffs about very small vascular structures in adjacent adipose tissue. A small vein in one of the sections had an organized, recanalized thrombus similar to those seen in the adjacent arteries. In the 6 months following the amputation, the patient has been well.

Case 6. (B.N.)

This 33-year-old white man was hospitalized in September 1959, with gangrene of two fingers of the left hand. Six years prior to admission, at age 27, he noted periodie pain in both feet at night and claudication in both calves after walking one block. The following year he had developed small gangrenous areas of several digits of both feet. Eventually a left transmetatarsal amputation had been performed. About this time he developed intermittent episodes of superficial thrombophlebitis in both legs. Shortly thereafter he developed
manifestations typical of the Raynaud phenomenon in both hands. Two years prior to admission he had had a left infragenicular amputation and bilateral lumbar sympathectomy. During the year prior to admission he had amputations of the terminal digits of several fingers of both hands. The patient had smoked two to three packages of cigarettes daily for many years. He had continued this, contrary to advice, to the time of admission.

At examination, there was gangrene at the tip of two amputation stumps of the left hand. The only palpable extremity pulses were in the femoral arteries, radial arteries, and right ulnar artery. The electrocardiogram, blood cholesterol, and tolbutamide tolerance tests were normal. There were no manifestations or findings suggestive of heart disease. Left cervical sympathectomy was performed. Arteriography of the left upper extremity (fig. 6) revealed the ulnar artery to be abruptly occluded in its distal third. The radial and brachial arteries appeared normal. The arteries of the hand were filled by collateral vessels from the anterior intersosseous and radial arteries.

Microscopic study of the three amputated fingers showed areas of extensive ulceration of skin with marked fibrosis and inflammation of the underlying dermis and subcutaneous fat. Occasional dermal arteries were found to contain completely organized thrombi, whereas others contained very recent thrombi with early organization. The recent thrombi showed early organization with some acute inflammatory cells in the thrombi and in the walls of the vessels. No necrosis of the vessel walls could be recognized. Giant cells were not seen. It should be noted that all of the involved vessels were located in diseased tissue adjacent to ulcerated areas.

Case 7. (A.K.)

This white woman entered the hospital in December 1957, at age 33, with a 6-month history of periodic cramping of the abdominal pain, claudication of the feet and Raynaud's phenomenon of the hands. Complete gastrointestinal investigation was negative and her digestive symptoms were relieved during hospitalization. Raynaud-like phenomenon had been present in both hands for 1 year. In the previous 5 months she had experienced intermittent claudication in both feet after walking one block. Rest pain and reddish-blue discoloration of the right fourth, left second, and both great toes had recently developed. There was no history suggestive of venous thrombosis. The patient had smoked over two packages of cigarettes daily for 20 years. Clinical and laboratory investigations revealed no evidence of diabetes, heart disease, or atherosclerosis. Electrocardiogram, blood cholesterol, and tolbutamide tolerance tests were normal.

All peripheral pulses were present except the right dorsalis pedis. A typical Raynaud-like phenomenon was produced in both hands after immersion in water at 12°C. There was no Allen sign. Both feet blanched completely after walking for 2 minutes. There was marked rubor of the right fourth, left second, and both great toes. Venous filling time was slow. The feet were cool and sweating. A diagnosis of thromboangiitis obliterans was made. A good circulatory reserve was apparent in both lower extremities following sympathetic nerve block; therefore, bilateral lumbar sympathectomies were performed. Postoperative sweating tests showed satisfactory anhidrosis.

The patient was readmitted 20 months later because of a rapidly enlarging ulcer of the dorsum of the right foot, which followed mild trauma 1 month before. The popliteal pulse was prominent, but neither pedal pulse was palpable. Attempts at conservative therapy failed, and an infragenicular amputation was performed.

The ulcer on the dorsum of the foot was 5 cm. in diameter and extended through the skin and subcutaneous tissue, thereby exposing tendons in its base. The ulcer margins were erythematous.
but not granular. The major vessels of the leg showed no arteriosclerotic lesions. The lumen of the dorsalis pedis artery was filled by brown fleshy material.

Microscopically, the luminal occlusions in the dorsalis pedis artery were cellular, highly vascular fibrous tissue, resembling an organized recanalized thrombus. Some of the recanalized channels contained recent fibrin thrombi. The more proximal vessels exhibited occasional small, eccentric, fibrous intimal plaques, typical of minimal arteriosclerosis. No changes were noted in the media of these vessels. Small foci of chronic inflammatory cells were present in the perivascular soft tissue of small vessels.

One year later the patient was found to have marked arterial insufficiency in the left foot. Pedal pulses were absent, but the popliteal pulse was full. A femorogram showed occlusions of the vessels of this leg just above the ankle, with poor collateral formation. There has been no clinical change since.

Arteriography

Fifteen arteriograms were performed in these seven cases: 10 of the legs, five of the arms, and one aortogram. Three to 12 serial exposures were obtained in each case. These arteriograms can easily be distinguished from films of patients with arteriosclerosis.

Oclusions of one or more of the main arteries distal to the knee or elbow were noted in all patients, and in one patient (E.L.H.) occlusion of the terminal branches of the profunda femoris was noted. Only two cases had a block of major arteries proximal to the knee and these developed late in the course of the disease.

Lengths of the occlusions varied from short segmental blocks (fig. 4) to the entire length of a tibial, peroneal, radial, or ulnar artery (fig. 1). Occlusions were found to begin at the origin of the artery from the popliteal or brachial arteries in two cases in the arm and four cases in the leg. More frequently, however, the occlusion does not begin at a large division or branch. These arteriograms show a striking paucity of collateral flow when compared with arteriograms of arteriosclerotic extremities, which show many large collateral vessels. Arteriograms of these patients frequently show evidence of vasospasm as evidenced by tapered ends of vessels proximal to an occlusion, and occasionally “corrugation” or pleating of the femoral artery (figs. 2 and 3). The main arteries as well as the collateral vessels are frequently uniformly narrowed. These phenomena seem to occur more frequently in these patients than in patients with arteriosclerosis.

The arteriographic hallmarks of arteriosclerosis were not observed in any of these films. There were no filling defects as are produced by intimal plaques. Partial occlusion was seldom noted. Occasionally a serpiginous, thread-like column of dye is seen in the course of the tibial, radial, or ulnar vessels for a distance of several inches. This is the recanalization seen in pathologic sections and does not represent partial occlusion by atheroma. These lumina are in the course of the main vessel and do not follow the meandering path of the collateral vessels that develop in arteriosclerosis.

Our observations are similar to those reported by Edwards in 1935.¹ Some other descriptions of arteriograms in thromboangiitis obliterans are difficult to interpret, since criteria for the clinical diagnosis were not clear. These other reports do not distinguish the rare patients with quadripedal involvement; however, Hines and Barker (1940)² remarked that half of their patients with thromboangiitis obliterans had occlusions of radial or ulnar arteries, whereas only three of 280 patients with arteriosclerosis had occlusions of radial or ulnar arteries. Allen and Camp, in 1935,³ briefly described arteriograms in thromboangiitis obliterans. Arteriograms in amputated legs have been described but small arteries including collateral branches are more evident in these amputated legs than are demonstrable in the living patient.⁴

Pathology

Anatomic material was available and reviewed in six of the cases reported here. Biopsies were made in three patients. When a major portion of an extremity had been amputated, no arteriosclerosis was observed in the major vessels (femoral, popliteal, and tibial), thus confirming the arteriographic
These findings. These larger vessels are the most common sites of arteriosclerosis. The smaller vessels showed the lesions described in the case reports.

Microscopically, the occlusions within the lumen of the vessels consisted of highly vascular fibrous tissue. Thin-walled, endothelial-lined channels, presumably instances of recanalization, were present. Groups of hemosiderin-laden macrophages were seen in the occlusive material. Usually no changes were found in the walls of the arteries although rarely one had the impression that they were more vascular than normal. The eccentric fibrous intimal lesions typical of arteriosclerosis were not found. No medial degenerative changes were seen.

In one patient (E.L.S.) multinucleated giant cells were present, and the occlusive tissue was rich in inflammatory cells. Some inflammatory cells were also present in the media of the vessel, but there was no necrosis in the media. These changes are unique. This lesion is quite different morphologically from that of granulomatous or temporal arteritis and is the inflammatory lesion described by Buerger and confirmed by others. This specimen, it should be noted, was obtained as a biopsy of the radial artery relatively early in the course of the disease before amputations became necessary.

Certainly these gross and microscopic anatomic changes are not those of arteriosclerosis. The single isolated finding of occlusive tissue being heavily infiltrated by inflammatory cells with multinucleated giant cells bears emphasis. All the other lesions are typical of organized thrombi. The hemosiderin within the occlusive tissue supports this conclusion.

Some of the specimens consisted of only portions of gangrenous digits in which there was chronic ulceration of the skin. Changes in dermal and subcutaneous vessels adjacent to such areas of cutaneous ulceration may be due to the local disease rather than being reflections of a systemic disease.

Clinical Manifestations

These seven cases of occlusive arterial disease of all four extremities were selected for study because the arteriographic and pathologic examinations were constant and different from other recognizable occlusive arterial diseases.

Onset began at ages 21 to 33. In one case superficial phlebitis of the legs began several years before arterial insufficiency occurred. In three cases intermittent claudication of the feet was the first symptom, and in the remaining three cases, arterial insufficiency of the hands and feet began simultaneously. After arterial insufficiency appeared, all four extremities were involved within 2 years. In six cases the onset of the disease was insidious (one patient had a history of frostbite several years before his disease became manifest). In the other patient, according to his history, the disease began as unheralded gangrene of several toes.

The course of the disease has been characterized by relapses and remissions in all cases. Five of the seven cases had episodes of superficial phlebitis. All of the patients were heavy smokers and relapse in some instances was preceded by the resumption of smoking. In the others tobacco abstinence was not verified by relatives or friends.

Relapse was more frequent during the winter months and all patients noted increased sensitivity to cold weather. Three patients had color changes, pain, and hyperhidrosis of the hands precipitated by cold. One patient had the classical Raynaud phenomenon precipitated by anxiety as well as cold.

All of these patients had episodes of severe arterial insufficiency and all have had a major or minor amputation. Four patients required amputation of the leg below the knee. Fingers were amputated in two cases, but no major amputation has been necessary in the hand or arm.

Bilateral lumbar sympathectomy was performed on all the patients reported. Cervical or dorsal sympathectomies were performed on five of the seven cases and were bilateral in three. All were improved temporarily but many later relapsed; stellate ganglionectomy
Figure 7
Photomicrograph of a radial artery (E.L.S.) showing inflammatory tissue with a multinucleated giant cell filling the lumen of the vessel. The media is intact. (Hematoxylin and eosin stain.)

Figure 8
A higher magnification of figure 7.

Figure 9
Photomicrograph of a small muscular artery (W.L.N.) showing cellular fibrous tissue with recanalized channels in the lumen. The media is intact. (Elastic tissue stain.)

Some of these patients have been observed for as long as 15 years. There have been no cardiac signs or symptoms in any of the patients and the electrocardiogram was normal in the six cases in which it was obtained. None had clinical evidence of impaired cerebral blood flow. Blood cholesterol was within the normal range in the six cases in which it was determined. There was no evidence of diabetes in any of these patients. Fasting blood sugars have been normal in all of the cases on one or more occasions. The tolbutamide and tolbutamide-meticorten tolerance test was normal in the four of these patients who were available for testing. None of these patients was Jewish or of Mediterranean origin.

The arteriograms in these patients are easily distinguished from those of patients with atherosclerosis; (1) there are no calcifications and no aberrations of the mural shadows such as are produced by plaques; (2) collateral channels are small and infrequent; (3) the involved arteries are normal or completely occluded, never irregularly narrowed as in atherosclerosis (although, as previously noted, serpiginous, thread-like recanalizations may be noted for short segments); and (4) the small arteries are invariably occluded first.

The pathologic findings are also distinctly different from arteriosclerosis. The biopsy of the radial artery done fairly early in the course of the disease exhibited the inflamma-

Etiology
A number of features distinguish this disease from arteriosclerosis. The patients reported here had severe quadrilateral arterial insufficiency early in the course of the disease. In these cases, the arteriography and pathology are distinctive, and there is no evidence of arteriosclerosis or diabetes.
tory changes described by earlier workers and is unique (figs. 7 and 8). The changes seen in the rest of the material are not specific but are consistent. The major arteries of the extremity are normal while the distal arteries are occluded by cellular fibrous tissue resembling organized thrombi with small recanalized channels (fig. 9). Hemosiderin granules are present. No consistent changes are present in the media of the arteries.

Embolism is an unlikely cause of the lesions in these patients. None showed a possible source of emboli over long periods of observation and no visceral or cerebral embolization has occurred.

It would seem that local factors are etiologic in the pathogenesis of this disease. Although primary thrombosis from systemic causes might be entertained as the etiologic factor this seems unlikely because of the distribution of the lesions, which are confined to the extremities and are initially acral.

Inflammation of the vessel walls incites thrombosis as seen in the collagen diseases and granulomatous arteritis. None of our patients has developed any of these diseases, however, and these arterial lesions are distinct from the lesions we observed.

These seven cases are distinct from other forms of chronic occlusive arterial disease. Intensive clinical study, longer follow-up, earlier and more frequent biopsies, and angiocagrams may offer clues regarding etiology.

The present data are incomplete. However, nothing is added by applying or disputing the label, Buerger's disease, or by unifying hypotheses that classify all cases of occlusive arterial disease as variants of arteriosclerosis. Wessler and associates have reviewed the experience with peripheral vascular disease in young adults at the Beth Israel Hospital in Boston and reported six instances of involvement of the upper extremity in 84 cases. Three of these had evidence of heart disease or arteriosclerosis. The other three cases could represent instances of the entity we describe; however, the data in his report are incomplete.

We are unwilling to make the diagnosis of arteriosclerosis, or chronic occlusive arterial disease of any other origin, by exclusion. However, until precise etiologies are known, the clinical, radiologic, and pathologic descriptions and classifications must suffice. When there are, indeed, separate clinical entities among chronic occlusive arterial disease they should be identified so that etiologies might be investigated.

Summary

Seven cases of quadrilateral chronic occlusive arterial disease different from other known chronic occlusive arterial diseases as evidenced by arteriography, pathology, and clinical manifestations are reported. They resemble some of the cases originally described by Buerger.

References

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