QUANTITATIVE STUDIES ON THE TIME FACTOR IN ARTERIAL INJURIES*

HARRY H. MILLER, M.D., AND C. STUART WELCH, M.D.

BOSTON, MASS.

FROM THE DEPARTMENT OF SURGERY, TUFTS COLLEGE MEDICAL SCHOOL, THE NEW ENGLAND CENTER HOSPITAL, AND THE ZISKIND RESEARCH LABORATORY, BOSTON, MASSACHUSETTS

THE PERIOD during which an extremity, deprived of its major source of blood, remains ischemic is a factor of particular importance influencing the chance for survival upon restoration of its circulation. The disappointing results which were obtained in the treatment of arterial injuries in the leg as observed in World War II could be attributed to some extent to the considerable "time lag" or period elapsing between wounding and receiving surgical attention. Long periods of ischemia with necrosis of tissue associated with thrombosis of small arteries may produce a leg that is beyond recovery. Progress in the field of early definitive surgery was disappointing in World War II.[1-3] The number of immediate anastomoses of severed arteries was relatively small although an advance was made in this field as compared with the number done in World War I.[4-6] The incidence of necessary amputation after femoral or popliteal injury treated by ligation was high.[7, 8] In the experience of one of us, gangrene of the leg occurred after ligation of the femoral or popliteal arteries in 70 per cent of patients.[9] It is true that not much more than ligation was possible or advisable in many instances. It must be said, however, that a vast field for improvement in the management of arterial injuries remained at the end of the war. In retrospect, several shortcomings in the overall management of vascular casualties seem to stand out after analysis of the recorded experience. In the first place it was not fully appreciated that anastomosis of the artery was essential for good results, although Blakemore strongly advocated the use of his non-suture method in battle casualties.[10] A program whereby casualties with arterial wounds might be detected early and receive priority treatment was not attempted. The general lack of surgical experience with arterial anastomosis in the absence of a highly satisfactory technic applicable to all cases also contributed to the unsatisfactory end results. In a previous work we have studied several methods of arterial anastomosis in experiments in which the survival of the dog's leg depended upon one artery which had been interrupted and rejoined. The results of these experiments exonerate all types of intima-to-intima anastomosis as an important primary cause of gangrene and failure in the salvage of limbs. Our findings in these experiments performed on dogs indicated that approximately 80 per cent of legs depending on a single anastomosed artery will

* Read before the American Surgical Association, St. Louis, Mo., April 20, 1949. This work was aided in part by a grant from the United States Public Health Service and the Charlton Research Fund of Tufts College Medical School.

survive and be restored to nearly normal under clean wound conditions if there is no appreciable period of ischemia or "time lag."[11]

In the present work we wish to present a study of the "time factor" in acute arterial injuries. The ideal time for restorative surgery is considered to be under six or eight hours.[4] Not much hope has been held for the success of anastomosis procedures after this time insofar as salvaging the leg is concerned. Clinical data on the survival of human legs after various periods of acute ischemia followed by restoration of the blood supply by anastomosis is insufficient. Furthermore, the variation in the extent of the wound and the amount of functioning collateral circulation remaining in the clinical case makes an accurate evaluation of the time factor difficult as a single item. The following experiments were projected to obtain data on the survival of extremities in a series of dogs subjected to varying periods of acute ischemia under conditions which have been sufficiently standard to have significant validity.

EXPERIMENTAL METHOD

The procedure to be described was carried out on 63 dogs. Immediate mortality and death from causes not related to the leg left 57 animals for evaluation. Three separate groups of dogs were subjected to periods of acute ischemia as follows: Group I for 1 to 6 hours; Group II for 12 to 18 hours; Group III for 24 to 30 hours. A standard procedure for producing arterial injury and acute ischemia and for restoration of the circulation was used in all experiments.

The arterial injury and period of ischemia. Acute arterial injury was produced by utilizing a modification of the Halsted-Reichert leg transection replantation procedure.[12, 13] After an especially careful skin preparation, a transection of the soft tissues of the leg was made in the mid-thigh region of anesthetized dogs. The femur, the femoral and sciatic nerves, the femoral artery and femoral vein were preserved. Anatomical replantation of the leg was then performed. At the end of this procedure the femoral artery was ligated and the vessel was effectively occluded throughout the desired period of ischemia. This preparation cuts off the main artery of supply and all collateral routes for blood via the soft tissues. Although a small amount of blood may reach the distal extremity beyond the transection by way of the medullary cavity of the femur, it is insufficient to sustain life in the leg. Previous work by Reichert[13] and by Callow and Welch[11] has shown that ligation of the femoral artery in this transection replantation preparation is followed by gangrene of the leg in 100 per cent of animals. This work established the controls for the present experiments.

During the period of ischemia the wound was completely closed and the leg was encased in a plaster of Paris splint for immobilization and avoidance of contamination. During the ischemia the animals were kept at ordinary room temperature at 70 degrees to 80 degrees Fahrenheit.

The restoration of circulation. At the conclusion of the ischemic period, the ligated femoral artery was exposed under aseptic conditions. It was then prepared for anastomosis by trimming off a cuff of adventitia. The ligated portion of the femoral artery was then excised. Thrombosis at the site of ligation was observed in less than 20 per cent of the arteries and when found was confined to the proximal segment. A good pulsating blood flow was demonstrated at the proximal end of the artery before anastomosis. The continuity of the femoral artery was restored by inserting an arterial graft between the severed ends. The suture technic was employed in all experiments. The graft was held in place by stay sutures and the anastomosis was completed by a continuous lock stitch. The technic of arterial graft was especially useful in these experiments since it permitted anastomosis with minimal tension in this situation in which a portion of the femoral artery had been excised. The use of a graft or bridging procedure is essential in the majority of clinical arterial wounds because extensive injury to the vessel involves loss of vessel substance making direct end-to-end suture difficult and hazardous. The application of arterial grafts to the problems of arterial injury was suggested to us by the recent work of Gross and his associates.[14] Autografts from the opposite femoral artery were used in 16 per cent of our experiments. Fresh homografts taken from other dogs were used in 24 per cent of the anastomoses and homografts preserved for varying periods were used in 60 per cent. These preserved or "bank" homografts were stored in a fluid medium at temperatures several degrees above freezing for as long as three weeks before they were used. Anticoagulants were not administered in these experiments either during operation or in the postoperative period.

During the course of the long transection replantation procedures intravenous fluids along with transfusions of whole blood were given. An initial dose of 300,000 units of penicillin was administered prior to operation and was continued with a daily dose of 150,000 units for 7 to 14 days. At the restorative operation wounds were completely closed and no dressings were applied.

EXPERIMENTAL FINDINGS

The experiments conducted allow observations upon three aspects of the problem of arterial injury: (1) the survival of ischemic legs after restoration of circulation, (2) the effectiveness of femoral artery grafts as a method of anastomosis, and (3) the late functional results in legs salvaged after different periods of ischemia.

Influence of Periods of Ischemia on Leg Survival. Group I. The legs of 21 dogs were transected and reimplanted using the arterial graft anastomosis after a period of ischemia ranging from one to six hours. There were an approximately equal number of animals operated at the extremes of time; *i.e.,* one and six hours. In only two animals was the leg lost, representing a 90 per cent salvage rate for this period of acute ischemia (Table I).

Group II. Of the 26 animals whose legs were transected and maintained ischemic for intervals ranging from 12 to 18 hours, 13 lost their legs. There were approximately an equal number of animals operated at the extremes of time in this group. The rate of leg survival was, therefore, 50 per cent for the group of animals of this ischemia period.

Group III. Ten animals did not have a restoration procedure performed until after 24 hours had elapsed. Only two viable extremities were obtained, a survival rate of 20 per cent in this group. It did not seem profitable to explore the late range of this 24 to 30 hour time period in more than two of the ten animals, in view of the findings in the first eight dogs, which were done after 24 to 26 hours of ischemia. Results in these first animals demonstrated at once that the upper limit of time lag had been approached. The two legs which survived were those of dogs with ischemia for 24 and 25 hours respectively.

The legs of the dogs in all groups were pulseless and cold during the ischemic period. Skin temperatures approached that of the room in which they were exposed. The ischemic part of the leg near the transection line in the thigh was noticeably warmer than the more distal parts of the lower leg and foot since it was warmed by the adjacent vascularized tissues of the thigh.

TABLE I.—*Restoration of Circulation after Acute Ischemia*

Period of Acute Ischemia	Experiments Number	Legs Survived Number	Legs Survived Percent
Group 1 (1 to 6 hours)........................	21	19	90
Group 2 (12 to 18 hours)........................	26	13	50
Group 3 (24 to 30 hours)........................	10	2	20

The skin coloration varied from a marked pallor to deep cyanosis. In Groups II and III having prolonged ischemia there was a firmness and inelasticity of the muscles which was accompanied by resistance to passive motion resembling rigor mortis.

After anastomosis had been completed, the legs became warm, the color improved and other evidences of restored circulation appeared. Usually the temperature of the operated leg rose several degrees above that of the other side. The mean rise in skin temperature was 14.5 degrees Fahrenheit at the calf as determined by a surface pyrometer. The superficial veins of the leg became obviously distended. In 80 per cent of the restored legs the pulse of the anterior tibial artery was immediately palpable at the ankle. The legs of the animals in Group I were of normal size immediately following restoration while those legs in Group II and Group III presented a moderate to marked tense swelling involving the muscular tissues throughout the extremity. In the transected replanted limbs of all groups there was a progressively increasing edema. The swelling reached a maximum in the one to six hour group on about the fourth day. On about the sixth postoperative day the edema began to subside and usually it had largely disappeared by the ninth day. Reichert has shown that the disappearance of the edema accompanies the regeneration of lymphatics across the transection.[13] In the two longer ischemic periods there was a more rapid increase in the edema so that after 24 hours it was marked and maximal on the third day. Several days more were required for its subsidence than in the one to six hour group of animals. When wound infection was present disappearance of edema was further delayed.

Discussion of Leg Failures. The nature of the experimental procedure invited a high incidence of wound complications. The long operating time which was divided into two stages and the prolonged periods of ischemia both contributed to complications. The importance of the interval of ischemia was evident when the rate of per primum healing was examined. Sixty-two per cent of the wounds in dogs' legs subjected to only one to six hours of ischemia healed per primum while the rate in those subjected to 12 to 18 hours was 14 per cent. In those having 24 and more hours of ischemia no wound healed without complication. The extensive operative wound and the presence of ischemic tissue offered an unequaled opportunity for bacterial invasion. Positive bacterial growths were obtained from 47 per cent of the wounds that were cultured at the time of the restorative procedure in spite of all precautions used in handling these animals. None of the cultures yielded Clostridia

TABLE II.—*Analysis of Failures after Restorative Surgery*

Ischemic Period	Experiments	Total Failures	Graft Failures Primary	Graft Failures Secondary	Wound Complications (Intact Graft)
1 to 6 hours.....	21	2	0	2	0
12 to 18 hours.....	26	13	1	10	2
24 to 30 hours.....	10	8	2	3	3
All periods.........	57	23	3	15	5

or anerobic Streptococci and none of the legs failed because of gas gangrene. Penicillin therapy greatly reduced infection in these wounds and it is possible that without it these ischemia experiments could not have been investigated, using the present technic.

The proximate cause of leg failure in 18 out of the total 23 was some accident that befell the arterial graft used to restore the circulation. The other five failures were the direct results of wound complications at the transection site.

In Table II an analysis of the findings in legs that failed has been tabulated. The majority of the graft failures were found to be secondary to wound infection with deep abscesses and dehiscence. Thrombosis of the graft, perforation of the graft by erosion, or disruption of the anastomotic suture line were variously found. There were only three instances of primary graft failure; all of these had intraluminal thrombosis. This low incidence of primary thrombosis in the graft augurs well for their use, especially since anticoagulants were not used.

It was found that the muscle mass at the line of transection in the jeopardized portion of the extremity invariably succumbed first to the effects of ischemia. This was due in part to the division which the transection effects of the small vessels usually supplying these muscles from above. The earlier death of these tissues, however, was not related to this factor alone, since dogs in Group I sustained the lack of this source of blood as evidenced by the rate of per primum healing and normal recovery of the legs in this group. It is probable that tissue necrosis at this level proceeds at an accelerated rate because of the higher local temperature. As the time of ischemia was extended, the degree of tissue necrosis was reflected in the greatly increased incidence of wound complications that were followed by leg failure. This finding can be explained satisfactorily only on the basis of degeneration of tissue to a point beyond which recovery was not possible after restoration of the circulation via the femoral artery.

The ischemic limbs of dogs in Groups II and III which were examined at post mortem showed grossly a softening of all the muscles, which was most evident just distal to the transection line. In those of the 24 to 30 hours group with far advanced changes there was actual liquefaction of the muscle tissues in the vicinity of the transection. In addition, liquefaction was observed to occur in the central portion of the anterior tibialis muscles. These findings are similar to the characteristic pathologic changes of early Volkmann's ischemic contracture as Griffiths has pointed out.[15, 16] The presence of these far advanced alterations in the muscular tissue indicated that the time limits of ischemia for leg survival imposed by tissue necrosis had been approached in the time period of 24 to 30 hours during which there had been deprivation of the circulation.

It may be speculated that thrombosis in the small end arteries supplying the muscle initiated, or simultaneously accompanied, muscle tissue death and that inadequate blood reached these tissues after restoration of the femoral artery. Histological tissue studies of these animals' legs are in progress.

Arterial Graft Anastomosis. The requirement for anastomosis without tension in arterial injury in which excision or loss of some part of the vessel generally occurs is fulfilled by the arterial graft method. This technic is superior to the vein graft method in a number of respects. We believe that it is easier to perform than the non-suture vitallium tube vein graft technic of Blakemore, Lord and Stefko. The artery graft is a sturdier bridge and does not result in the narrowing of the lumen that is unavoidable when metal cuffs are employed. If autogenous grafts were an absolute requirement the disadvantage of the arterial graft technic for patients would be obvious. Suitably sized fresh autografts cannot be taken from the human subject without danger of impairing circulation to the part supplied. The development of a "bank" for arteries removed from cadavers as suggested and utilized by Gross, however, is a practical solution to this problem. The experimental conditions in the transection-replantation wound have subjected these grafts to a rigid test. In one dog in the 12 to 18 hour group which had an extensive dehiscence of over half of the tissues at the transection site which left the femoral sheath structures suspended without support, the artery graft continued to function and to supply satisfactorily the distal leg until slow healing by granulation took place. In Fig. 1 a roentgenogram of the injected arterial tree demon-

FIG. 1.—Arteriogram in an animal sacrificed at four months showing a functioning preserved arterial homograft. Arrows indicate the site of the graft. Observe the interruption of the major collateral arterial channels produced by the previous transection procedure at the level of the graft.

strates an intact and patent graft in this same animal sacrificed when healed four months after the dehiscence. A photograph of this graft appears in Fig. 2.

There was little difference in the early and later results whether fresh autogenous, fresh homografts or preserved homografts were employed. A similar incidence of secondary graft failure occurred with all three types of grafts;

namely, 30 per cent, 23 per cent, and 24 per cent for fresh autografts, fresh homografts and preserved homografts respectively. The three primary graft failures with thrombosis were represented by one case in each variety of graft. There was no evidence in the course of these experiments that the preserved graft is any more susceptible than the fresh graft to the stress and infection encountered with wound complications. The ready availability of the preserved grafts of several sizes from the artery bank constituted a definite convenience for this work.

Late Function. The most significant differences in late function in those dogs surviving a sufficient time for evaluation were apparent between Group I and II animals. Dogs subjected to only one to six hours of ischemia had partial use of their legs after one or two weeks and in six weeks they had all

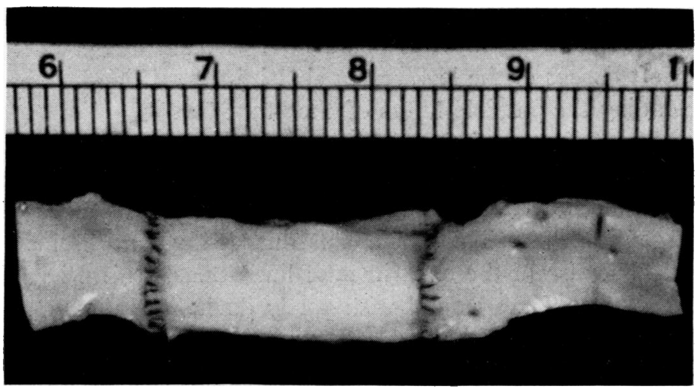

Fig. 2.—Photograph of the arterial graft shown in Fig. 1 after fixation. There is no thrombosis or erosion of the intima in this specimen.

regained nearly normal function. There was only one animal in Group I that had more than a slight weakness or slight limitation of motion, and this dog had had a postoperative abscess of the thigh which had to be drained.

When ischemia was continued for 12 or more hours, the return of function was always delayed and incomplete with limitation of motion and loss of strength as a constant finding. Response to stimulation by pin prick of the skin of the restored leg was present in these animals. The growth of hair continued in those with more prolonged ischemia at reduced rates. All had some muscular atrophy. Contractures were present in the muscles of all the late restored legs of these dogs. In a few of Groups II and III dogs, the contractures were only slight. The majority, however, had a moderate degree of contracture. In two of the animals having ischemia for 18 and 24 hours respectively, the contractures were virtually complete, producing extremities fixed in full extension. Ambulation has been good in both of these animals on a "peg leg" and the function has been surprising. The picture which these two dogs with advanced muscular contracture present is essentially similar in certain respects to that seen in the late result of Volkmann's ischemic contracture in the human subject.

DISCUSSION

The data from these experiments, projected into terms of arterial injuries in human subjects, lend support of the view that reparative surgical treatment with early anastomosis of severed major arteries of the extremity should be practiced whenever possible. The salvage of 50 per cent of limbs ischemic for 12 to 18 hours and of 20 per cent of those ischemic for more than 24 hours in the experimental animal offers decided encouragement for the recovery of human extremities with severe vascular injuries when treatment has been delayed beyond the accepted optimum time of six to eight hours. While none of the legs in the animal preparation used in these experiments escaped gangrene when the femoral artery was ligated, it has been surmised that some collateral circulation is partially intact and sufficient to prevent gangrene in approximately 30 per cent of instances when femoral or popliteal vessels have been ligated in human leg injuries in warfare. Seldom is a complete transection of the soft tissues of the leg seen in civil injuries which is a great advantage in extending the possible limits of the "time lag."

The modifying factor of the clean wound technic used throughout these experiments has, without doubt, been an advantage in favor of these animals. On the other hand, infection and dehiscence was the prime cause of leg failure after prolonged ischemia. This was a consequence in part of ischemic necrosis of the tissues but also of the experimental limitations, which, in animals, has necessitated closure of the wound with partly devitalized tissues and bacteria buried in closed spaces. In the human subject an open wound technic is possible and desirable in the contaminated wounds and much of the infection we encountered might be avoided, and secondary hemorrhage from the anastomosis in failures reduced. The experience in the last war with wound infection was surprising.

Homograft arteries have survived sufficiently long in our dogs to pass the critical period before collateral circulation becomes effective. In fact, we believe that they have a good longevity, although other investigators[17] have doubted their durability. Late studies of these grafts in surviving animals are contemplated.

We believe that the arterial graft anastomosis is the best method for joining arteries of the extremities when there is loss of arterial substance, although we have no experience in human subjects. The use of banked arteries should be practical for both civilian and military hospital groups.

Survival of the leg itself with a damaged major vessel cannot be the sole desideratum; rather, the aim should be to secure a viable leg that functions as well as possible under the existing circumstances. To accomplish this it is essential that the main vascular channel be restored to function. The few long term follow-up studies of vascular casualties available indicate a sizable incidence of functional limitation in legs with femoral and popliteal injury. Even in legs with arteriovenous fistulas which are believed to have so well developed a collateral circulation that safe ligation of the femoral or popliteal vessels is possible without resulting gangrene, the occurrence of chronic circulatory deficiency after quadruple ligation is high.[18] These legs are frequently susceptible to cold; claudication is often observed and sometimes trophic changes follow. It is, therefore, of importance to provide a permanent means of arterial restoration in the case of vascular injuries if good results are to be expected. It is difficult to compare the impaired function seen in the legs of the dogs in the present experiments with results in human subjects. As a rule the acute ischemia in the injured human leg would not be expected to reach the degree seen in these animals' legs except in the unusual transection type of wound.

Although severe muscular contractures were present in some of the legs of dogs in the longer ischemia periods, the possibility of this disability occurring in the human subject should not be a deterrent to efforts to salvage the leg. There is no method of determining slight variations in ischemia in legs with wounds of unknown extent and variable loss of collateral vessels. As long as the extremity does not show signs of gangrene or extensive tissue deterioration, attempts to restore the circulation through the damaged main vessels should be carried out. Some impairment of function can be expected in certain cases. However, such sequelae can be dealt with as they present at a later observation.

SUMMARY

In these experiments estimations have been made in animals on the probability of the survival of legs undergoing acute ischemia for time intervals of specific duration. Three time periods which extended from the onset of the ischemia to its abolition by restoring the circulation, corresponding to the clinical "time lag," were investigated. Under standard conditions of injury depriving the legs of their blood supply it was found that following restoration by arterial anastomosis the survival rate for these legs were as follows: (1) for periods of ischemia ranging from one to six hours, 90 per cent survival; (2) for periods of ischemia ranging from 12 to 18 hours, 50 per cent; and (3) for periods of 24 hours or over, 20 per cent.

Arterial grafts of three sorts were used with equal success. These were fresh autografts, fresh homografts and preserved homografts. Intravascular thrombosis in the grafts seldom occurred primarily. Failure of these grafts from thrombosis or hemorrhage was secondary to infection and wound dehiscence in all but three of 23 failures of legs to survive. The incidence of secondary failures were related to the period of ischemia. Anticoagulants were not used in these experiments.

Ischemia for a period beyond 12 hours in animals whose leg survived resulted in a variable degree of disability of the limb which was principally the consequence of contracture and atrophy.

BIBLIOGRAPHY

1 Odom, C. B.: Vascular Injuries in Battle Casualties. Inter-Allied Conferences on War Medicine 1942–1945, (pp. 167–171), edited by H. L. Tidy, and J. M. B. Kutschbach. London, Staples Press, Ltd., 1947.

[2] MacFee, W. F.: Arterial Anastomosis in War Wounds of the Extremities. Surg. Clin. N. America, pp. 381–389, April, 1948.
[3] Smith, M. K.: Arterial Injuries. Ann. Surg., **126**: 866, 1947.
[4] DeBakey, M. E., and F. A. Simeone: Battle Injuries of the Arteries in World War II. Ann. Surg., **123**: 534, 1946.
[5] Stewart, C. F.: War Experiences with Nonsuture Technic of Anastomosis in Primary Arterial Injuries. Ann. Surg., **125**: 157, 1947.
[6] Weisel, W.: Experiences with Peripheral Vascular Wounds. Inter-Allied Conferences on War Medicine, 1942–1945 (pp. 173–179), edited by H. L. Tidy and J. M. B. Kutschback. London, Staples Press, Ltd., 1947.
[7] Bradford, B. Jr., and M. J. Moore: Vascular Injuries in War. Surg., Gynec. & Obst., **83**: 667, 1946.
[8] Odom, C. B.: Causes of Amputations in Battle Casualties with Emphasis on Vascular Injuries. Surgery, **19**: 562, 1946.
[9] Rose, C. A., O. W. Hess, and C. S. Welch: Vascular Injuries of the Extremities in Battle Casualties. Ann. Surg., **123**: 161, 1946.
[10] Blakemore, A. H., J. W. Lord, Jr., and P. L. Stefko: The Severed Primary Artery in the War Wounded: A Non-Suture Method of Bridging Arterial Defects. Surgery, **12**: 488, 1942.
[11] Callow, A. D., and C. S. Welch: Arterial Anastomosis in Experimental Arterial Injury. Surg., Gynec. & Obst. (In Press).
[12] Halsted, W. S.: Replantation of Entire Limbs without Suture of Vessels. Proc. Nat. Acad. Sci., **8**: 181, 1922.
[13] Reichert, F. L.: The Importance of Circulatory Balance with Survival of Replanted Limbs. Bull. Johns Hopkins Hospital, **49**: 86, 1931.
[14] Gross, R. E., E. S. Hurwitt, A. H. Bill, Jr., and E. C. Pierce: Preliminary Observations on the Use of Human Arterial Grafts in the Treatment of Certain Cardiovascular Defects. New England J. Med., **239**: 578, 1948.
[15] Griffiths, D. L.: Volkmann's Ischaemic Contracture. Brit. J. Surg., **28**: 239, 1940.
[16] Brooks, B.: Pathologic Changes in Muscle as a Result of Disturbances of Circulation. Arch. Surg., **5**: 188, 1922.
[17] Williamson, C. S., and F. C. Mann: Functional Survival of Autogenous and Homogenous Transplants of Blood Vessels. Arch. Surg., **54**: 529, 1947.
[18] Bigger, I. A.: Treatment of Traumatic Aneurysms and Arteriovenous Fistulas. Arch. Surg., **49**: 170, 1944.