STUDIES IN VASCULAR REPAIR

IV. THE USE OF FREE VASCULAR TRANSPLANTS FOR BRIDGING ARTERIAL DEFECTS. AN HISTORICAL REVIEW WITH PARTICULAR REFERENCE TO HISTOLOGICAL OBSERVATIONS*

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At the close of the last century, during the same period in which the first important steps were being made towards the development of safe and reliable methods for lateral suture and end-to-end anastomosis of arteries and veins, the first efforts were being directed to the possible use of free vascular transplants for bridging defects of arteries. A high degree of success was obtained in the experiments of Carrel and his associates during the early years of the present century—experiments which were hailed with enthusiasm and repeated by investigators in a number of countries. A few instances of successful clinical use of free vein transplants in the surgery of aneurysms were also reported. The hoped-for success of this method was not, however, realized when it was put to clinical trial during World War I. Thrombosis and infection were two factors which vitiated efforts to save extremities with damaged arteries by blood vessel transplantation. Once again ligation became the method of choice. Undoubtedly, in part at least, it was because of these disappointing results that little work in this field was carried out in the years between the two world wars.

Interest in the use of vascular grafts arose anew during World War II. Again large numbers of patients with traumatic division of important arteries served as an urgent incentive for the development of some method which would permit restoration of the continuity of the artery. New chemotherapeutic agents and antibiotics were available and offered promise of less difficulty from wound infections. Anticoagulants were also available and had been demonstrated to be effective in reducing the hazard of thrombosis. Again, however, few successes were achieved in the acutely wounded. The exigencies of warfare, the inevitable delay before battle casualties could be given definitive surgical treatment, the relatively few medical officers with experience in the techniques of vascular repair, and

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the common widespread character of the injuries which obviated sufficiently secure hemostasis to permit the use of anticoagulants were all important factors. Nevertheless, the obvious desirability of restoring blood flow through the damaged artery in these cases and the successes obtained with the maintenance or restoration of the continuity of the affected artery in the elective surgery of aneurysms and arteriovenous fistulas did much to arouse interest in the general problem of vascular repair and in the use of free transplants for bridging arterial defects. This interest has been further increased by the recent extension of the scope of vascular surgery in the field of congenital malformations of the heart and great vessels.

As a concomitant of our own investigations into the function and ultimate fate of vascular transplants we have thought it wise to review the literature in order to bring the past experiences with such grafts up to date. Our attention will be directed primarily to the histological alterations which have been observed in the transplants. It should be mentioned in passing, however, that the actual technique of anastomosis has been of the same concern in the interposition of vascular grafts as it has been in the problem of direct suture of divided vessels. Almost every conceivable method has been tried to facilitate vascular suture, or to substitute a non-suture method, or to bridge gaps in arteries by the insertion of inert tubes. De Gaetano used a removable glass splint during suture anastomosis. In recent years Smith has reported the facilitation of vascular suture by the use of soluble dextrose rods within the lumen. In general, however, no intraluminal splints have been found necessary for successful suture either in direct anastomosis or in the interposition of grafts. The use of stay sutures to triangulate or quadrangulate the opposed ends of the vessel has proved generally adequate.

A number of methods have been proposed for uniting vascular structures without sutures. Payr used absorbable magnesium rings. They were modified by Lespinasse, Fisher, and Eisenstaedt. Recently a similar nonsuture technique utilizing vitallium tubes has been advocated by Blakemore, and his associates. Swenson and Gross have employed absorbable fibrin tubes with success. There can be no doubt that these methods are contributions of value and they will certainly have a place in vascular repair in certain situations where suture techniques are impossible or can not be carried out properly. That suture techniques are preferable, however, is indicated by the experiments of Murray and Jones and Johns, and most vascular surgeons prefer suture methods except in the most unusual circumstances.
Abbe' had tried without success the use of glass tubes as a permanent intraluminal prosthesis. Whenever glass tubes have been used to bridge gaps in blood vessels, thrombosis has invariably occurred. Recently, to be sure, more promising results have been reported with lucite and polyethylene tubes. At the present time, however, it seems fair to say that it is unlikely that any inert tubing will prove as satisfactory as properly utilized vascular transplants for permanently bridging gaps in arteries.

It should also be mentioned that there has been general agreement since the experiments of Murray that the use of anticoagulants enhances the chance of success of any vascular repair.

In reviewing the literature concerning the histological fate of vascular transplants it is apparent that, except for work currently being carried out, this aspect of the problem has received little or no consideration in recent decades. Unfortunately too, most of the work recently completed has not yet been published. A great deal of valuable information is to be found in the older literature. Nevertheless it must be recognized that some of the early descriptions are incomplete and lack clarity. Moreover, most authors dealing with this phase of the problem have had at their disposal few successful grafts of more than the briefest duration. We have excluded from consideration remarks concerning the histological appearance of grafts which were occluded by an obturating thrombus since pressure of the circulating blood upon the wall of the graft is an important factor in the histogenesis of structural changes in its wall. We have, however, included cases in which small flat mural thrombi were present without impairing blood flow through the transplant.

*Fresh autographs*

*Arterial autographs.* The first vascular transplants were the arterial autographs of Clementi and Jaboulay and Briau, but thrombosis occurred in all of them as well as in the experiments of Exner. Höpfner was the first to perform a successful arterial autograft. Sixteen histologically studied cases of arterial autografts were found in the literature. All of them had been performed in dogs.

Borst and Enderlen reported three observations. One was a carotid reimplantation of 122 days' duration; one a contralateral carotid transplantation of 10 days' duration; another a contralateral carotid transplantation of 14 days' duration. The grafts were described as unchanged except for a thickening of the intima by a growth of young connective tissue which extended from the suture lines; the thickened area contained delicate newly
formed elastic fibers. Stich and Zoeppritz\textsuperscript{a} described the same intimal thickening in a femoral transplant to a carotid defect 14 days old; they thought this process arose in the graft itself. Yamanouchi\textsuperscript{a} made essentially the same observations as Borst and Enderlen, a thickening of the intima with newly formed elastic fibers extending on the transplant from the suture lines. His studies were based upon examination of four transplants varying in age from 7 to 108 days. The youngest was a reimplantation of the abdominal aorta, the oldest a carotid reimplantation. Two carotid transplants to a femoral defect were 86 and 95 days in age. Castiglioni\textsuperscript{18,19} in studying five grafts, carotid reimplantations, or contralateral transplantations varying in age from 63 to 250 days, also noted no alteration except intimal thickening with newly formed elastic fibers near the suture lines. In a 250-day-old graft this thickening, though slight, was found throughout the graft.

In contrast, a few observers described the transplants as entirely normal. Such was the case with the 28-day-old contralateral carotid graft of Guthrie and his associates,\textsuperscript{5,18,19} with the 93-day-old carotid reimplantation of Villard and his co-workers,\textsuperscript{15,16,17} and with the 91-day-old femoral artery graft to a carotid defect recorded by Moure.\textsuperscript{50}

In summary it may be said that the wall of the fresh arterial autograph upon examination from 10 to 250 days after operation is described as undergoing no change or only intimal thickening. The graft would appear to survive as a living structure.

\textit{Venous autografts.} The earliest experiments with venous autografts were those of Gluck,\textsuperscript{29} Exner,\textsuperscript{51} and Höpfner\textsuperscript{29}; all resulted in failure. Carrel and Guthrie\textsuperscript{14,15,16} were the first to succeed; they transplanted in dogs the external jugular vein to the carotid artery and the femoral vein to the femoral artery. At the same time Goyanes\textsuperscript{51,52} performed 15 transplants of inferior vena cava to the abdominal aorta of dogs, but all save one ended in failure, the exceptional case showing grossly only a fibrinous layer over the suture lines when examined on the thirteenth day. Altogether 40 cases of venous autografts examined histologically were found in the literature. They were all performed on dogs unless otherwise indicated.

Carrel and Guthrie\textsuperscript{15,16} described intimal thickening and an increase in connective tissue in the media and adventitia in a 14-day graft of jugular vein to carotid artery. Subsequently Carrel\textsuperscript{50} reported studies in three cases—two instances of transplantation of vena cava to abdominal aorta in the cat, 32 and 303 days in age, and one 415-day-old similar transplant in a dog. In 32 days he found the media was composed chiefly of connective
tissue. Elastic fibers were absent in this specimen and were seen infrequently in the 303-day-old graft, the media of which was entirely composed of connective tissue. In the specimen 415 days old, however, the muscle cells seemed to be increased in number in addition to the increase in fibrous tissue in the media. In this case there was also a little intimal thickening. The adventitia was considerably thickened by fibrous tissue in all three cases. Carrel supposed that a vein graft could undergo functional hypertrophy (increase in muscle and connective tissue) with a tendency towards arterialization, or could undergo progressive sclerosis with disappearance of the muscle cells; he further supposed that the sclerosis might develop as an aftermath of the hypertrophy. He found some evidence for this assumption in another case\textsuperscript{19,38} in which a small piece of a jugular vein transplant into a carotid defect was extirpated in 143 days and showed a sclerosed media containing an increased number of muscle cells, while in 605 days the remaining graft showed further sclerosis with disappearance of all the muscle. Watts\textsuperscript{20} found an increase in the subendothelial tissue resulting in intimal thickening, as well as fibrous thickening of media, adventitia, and periaventitia in a 26-day-old transplant to the carotid artery.

On studying seven cases of jugular transplants to the carotid artery ranging in age from 19 to 86 days, Fischer and Schmieden\textsuperscript{39} found the intima for the most part unchanged. In some instances, however, there were between the endothelium and media large flat thickenings composed of a dense layer of long spindle-shaped cells which appeared to be connective tissue cells but which at times had a striking resemblance to smooth muscle cells. These thickened areas were only found near the suture lines and were almost entirely free of elastic fibers. The authors assumed an inflammatory histogenesis, an endothelial proliferation provoked by minute lesions of the intimal surface during operation. Against the assumption that these thickenings were of a compensatory nature due to the high blood pressure the authors stated (i) that these thickenings were found relatively early and did not increase in thickness later, (ii) that they were not found in places remote from the suture lines, and (iii) that they did not occur in other experiments in which jugular veins were subjected to arterial pressure by anastomosis with the carotid artery. In addition to the intimal changes described, the media of the transplants showed hypertrophy and hyperplasia of the muscle cells and an increase in connective tissue. It could not be determined whether the diminution in elastic fibers was the result of stretching of the vessel wall or represented a real reduction in number. The
adventitial connective tissue was described as tighter and firmer than normal.

Stich and Zoeppritz studied three cases of jugular grafts to the carotid artery, 26, 211, and 409 days in age. In all three they found a considerable thickening of the intima with new formation of elastic fibers. In the 211-day specimen this thickening was irregular and wave-like. In the 409-day specimen the intima in the mid-portion of the graft was composed of a single layer of cells whereas there was considerable thickening nearer the suture lines. The media and adventitia were described as unchanged in all three instances except for a stretching of the elastic fibers. The authors assumed that the thickening of the intima was the result of the arterial pressure and that the new cells arose from the venous endothelium.

Borst and Enderlen described the same intimal thickening in a 19-day-old jugular transplant to the carotid artery. This thickened intima showed newly formed elastic fibers and it decreased in thickness towards the middle of the graft. There were smooth muscle cells in the thickened areas. Since these changes were observed at a distance from the suture lines, the authors assumed that they resulted from the arterial blood pressure. The media showed hypertrophy and hyperplasia of muscle cells, there was a marked increase in the connective tissue of media, adventitia, and periadventitia, and the elastic fibers appeared to be stretched far apart.

Guthrie and his associates described complete absence of muscle cells and a very pronounced adventitial fibrosis in a 28-day-old transplant of jugular vein to carotid artery. In studying one 85-day-old graft of femoral vein to femoral artery and three grafts of jugular vein to carotid artery 51, 66, and 297 days in age, Yamanoiichi described intimal thickening of the entire graft with newly formed elastic fibers, moderate increase in the number of muscle cells, and marked connective tissue proliferation in the media and adventitia. He, too, assumed that the intimal thickening was produced by the blood pressure. Curcio examined a 23-day-old jugular transplant to the carotid artery and found fibrous thickening of the intima with delicate elastic fibers which decreased in number towards the mid-part of the graft. Palazzo reported no changes in a 10-day-old jugular graft to the carotid artery. In similar specimens studied 50, 100, 475, and 483 days after transplantation, however, he described a newly formed subendothelial layer of connective tissue without smooth muscle cells or elastic fibers, as well as hypertrophy and hyperplasia of the muscle cells of the media and an associated increase in collagenous and elastic tissue. Villard and his associates, on examining a similar jugular trans-
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plant 113 days old, described the same thick subendothelial layer of connective tissue. Although they found no elastic fibers they did find smooth muscle cells, the presence of which led them to assume that arterialization of the venous graft had taken place. They noted no changes in the media; the adventitia was thickened by fibrous tissue. Castiglioni examined two jugular transplants to carotid arteries 20 and 37 days old and a 195-day-old graft of femoral vein to carotid artery. He described a thickening of the intima from proliferation of endothelial cells and new elastic fibers and he, too, assumed these changes to be of a compensatory character. Hyperplasia of the medial and adventitial connective tissue as well as hypertrophy of the medial muscle cells were noted.

Moure studied six similar jugular grafts varying in age from 23 to 137 days. He found a subendothelial layer of spindle-shaped cells, which he considered to be smooth muscle cells, and newly formed elastic fibers. Again hypertrophy of the muscle cells and elastic fibers of the media was noted as well as fibrous thickening of the adventitia. In an additional case Moure excised a segment, one cm. in length, from the mid-portion of an 801-day-old jugular graft and in its place inserted a segment from the normal contralateral jugular vein. Histological description of the excised specimen was limited to the remark that there was hypertrophy of the wall and formation of a subendothelial layer. Thirty-seven days later the dog was sacrificed, and the second venous graft was said to have been as thick as the original graft. The author considered that the experiment gave evidence that the venous autograft persists as a living structure since it is capable of receiving and gaining firm union with a second graft. No histological study was reported.

Goodman’s 8-day-old femoral vein transplant to a carotid artery was said to have shown degeneration of the wall.

In summary it may be said that histological examination of specimens ranging in age from 8 to 801 days led all investigators to the general conclusion that venous autografts persist as living structures but undergo certain histological changes consisting chiefly of fibrous reinforcement. It was generally supposed that these alterations resulted from the arterial pressure exerted upon the transplant. There was considerable difference of opinion concerning the nature and degree of the structural changes.

Fresh homografts

Arterial homografts. Höpfner was the first to perform a successful arterial homograft; he transplanted the femoral artery of a dog to the
carotid artery of another dog. We have found in the literature histological studies of 22 arterial homografts ranging in age up to a maximum of 3 months. Unless otherwise indicated, all were transplants from one dog to another.

Ward examined an aortal graft to another aorta 70 days after operation. He found the muscular and connective tissue layers well preserved; there was a very slight decrease in the amount of elastic tissue. Borst and Enderlen studied two specimens, one a 22-day-old carotid transplant to the carotid artery of a second dog, the other a 29-day-old carotid artery transplant to the carotid artery of a second goat. In both they found signs of destruction of the graft—lack of nuclear staining, break-down of elastic fibers, swollen adventitial collagenous tissue, and infiltration of the wall with polymorphonuclear leucocytes. There was a layer of young connective tissue on the external surface of the adventitia. Flat mural thrombi were seen on the intima in the specimen from the dog. The whole intimal surface of the goat transplant was covered with a thin layer of connective tissue containing smooth muscle cells and elastic fibers. The same tissue filled the suture lines. The authors assumed that the fibroblasts in this tissue were derived from the endothelium of the carotid of the host and that the smooth muscle cells had, in turn, been derived from these fibroblasts.

Stich and Zoeppritz found no changes in three carotid transplants to other carotid arteries when examined 4, 5, and 11 days after operation. Yamanouchi also found a 10-day-old aorta to carotid graft normal in appearance. Only a thickening of the intima with newly formed elastic fibers was noted extending for some distance from the suture lines. In a similar graft 36 days old, however, the nuclei in the media did not stain, the elastic fibers were fragmented, and the adventitia contained polymorphonuclear leucocytes and fibroblasts extending towards the media. The internal surface of the graft was covered by a thickened intima which contained elastic fibers. Two additional grafts of carotid artery to carotid artery, 27 and 74 days in age, showed the same alterations with the exception that the intimal thickening was confined to the ends of the transplants.

Villard and his associates studied two cases, one an 11-day-old graft of iliac artery to carotid, the other a 62-day-old carotid to carotid transplant. Again in the early specimen no alterations were noted. In the older specimen, however, the muscle cells had disappeared though the elastic fibers were still visible. The internal surface was covered by a layer of young connective tissue and smooth muscle cells and there was newly formed connective tissue in the adventitia. Similar observations were made
by Ingebrigtsen who examined eight specimens 3 months in age, all carotid to carotid transplants in cats. The muscle cells were either normal, degenerating, or absent, the elastic fibers were normal, there was a fibroblastic thickening of the intima, and in some there was increased connective tissue in the adventitia. In a 63-day-old carotid to carotid graft Castiglioni noted almost complete absence of muscle cells, breaking down of elastic fibers and some intimal thickening. Goodman described a 21-day-old carotid to carotid transplant as undergoing destruction with the elastic tissue in the process of fragmentation. An increase in connective tissue was noted on the outer surface of the adventitia.

In summary it may be stated that the majority of authors seemed agreed that after a brief interval the arterial homograft exhibited signs of destruction and of reinforcement by connective tissue proliferation from the outside.

Venous homografts. Only one histological description of a venous homograft was found in the literature. Yamanoichi described a jugular transplant to a carotid artery 119 days in age. The wall was replaced by dense connective tissue. Muscle cells and elastic fibers were absent. The entire internal surface was covered by a thickening of the intima; newly formed elastic fibers were contained in this layer.

Fresh heterografts

Arterial heterografts. The initial efforts with arterial heterografts made by Höpfner resulted in failure. Carrel and Guthrie were the first to achieve success with heterografts; Carrel's early investigations were with preserved arteries. Ten instances of histological examination of fresh arterial heterografts were found in the literature.

Ward examined a 20-day-old transplant of cat aorta to the carotid artery of a dog. He found very slight loss of elastic tissue, a beginning breaking down of muscle fibers, and proliferation of new connective tissue. In a 70-day-old transplant of rabbit aorta to the carotid of a dog the intima was found replaced by a layer of hyalinized fibrin and blood. The muscle cells had disappeared almost entirely and the elastic fibers had disappeared completely. Newly formed connective tissue had replaced the original vessel wall to a considerable extent.

Stich and Zoeppritz examined two grafts of cat aorta to the carotid artery of dogs. In one, 15 days old, the intima and the inner layers of the graft were well preserved.Externally the graft was surrounded by fresh scar tissue which was growing into the graft. In the other, which was 52
days old, only scanty rests of media showing degeneration of elastic fibers were seen. The adventitia was replaced by scar tissue. A thick layer of vascular granulation tissue was found growing from the suture lines into a flat mural thrombus which covered the whole inner surface of the graft. A third transplant, a 51-day-old graft of rabbit aorta to the carotid of a dog, also showed only scanty remnants of media infiltrated by granulation tissue. The internal surface of the graft was covered by flat mural thrombi and a thick fibrous layer containing newly formed elastic fibers. Scar tissue had replaced the adventitia. In another case, a 14-day-old transplant of human posterior tibial artery to the carotid of a dog, granulation tissue was found growing from the suture lines into a flat mural thrombus which covered the whole inner surface of the graft.

In a 214-day-old transplant of rabbit aorta to the carotid of a dog Guthrie and his associates found the muscle cells and elastic fibers had disappeared and been replaced by dense, partly hyalinized connective tissue with some calcification and osteogenesis. There was a layer of living connective tissue between the endothelium and the transplant, and another layer of connective tissue covered the external surface of the graft.

Yamanoũchi found the media somewhat necrotic in a 12-day-old transplant of dog iliac artery to the aorta of a cat. There was an intimal proliferation with newly formed elastic fibers extending over the graft from the suture lines. In a 42-day-old specimen of cat aorta transplanted into a carotid defect in a dog the media was amorphous, the elastic fibers fragmented, and, as in the other case, intimal proliferation. Both specimens showed growth of connective tissue on the external surface of the graft.

A 35-day-old transplant of rabbit aorta to the carotid of a dog was described by Villard and his associates as showing some intimal thickening near the suture lines with the mid-portion of the inner surface of the graft covered with fibrin. There were islands of fragmented elastic fibers in the media and inflammatory infiltration in the adventitia.

No histological study of fresh venous heterografts was found.

In summary it may be concluded that after a short interval fresh arterial heterografts show evidence of destruction and of reinforcement by connective tissue proliferation.

Preserved vascular transplants

Preserved arterial homografts. Carrel was the first to investigate the functional and histological results with preserved arterial homografts. In
an extensive study he used as grafts carotid arteries of dogs kept in a refrigerator in different media for varying periods of time. The media used were physiological saline solution, Locke's solution, humid air, vaseline, serum, and defibrinated dogs' blood. Carrel arrived at the conclusion that these blood vessels were in a condition of "latent life," based upon the observation that after transplantation there occurred only partial or no degeneration of their walls and the muscle cells maintained their normal appearance for a long time after operation, while rapid degeneration of the wall occurred after transplantation of "dead" blood vessels. According to the histological descriptions, however, there can be no doubt that these grafts preserved in "latent life" underwent the same degenerative changes observed in fresh arterial homografts. When examined shortly after transplantation the elastic fibers were found unchanged and the muscle cells only partially destroyed. After longer periods of observation, the longest being 660 days, the elastic fibers were in large part well preserved but the muscle cells were replaced by connective tissue. In some cases the intima was thickened by connective tissue composed of elongated cells, the nuclei of which resembled muscle cell nuclei, and by newly formed elastic fibers. The thickened intima was covered by endothelium. The adventitia was thickened by connective tissue proliferation.

In reviewing these studies it is impossible to decide which of these preserved vessels were still in a condition of "latent life" at the time of transplantation and which were completely dead. The criteria which Carrel used would seem applicable only to autografts in which survival or death of tissue after transplantation would be the basis for judging whether the graft was alive at the time of transplantation or not. The histological results might be similar in living or dead homografts. If the tissues were viable they would probably also possess their serological properties and would be destroyed by the host. If already dead, the result might be the same. It would appear that the questions he attempted to answer—the length of time vessels could be kept in "latent life" and the best medium for storage—were not answered.

Carrel also carried out three experiments with homografts preserved by drying over calcium chloride and placed in Locke's solution immediately before transplantation. One graft was successful and was examined after 202 days. The muscle cells had disappeared, the elastic fibers were normal, the adventitia somewhat thickened, and the intima was thickened by connective tissue cells and thin elastic fibers. In two other experiments homografts were left at —3° C. for several days. Both were thrombosed
when examined after 5 and 85 days respectively. Bode and Fabian\textsuperscript{*} repeated Carrel's experiment, but thrombosis occurred in most of the grafts and the age of the graft was only a few days in the successful experiments.

Yamanoōchi\textsuperscript{7} used as transplants to carotid or femoral arteries specimens of aorta kept for from 3 to 9 days in Locke's solution in a refrigerator. The grafts were 9, 24, 103, and 143 days old at the time of study. The same observations were noted as in fresh homografts—intimal thickening with newly formed elastic fibers, disappearance of muscle cells, fragmentation and reduction in number of elastic fibers, ingrowth of granulation tissue from the outside into adventitia and media. The two oldest specimens also showed calcification. In another 24-day-old graft to carotid artery of a segment of aorta, kept refrigerated for 5 days in physiological saline solution, the muscle cells and elastic fibers were well preserved; there was a growth of granulation tissue extending into the adventitia and media. In two other experiments Yamanoōchi used for grafts to the abdominal aorta transplants kept for 5 and 10 days respectively in sterile water in a refrigerator. One was examined 8 days after operation. The muscle cells stained poorly or not at all, the elastic fibers were fragmented and irregularly stained, and granulation tissue was seen growing into the adventitia from the surrounding tissues. The other specimen was studied 81 days after transplantation. The muscle cells were necrotic, the elastic fibers degenerated and reduced in number, the periadventitia and adventitia occupied by dense connective tissue which also was observed to be growing into the outer portion of the media. There was intimal thickening over the entire graft.

Villard and his associates\textsuperscript{65, 66} examined one 48-day-old transplant of a carotid artery kept for 19 days in a refrigerator before being used as a graft to a carotid artery. An entirely newly formed intima was found. Again the muscle cells had disappeared. The elastic fibers were still visible. The adventitial area was occupied by newly formed connective tissue, the fibroblasts of which were growing into the media. The original graft was described as interposed like a "sequester" between newly formed intima and adventitia. In another experiment Villard and his associates\textsuperscript{65, 67} also studied a 34-day-old graft of an iliac artery kept for 67 days in artificial serum in a refrigerator before transplantation to a carotid. The more resistant parts of the elastic framework of the graft were preserved, while the rest had undergone atrophy and resorption. No newly formed intima could be seen.

In summary it would appear that preserved arterial homografts
behave much like fresh homografts, undergoing degeneration and fibrous replacement.

*Preserved venous homografts.* Only one specimen studied histologically was found in the literature. In this case Carrel\textsuperscript{a} kept a jugular vein in cold storage for 24 hours before transplanting it to the thoracic aorta. When examined 802 days later, neither muscle cells nor elastic fibers were found preserved. Endothelial cells were seen on the internal surface of the graft.

*Preserved arterial heterografts.* Carrel\textsuperscript{a} had two successful results in four arterial heterografts preserved in the refrigerator for from 3 to 20 days in physiological saline solution, defibrinated blood, or Locke's solution. No histological examination was carried out. Subsequently\textsuperscript{a} he transplanted a human popliteal artery to a dog's abdominal aorta after keeping it for 24 days in a refrigerator in physiological saline solution. The specimen was examined 4 years and 2 months later. No muscle cells or elastic fibers were seen, the vessel consisting exclusively of connective tissue with areas of hyaline degeneration.

Moure\textsuperscript{a} transplanted a human popliteal artery to a dog's carotid after keeping it for 24 hours in physiological salt solution in a refrigerator and for another 48 hours in vaseline at room temperature. The graft was studied 53 days after operation. Muscle cells were absent. The graft was composed of a fibrous-elastic scaffold embedded in fibrin.

*Preserved venous heterografts.* Carrel\textsuperscript{a} made the first attempt to transplant a preserved venous heterograft. After keeping a segment of jugular vein from a dog in physiological saline solution in a refrigerator for 7 days he sutured it into an aortic defect in a cat. When examined 22 days later, the segment was occluded by a thrombus. Only two histological studies of preserved venous heterografts were found in the literature.

Bode and Fabian\textsuperscript{a} kept a human saphenous vein in a refrigerator for 2 days and then transplanted it to a dog's brachial artery. Upon examination 130 days later, a spindle-shaped dilatation of the graft with marked thickening of its wall was noted. No muscle cells and only remnants of elastic fibers were seen. The wall of the graft was replaced by connective tissue, partly hyaline in appearance. Villard and his coworkers\textsuperscript{f,g} kept a human popliteal vein in artificial serum in a refrigerator for 24 hours before suturing it into a defect of a dog's abdominal aorta. Twenty days later an aneurysm was found in the region of the graft. The original vein was almost entirely degenerated and only the elastic fibers were visible.

In summary, the preserved arterial and venous heterografts underwent degeneration with replacement of connective tissue from the host.
Fixed vascular transplants

Arterial transplants. Guthrie7 was the first to transplant successfully a formalin-fixed arterial graft. In this instance a segment of cat aorta was transplanted to the carotid artery of a dog. We have found in the literature six histologically studied cases of successful transplantation of fixed arterial grafts. They ranged in age from 6 days to 3 months; all were homografts in dogs.

Levin and Larkin44,45 studied 3 grafts of formalin-fixed thoracic aorta used as transplants to abdominal aorta, 9 and 11 days and 10 weeks after operation. In the earliest specimen the inner half of the graft was entirely necrotic and the outer half appeared to be undergoing degeneration. The elastic fibers were preserved. In the 11-day-old graft the entire wall was homogeneous; elastic fibers were stained but seemed swollen and diminished in number. In the oldest specimen the wall of the graft showed zones of calcified material interlaced with badly damaged and swollen elastic fibers. There were occluding thrombi at both ends of the graft. In all three specimens the external surface of the transplant was covered with a sheath of connective tissue.

Bode and Fabian45 found normal staining quality of nuclei and elastic fibers in a 6-day-old transplant to femoral artery of a formalin-fixed segment of carotid artery. Yamanouchi46 found no nuclear stain in the media and fragmentation and reduction in number of elastic fibers as well as thickening of the intima containing elastic fibers. His specimen was a 24-day-old graft of formalin-fixed aorta transplanted to a carotid artery.

Nageotte and Sencert49,54 studied a 3-month-old alcohol-fixed carotid graft transplanted to another carotid. The inner surface was said to be covered by a new intima formed by proliferation and overgrowth of the endothelium of the artery of the host. Underneath the new intima, near the suture lines, there was a layer of smooth muscle cells thought to be derived from the media of the host artery; these cells were called "myome de régénération." The muscle cells of the media of the graft had disappeared but immigrated fibroblasts, transitional cells from fibroblasts to muscle cells and smooth muscle cells were visible. The elastic fibers were preserved. Adventitia and periadventitia had a relatively normal appearance due to immigration of fibroblasts which replaced the original connective tissue cells; the original collagenous fibers remained unchanged. This process was termed connective tissue "reviviscence."

Several later workers had less success. Fici and Speciale55 found all six of their formalin-fixed grafts thrombosed when studied from 3 days to 3
months after transplantation. Hosomi found the lumen obliterated in 21 alcohol-fixed grafts examined from 8 to 407 days after operation.

Venous transplants. Only one histological study of a previously fixed venous graft was found in the literature. This specimen studied by Guthrie and his associates is, however, of remarkable interest since it was examined 11 years and 2 months after transplantation. A segment of vena cava of a dog was fixed in 2.5 per cent formalin for 60 days, washed in dilute ammonia, dehydrated in absolute alcohol, and impregnated with paraffin oil before transplantation to the carotid of another dog. The animal died over 11 years later of a metastasizing sarcoma of the sternum. At the site of the graft a spindle-shaped aneurysmal dilatation was seen. A small strip of the original graft was still recognizable histologically; it consisted of hyaline connective tissue with some granules representing remnants of elastic fibers. The original transplant was surrounded on intimal and external surfaces by a sheath of connective tissue; endothelium covered the intimal surface. There was calcification in the remainder of the graft and in the subendothelial layer of connective tissue.

In summary it would appear from the few observations reported that dead fixed arterial and venous transplants may result in functional success. The graft tends, like fresh and preserved homo and heterografts, to be replaced by connective tissue.

Discussion and summary

In spite of certain limitations and points of disagreement the early studies of vascular transplants have given us valuable information concerning the histological fate of these grafts. There seems to be general agreement that fresh arterial autografts survive as living structures with either no change or only intimal thickening. There is also general agreement that fresh venous autografts likewise survive as living transplants but undergo more marked histological changes consisting chiefly of fibrous reinforcement. Most investigators assumed that these changes were the result of the arterial pressure upon the graft. Considerable difference of opinion was expressed concerning the nature and degree of the structural changes, especially as to whether the smooth muscle cells of the media remain unchanged, or undergo hypertrophy and hyperplasia, or disappear after a short interval. These differences may be explained, in part at least, by the variation in the histological appearance of the normal vein, not only in different regions of the body, but also in the same region of different individuals of the same species, and even in the course of the same vein.
After a brief interval most of the fresh arterial homografts were found to show signs of destruction and of reinforcement by connective tissue proliferation from the host; the same was true of the one fresh venous homograft studied. Fresh arterial heterografts similarly seemed to undergo destruction with fibrous replacement. No histological study of fresh venous heterografts was found in the literature. In general, arterial and venous homografts and heterografts preserved in a cool atmosphere in various media before transplantation similarly showed evidence of degeneration and fibrous replacement. Previously fixed vascular transplants showed fibrous reinforcement and varying degrees of disintegration.

A question of considerable interest concerns the structure and histogenesis of the intimal thickening of the transplants the cells of which have been described by several investigators as smooth muscle cells derived from fibroblasts. Since the transformation of fibroblasts into smooth muscle cells in postembryonic life is a much-debated problem, a clear-cut definition of these cells would be valuable. This point will be discussed further in connection with our own studies of venous transplants.

It appeared evident from our review that, in spite of marked differences in histological fate, all types of vascular transplants were capable of functionally bridging arterial defects.

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