Studies in Peripheral Arterial Occlusive Disease

III. Acute Arterial Occlusion

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Material for an analysis of the pathogenesis and course of acute peripheral arterial occlusion was provided by patients with acute arterial occlusion in a lower extremity, special arterial injection studies of amputated limbs, arteriograms performed on cadavers, and data from an experimental investigation of acute femoral artery embolism in dogs. This correlative study offers a basis for the evaluation of procedures recommended for the prophylaxis and treatment of acute ischemia.

CONFUSION and disagreement concerning the choice of therapy for patients with acute peripheral arterial occlusion are readily understandable. Many patients compensate so effectively for an acute obstruction that they do not seek medical attention. Among patients who do consult physicians, the majority recover without specific therapy. Many factors other than the specific therapy employed influence the ultimate result. Acute myocardial infarction, pulmonary embolism, congestive heart failure, renal insufficiency, or a cerebral vascular accident may complicate the clinical picture and cause a fatal outcome. Many patients have old peripheral arterial occlusive disease that limits the efficacy of collateral circulation. The therapeutic problem is often increased because some patients have associated conditions that preclude anticoagulant therapy, such as a bleeding peptic ulcer, or shock, which favors the propagation of intravascular clot. Evaluation of the net physiologic gain from induced alterations in autonomic tone remains obscure. Whether the direct surgical relief of acute arterial obstruction is preferable to anticoagulant therapy has not been established. In addition, the use of lytic agents in the dissolution of arterial thrombi is still in the stage of experiment. Finally, generalizations from one hospital experience to another are inherently limited by the variations in the type of patient admitted to each institution. It is for these many reasons that there has been as yet no agreement as to an optimal plan of therapy.

With these reservations clearly in mind, we have reviewed data on the pathogenesis and the course of acute arterial occlusion that were obtained from 5 sources: (1) the immediate and long-term outcome of patients with acute arterial occlusion of the lower extremity who were admitted to the Beth Israel Hospital in Boston during the 6½-year period ending December 31, 1955; (2) the pathologic examination of all limbs amputated at the hospital during this same period by a special injection and dissection technique; (3) femoral arteriograms performed on cadavers; (4) necropsy material on patients with acute arterial occlusion; and (5) data from an experimental investigation of acute arterial occlusion in dogs. The therapeutic implications derived from these data are discussed.

METHODS AND MATERIAL

Clinical Studies

Patients were included in this study only when information was adequate to establish that an acute arterial occlusion had occurred. Appropriate historical information, as well as changes in
pulsation, oscillographic excursion, color, temperature, and sensory and motor modalities were all utilized in arriving at a clinical diagnosis. On each entry to the hospital or outpatient clinic the patients were questioned and examined independently by house officers, third or fourth year clinical clerks, and visiting staff members. Many of the patients had been seen by one of us during the hospitalization for the acute occlusion or in the vascular or cardiac clinics prior or subsequent to the acute obstruction. Several patients had been followed in private practice by associates. In some instances additional data about these patients were obtained from records of other hospitals, from the patients themselves, from their families, and from private physicians.

Traditionally, acute arterial occlusions are classified according to whether the obstruction is caused by an embolus or thrombus. Although in many instances it was clear that the obstruction was embolic in origin, it was not possible to make this decision with any assurance in several patients in this study. Therefore, we have distinguished neither the etiology nor the source of each acute obstruction but have classified all such episodes as "acute arterial occlusions."

During the period of this investigation 75 patients were hospitalized in whom a diagnosis of acute arterial occlusion of a lower limb could be made. This material was obtained from an examination of the records of 437 patients discharged with diagnoses indicative of peripheral arterial occlusive disease. An unknown number of patients with acute arterial obstruction were missed because the diagnosis could not be derived from a careful examination of the hospital record. The clinical material studied, therefore, represents a selected portion of the total hospital population with acute leg artery occlusions.

Pathologic Studies

The technic used in injecting and dissecting amputated limbs has been previously described.\textsuperscript{1} Briefly, the arteries of each amputated leg were injected with radiopaque mass, the leg was unrolled so that the major arteries lay in one plane, the unrolled extremity was x-rayed, and the arteries were then dissected with the roentgenograms as a guide. The criteria for the determination of the presence or absence of arterial occlusion, narrowing, or interarterial anastomosis have also been previously described in detail.\textsuperscript{1} The term "occlusion" as used in this communication always denotes complete occlusion.

From July 1, 1949, through December 31, 1955, 105 limbs were amputated for vascular or non-vascular diseases at the Beth Israel Hospital and were examined by the technic outlined above. In addition, the femoral arteries of 52 cadavers were injected with the same radiopaque mass used for the amputated limbs, and the arteriograms were studied. Finally, the complete necropsy findings in 9 patients who died following an acute arterial occlusion during the period of this study were reviewed.

Experimental Studies

Serum or fractions derived from serum are known to accelerate coagulation in vitro and induce thrombosis in animals.\textsuperscript{2,3} In dogs, the intravenous infusion of heterologous canine serum induces a transient hypercoagulable state during which massive thrombosis develops in venous and arterial segments containing stagnant blood far removed from the site of infusion. When fresh, such thrombi may exhibit many of the gross and microscopic features of postmortem clot, but are easily recognized when agonal or postmortem coagulation is prevented by the administration of heparin. The technic utilized for the induction of these intravascular thrombi has been described previously.\textsuperscript{3} Briefly, in dogs under sodium pentobarbital anesthesia, a segment of each femoral artery was freed from its surrounding structures and its branches were ligated. Serum prepared from normal dogs was then infused into a distant antecubital vein. One minute later, after the infused material had been dispersed throughout the circulation, the femoral artery segments were gently occluded with clamps. Single large red clots were routinely formed in each artery segment within 60 seconds after isolation. In 30 animals so treated, the thrombus induced in one femoral artery was released to the periphery. The clot in the contralateral extremity was retained as a control at the site of its formation. The animals were sacrificed at varying times and the locations of the residual emboli were determined with the aid of the injection and dissection technic used in the study of amputated human legs.

RESULTS

Clinical Findings

Sex, Race, Age. Among the 75 patients, 38 were men and 37 women: all were white. The average age on hospital entry was 62.6 ± 12.8 years (standard deviation). Although the population was somewhat older than that reported in other comparable series,\textsuperscript{4,7} there was no evidence that this influenced the mortality rate or the incidence of amputation.

Location of Arterial Occlusion. The 75 patients in this series sustained a total of 79 recognized arterial occlusions at their first hospital admission. Forty-three of these occurred in the left leg; 28 in the right; 8 were diagnosed as acute obstructions of the aortic bi-
furation. We have no explanation for the preponderance of left leg occlusions.

**Outcome of Hospitalization.** Fifty-nine patients (79 per cent) survived the initial hospital stay. Sixteen patients (21 per cent) died in the hospital, 5 within 24 hours, and the remainder within 6 weeks after the onset of symptoms. Similar mortality rates have been reported by others.5, 7-11 Eleven of the survivors sustained a major amputation; 4 of those who died in the hospital also had a major limb resection. Among the 8 patients with occlusion of the aortic bifurcation, 5

* A major amputation was defined as any resection proximal to a transmetatarsal amputation site. The only amputation among the remaining 48 survivors was a transmetatarsal resection that healed uneventfully.

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**TABLE 1.—Incidence of Clinical Factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Non survivors (16 patients)</th>
<th>Survivors (59 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (present/total*)</td>
<td>%</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>16/16</td>
<td>100</td>
</tr>
<tr>
<td>arrhythmia1</td>
<td>11/16</td>
<td>68</td>
</tr>
<tr>
<td>hypertensive heart disease3</td>
<td>9/15</td>
<td>60</td>
</tr>
<tr>
<td>valvular heart disease3</td>
<td>6/16</td>
<td>38</td>
</tr>
<tr>
<td>coronary heart disease4</td>
<td>8/16</td>
<td>50</td>
</tr>
<tr>
<td>congestive heart failure</td>
<td>11/16</td>
<td>68</td>
</tr>
<tr>
<td>Diabetes mellitus6</td>
<td>7/8</td>
<td>88</td>
</tr>
<tr>
<td>Cerebral vascular accident</td>
<td>8/16</td>
<td>50</td>
</tr>
<tr>
<td>Shock8</td>
<td>5/16</td>
<td>31</td>
</tr>
<tr>
<td>Uremia1</td>
<td>3/12</td>
<td>25</td>
</tr>
<tr>
<td>Anemia7</td>
<td>3/14</td>
<td>21</td>
</tr>
<tr>
<td><strong>Local</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Old arterial oclusive disease8</td>
<td>8/16</td>
<td>50</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>1/8</td>
<td>12</td>
</tr>
<tr>
<td>Trauma9</td>
<td>2/16</td>
<td>12</td>
</tr>
<tr>
<td>Uleration, local infection</td>
<td>2/16</td>
<td>12</td>
</tr>
<tr>
<td>Rest pain</td>
<td>3/16</td>
<td>19</td>
</tr>
<tr>
<td><strong>Therapeutic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin1</td>
<td>10/12</td>
<td>83</td>
</tr>
<tr>
<td>Dicumarol</td>
<td>0/12</td>
<td>0</td>
</tr>
<tr>
<td>Femoral and iliac arterial embolectomy</td>
<td>4/16</td>
<td>25</td>
</tr>
<tr>
<td>Vasodilator drugs</td>
<td>1/16</td>
<td>6</td>
</tr>
<tr>
<td>Autonomic and peripheral nerve blocks</td>
<td>1/16</td>
<td>6</td>
</tr>
<tr>
<td>Lumbar sympathectomy</td>
<td>0/16</td>
<td>0</td>
</tr>
</tbody>
</table>

* The denominator varied because information was not always adequate concerning each patient.
1 All these patients were in atrial fibrillation, except one who had paroxysmal atrial tachycardia.
2 Hypertensive heart disease was defined as cardiomegaly in association with repeated diastolic pressures above 90 mm. Hg.
3 Valvular heart disease was defined as structural deformity of a valve determined by physical or roentgenographic findings.
4 A diagnosis of coronary heart disease was accepted if a patient had angina pectoris or myocardial infarction.
5 Diabetes mellitus was established either by elevated fasting blood glucose values or an abnormal oral glucose tolerance curve.
6 Shock was diagnosed by systolic pressures below 90 mm. Hg.
7 Anemia was diagnosed when the hemoglobin was under 11 Gm. per 100 ml.
8 A diagnosis of old arterial occlusive disease was made on the basis of absent pulses, a history of acute arterial occlusion, or intermittent claudication.
9 Trauma was defined as a mechanical or thermal injury initiating an acute arterial occlusion.
survived without embolectomy or amputation.

Among these patients with acute leg artery occlusion the threat to life was at least as great as the threat to limb. This was particularly true during the first 24 hours of symptoms when 31 per cent of the deaths occurred. These deaths were caused by thromboembolic phenomena to visceral organs, congestive heart failure, acute myocardial infarction and renal failure. Peripheral ischemia, per se, played no discernible role in the mortality.

In table 1 are listed clinical, laboratory, and therapeutic factors that may have influenced survival. None of the factors was significantly different in the 2 groups (p > .01 by chi-square test for all comparisons in table 1). Although a factor in a particular patient may be of such magnitude and duration that the likelihood of a fatal outcome is clear, this type of quantitative information could not be obtained from a retrospective analysis of the available data in a sufficient number of patients.

**Follow-up Studies.** Follow-up information was obtained on all but 3 of the 59 patients who survived their initial episode of acute arterial occlusion. Eight of these 56 patients had a lumbar sympathectomy and 3 an embolectomy prior to discharge; 1 patient received prolonged anticoagulant therapy; no patients had reconstructive arterial surgery. No evidence was available from this limited study that sympathectomy, embolectomy, or prolonged anticoagulant therapy played any role in the long-term results. The proportion of amputees among the survivors (19 per cent) was similar to that reported in a number of published series,7-9,11 so that our group was not atypical in this regard. Therefore, the follow-up data provide an important control group for long-term evaluation of proposed therapeutic procedures.

**Survival Rate.** The information available concerning the 56 patients following the termination of their initial hospitalization and to the fifth anniversary of their discharge is shown in life table form12 (table 2). To obtain a reasonable frame of reference for evaluating the survival of our population, we applied to our sample the survival rates derived from the New England life table for 1949 to 1951 adjusted for age, sex, and race.13 These calculations yielded an expected 5-year survival rate of 82 ± 7 per cent (standard error) for our population. However, the estimated 5-year survival rate of our patients was only 46 ± 8 per cent. This increased estimated mortality presumably is related to the presence of serious systemic disease among our 56 survivors.

**Recurrence Rate.** Nine of the 56 patients sustained 12 additional clinically recognized episodes of acute arterial occlusion in a lower extremity during the 5-year follow-up period. To estimate recurrence rates it was necessary to derive the cumulative proportion of those who would escape such an episode if all 56 patients survived 5 years. By means of the

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**Table 2.** Survivorship of 56 Patients During First Five Years Following Initial Hospital Discharge

<table>
<thead>
<tr>
<th>Year from discharge</th>
<th>Number observed x or more years after discharge</th>
<th>Number reaching end of observation period alive between x and x + 1 years</th>
<th>Number dying between x and x + 1 years</th>
<th>Estimated rate of death between x and x + 1 years among survivors at x years</th>
<th>Cumulative percentage of the total who survive for x years</th>
<th>Cumulative percentage expected to survive for x years in a normal population</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>56</td>
<td>4</td>
<td>10</td>
<td>.185</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>42</td>
<td>8</td>
<td>3</td>
<td>.079</td>
<td>82</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>0</td>
<td>4</td>
<td>.129</td>
<td>75</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>3</td>
<td>5</td>
<td>.196</td>
<td>65</td>
<td>88</td>
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<tr>
<td>4</td>
<td>19</td>
<td>5</td>
<td>2</td>
<td>.121</td>
<td>53</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>46 ± 8*</td>
<td>82 ± 7*</td>
</tr>
</tbody>
</table>

*Estimated standard errors computed for 5-year survival rates (see note on method for table 3).
"multiple decrement life table" it was estimated\* that one fourth of this group would sustain at least 1 recurrence of an acute occlusion of a leg artery. There is nothing in the data to suggest that recurrences had a greater tendency to occur early or late in the follow-up period. It was also estimated that the cumulative 5-year survival rate without a recurrence in this group would be 40 ± 8 per cent (table 3).

In addition there were among the 56 survivors, 1 acute brachial artery occlusion, 1 acute mesenteric artery occlusion, 10 cerebral vascular accidents, and 10 acute myocardial infarctions. These observations represent 22 additional episodes of clinically recognized possible thromboembolic phenomena among these 56 patients.

Pathologic Findings

Incidence of Fresh Occlusions. Among the 105 lower limbs amputated at the Beth Israel Hospital and examined by the injection and dissection technique, 98 were removed either for gangrene or unremitting rest pain secondary to arterial insufficiency. Forty-seven of these 98 legs (48 per cent) had 1 or more fresh occlusions in the amputated specimen. Since many of the fresh occlusions, as estimated clinically, undoubtedly originated at sites above the level of amputation, the true incidence of fresh occlusion was greater than that observed in the amputated legs. In 39 of these 47 legs with fresh occlusion, the lesions were multiple; in some instances lying immediately below the most proximal clot, in others forming distal to sites of marked narrowing or old occlusion. It was not possible to determine whether the most proximal fresh occlusion in each resected specimen was embolic or thrombotic in origin. In some extremities, it was clear that a fresh occlusion distal to an old one was thrombotic in nature. Furthermore, in some legs without old occlu-

TABLE 3.—Combined Rates for Survivorship and Initial Recurrence of Acute Arterial Occlusion in Leg among 56 Patients during the First Five Years Following Hospital Discharge

<table>
<thead>
<tr>
<th>Year from discharge</th>
<th>Number observed without a recurrence x or more years</th>
<th>Number reaching end of observation period alive and without a recurrence between x and x + 1 years</th>
<th>Number dying without a recurrence between x and x + 1 years</th>
<th>Number having initial recurrence between x and x + 1 years</th>
<th>Estimated rate of initial recurrence between x and x + 1 years among survivors at recurrence x years</th>
<th>Cumulative estimated percentage of the total who survived without recurrence for x years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>56</td>
<td>4</td>
<td>9</td>
<td>4</td>
<td>.081</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>39</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>.029</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>.070</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>.093</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>75 ± 7†</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>40 ± 8†</td>
</tr>
</tbody>
</table>

\* \( v_x \), the incidence of initial recurrences among survivors was calculated as: \[ v_x = \frac{r_x}{O'_x - \frac{1}{2} w'_x - \frac{1}{2} d'_x} \]

\( N_x \), the cumulative percentage of survivors who reached the year x without a recurrence was calculated as: \[ N_x = (100) (1 - v_1) (1 - v_2) \ldots (1 - v_x) \]. The incidence of at least one recurrence during the first x years among those who survived may be estimated as \( 100 - N_x \).

\( q'_x \), the combined incidence of initial recurrence or death for any year was calculated as: \[ q'_x = \frac{r_x + d'_x}{O'_x - \frac{1}{2} w'_x} \]

\( P'_x \), the cumulative percentage of patients who escaped both death and recurrence was calculated as: \[ P'_x = (100) (1 - q'_1) (1 - q'_2) \ldots (1 - q'_x) \].

† The estimated standard errors at 5 years shown for \( N_x \) and \( P'_x \) were calculated by making appropriate substitutions in Greenwood's formula. These standard errors, like those shown in table 2, are approximations and may be quite inaccurate because of the small numbers involved. They are shown primarily to emphasize that an error does exist in the estimates.

See footnote in table 3.
sions in which the clinical impression of embolism had been strong, and in which fresh clot was found in the amputated extremity, it was evident that at least some of the observed proximal fresh occlusion was caused by a propagated thrombus.

**Fresh Occlusion without Old Occlusion.** Only 7 legs amputated for gangrene secondary to fresh occlusion showed no old occlusive disease in the resected specimen. Two of these limbs were removed from patients with satisfactory clinical evidence of old occlusive disease above the amputation site prior to the fresh occlusion. Thus, from the pathologic view, in only 5 of 98 legs amputated for arterial insufficiency was fresh occlusion the only anatomic obstruction to normal blood flow. In each of these 5 instances the fresh occlusion was more than 22 cm. in length and was present at the level of amputation. The remaining 95 per cent of amputated limbs had old occlusions 1 to 44 cm. in length in addition to varying degrees of luminal narrowing.

**Relation of Total Length of Fresh Occlusions to Clinical Diagnosis.** In less than half (47 per cent) of those legs in which fresh occlusions were demonstrated pathologically, was the diagnosis of fresh occlusion entertained clinically. As shown in table 4, there is a significant positive correlation ($p < 0.001$) between the total lengths of all the fresh occlusions in an amputated leg and the frequency with which fresh occlusions were recognized clinically. Thus, when fresh occlusions exceeded 10 cm. in length, the diagnosis was made in 94 per cent of the cases, whereas when fresh occlusions were less than 5 cm. in length, the diagnosis was made in only 10 per cent of cases. These data, therefore, offer evidence that many fresh occlusions will be asymptomatic because of their small size. They may, nevertheless, impair the effective development of an adequate collateral circulation either by their strategic location or by serving as a nidus for the deposition of further clot. Although clinically unrecognized as an acute occlusion, they may in this way lead to progressive gangrene or prevent healing of an ulcerated lesion.

**Necropsy Data.** Nine complete necropsies were performed on patients who died in the hospital at the time of or subsequent to an acute arterial occlusion of the lower extremity. Eight of these patients showed cardiac enlargement associated with coronary artery or valvular heart disease. Six patients had mural thrombi; 7 had recent or old systemic arterial thromboemboli; and 4 had pulmonary emboli. The ninth patient, in whom the clinical diagnosis of heart disease had been made, showed instead massive pulmonary emboli of varying age. These pathologic data confirm the clinical evidence of the high incidence of cardiovascular disease and the multiplicity of thromboembolic phenomena among the patients who succumbed.

**Compensatory Responses to Fresh Arterial Occlusions**

The frequency with which fresh arterial occlusions are not recognized clinically and the large number of patients who sustain a clinically recognized episode of acute occlusion without gangrene suggest that one or more mechanisms may compensate for sudden obstructions to major peripheral arteries. In this section clinical, pathologic, and experimental data, suggesting or confirming the ex-

<table>
<thead>
<tr>
<th>Length of fresh occlusion in amputated leg (cm.)</th>
<th>Total number of patients</th>
<th>Patients with diagnosis of acute occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>5-10</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>&lt;5</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Totals</td>
<td>47</td>
<td>22</td>
</tr>
</tbody>
</table>

In no patient without pathologic acute occlusion was a clinical diagnosis of acute occlusion made prior to amputation. $X^2=22.11, p<0.001$.  

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*There were 21 limbs removed from 15 patients in this study following their initial or subsequent acute arterial occlusion.
Clot Fragmentation. Several patients in this series exhibited sudden and often dramatic improvement in the degree of ischemia within 24 hours following the onset of the acute occlusion and without the aid of any specific therapy. In 1 patient clot fragmentation was clearly demonstrated when, during the administration of anesthesia for the removal of a saddle embolus, the femoral pulses returned and fragments of clot were subsequently recovered from both femoral arteries. Others have observed similar phenomena.15

In the experimental studies on clots that were formed in the femoral artery and then released, it was found that emboli were frequently arrested and broken at arterial bifurcations. It would appear that the very rapid improvement in ischemia that occurs within a matter of minutes can be related to clot fracture with subsequent movement of the fragments to more peripheral arteries.

Clot Lysis. Although lytic mechanisms are known to exist in man, direct evidence of clot dissolution is difficult to obtain, since the length of an embolus or thrombus cannot be measured when it first obstructs a vessel and then compared with the amount of clot found at the time of examination of the amputated specimen. Moreover, the return of a previously obliterated pulse may be accounted for by clot fracture, or by the enlargement of pre-existing collateral vessels or the development of new channels that bypass the obstruction. It was therefore necessary to turn to the experimental studies in which clots formed in femoral arteries were released to the periphery. Often within hours after their release to the periphery these emboli showed definite diminution in size when compared with the control clot in the contralateral femoral artery. Emboli were invariably recovered within 3 days after release, sporadically recovered between 4 and 6 days after release, and never recovered after 7 or more days. Since these studies were made on arteries that were injected with radiopaque mass and subsequently dissected, it was possible to conclude that these emboli had either diminished so markedly in size that they were lodged in peripheral arteries not visible to the naked eye or that they had actually dissolved completely. These observations disclose that the dog and, by analogy, man have the ability to dissolve fresh thrombi.

Interarterial Anastomoses. Careful dissection of 5 limbs, removed for nonvascular pathology, in which the arteries were normal, revealed small but grossly visible interarterial anastomotic communications. Further evidence of a rich preformed collateral circulation higher in the limb was obtained by the injection of radiopaque mass in the direction of blood flow in the femoral arteries of 52 cadavers. This mass filled the entire pelvic arterial circulation as well as the lower arterial tree of the extremity (fig. 1). These observations demonstrate the extent of the pre-existing interarterial anastomotic circulation above and below the femoral artery in man.
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

Examination of injected limbs amputated for severe arterial insufficiency demonstrated not only that these interarterial communications enlarged in legs with occlusive disease but that this enlargement was "tailored" to supply the ischemic zone (fig. 2).

The effectiveness of such collateral vessels in occasionally delivering pulsatile flow was exemplified by one patient with a good dorsalis pedis pulsation whose extremity was removed because of a sarcoma. The anterior tibial artery in this amputated specimen was occluded by atherosclerosis for 10 cm. in the mid leg; pulsatile flow had been delivered to the dorsalis pedis artery by a grossly demonstrable collateral from the peroneal artery.

While it has been shown that preformed interarterial anastomoses exist and may specifically enlarge in response to main vessel obstruction, these observations provide no information as to the time required for the maximum enlargement of these collateral channels. On the basis of personal clinical observations relating to the improvement in ischemia following recovery from acute occlusion, maximum enlargement may require several weeks or longer.

Clot fragmentation and lysis and preformed interarterial anastomoses may be responsible for asymptomatic acute arterial occlusions. These mechanisms may also be responsible for the dramatic spontaneous resolution of severe acute ischemia. Although not disproving the role of "spasm" they provide alternatives to the concept of the release of "spasm" as an explanation for the sudden relief of arterial insufficiency in some individuals. The gradual enlargement of anastomotic channels that bypass complete obstructions can account for the delayed and gradual improvement observed in some individuals weeks to months after the initial occlusion.

DISCUSSION

There is ready agreement that in the treatment of acute peripheral arterial occlusion all systemic factors that increase the disparity between local blood supply and demand should be corrected. Thus, anemia, heart failure, shock, electrolyte imbalance, and infection should be promptly treated and thermal, chemical, and mechanical trauma should be avoided. In the selection of more specific therapy, agreement is not so universal. However, among our patients with acute arterial occlusion it was clear that the threat to life was at least as great as the threat to limb. Thus, any diagnostic or therapeutic procedure that was designed to save a limb but that increased the risk to life was not justified. This was particularly true during the first 24 hours of symptoms when 31 per cent of the deaths occurred. When these observations are considered in relation to the data presented herein on the pathology of acute arterial occlusion and on the nature of the compensatory responses to arterial obstruction, the potential value of embolectomy, autonomic blockade, anticoagulant and fibrinolytic agents can be critically reviewed.

Management of Early Phase of Acute Peripheral Arterial Occlusion. Prompt removal of an embolus from a major leg artery has
been repeatedly shown to reverse ischemia and often result in pulsatile pedal flow. Although embolectomy frequently requires general anesthesia and appreciable trauma, obstructions in some arteries can be removed swiftly under local or regional anesthesia without extensive injury, hemorrhage, or marked systemic response. However, when embolectomy is considered in relation to the population reported upon in this paper, the advisability of the procedure can be questioned in terms of the net gain to the patient as a whole. Both regional and systemic factors should be considered in this regard. Not infrequently collateral vessels are severed in approaching the occluded artery. When the obstructed vessel is opened, clot adherence may be so great that its removal may result in extensive intimal damage. Local injury alone or combined with stasis and hemorrhage may induce local thrombosis. Furthermore, it is not always possible to remove all clot above or below the incision. Fresh clot deposited distal to sites of old occlusion in the lower leg is not amenable to surgical removal by embolectomy. In studies of experimental arterial embolism in our laboratory, it has been found that a free flow from above the area of incision does not insure the removal of all proximal clot, particularly if it is trapped at an arterial bifurcation. Moreover, embolectomy, as any operative procedure, may provoke the development of a "temporary thrombotic state" leading to venous thrombosis and pulmonary embolism. Finally, the presence of a fresh wound limits the full use of anticoagulant therapy by the risk of hemorrhage from granulating surfaces.

There is, as yet, no statistically sound study indicating the superiority of embolectomy over any other procedure in the treatment of all or, even, of selected patients with acute arterial occlusion. In this regard it is important to recall the high spontaneous recovery rate among the patients in our series including those with acute obstruction at the aortic bifurcation. Moreover, when embolectomy has been recommended, it is usually with the provision that it be performed within hours of the onset of symptoms; yet this is precisely the period of the greatest anticipated mortality. Early embolectomy can thus contribute—even if slightly in many individuals—to this risk to life.

Unlike embolectomy, autonomic blockade for the relief of ischemia secondary to arterial occlusion has neither a sound physiologic rationale nor satisfactory clinical documentation of its efficacy. Sympathectomy for acute arterial obstruction shares with embolectomy the objection that it represents a surgical procedure in a cardiac patient and thereby may add a burden to the heart, increase the risk of venous thrombosis and pulmonary embolism, and limit the use of anticoagulant drugs in the postoperative period. One of the most compelling arguments for the ablation of sympathetic tone has been the belief that this procedure would relieve the "spasm" induced by the obstruction itself. Not only is there little evidence that the arteriolar vessels in the ischemic zone are in "spasm" in organic arterial insufficiency, but the observations reported in this paper, although presenting no direct evidence against "spasm," do offer alternatives to the concept that the release of "spasm" is responsible for the sudden and often marked improvement in peripheral blood flow that may occur spontaneously.

Anticoagulant drugs are of value in preventing the formation of new clot or the propagation of existing clot; they do not dissolve thrombi already formed. Since clots often have propagated extensively before the patient sees a physician, the value of anticoagulants for the local arterial lesion may be limited. Moreover, in ischemic limbs the use of these drugs invites the small but potential hazard of hemorrhage within the walls of sclerotic arteries with subsequent thrombosis. The principal recommendation for anticoagulant therapy aside from its ability to retard the propagation of clot locally is that it is effective in preventing further thromboembolic phenomena in the pulmonary and systemic circuits. It should be emphasized, however, that, as with embolectomy, there is still no statistically valid clinical evidence that
routine anticoagulant therapy for acute arterial occlusion will significantly decrease the incidence of death or amputation occurring in these patients at the time of initial hospitalization.

Of all the procedures recommended for the treatment of acute arterial occlusion, fibrinolytic agents or substances that activate the normally present fibrinolytic mechanism appear to offer the most valid therapeutic approach, for these agents may induce clot dissolution throughout the extremity. In the past, compounds recommended for this purpose have had such nonspecific proteolytic effects or have been so toxic that they could be used neither effectively nor safely. With the advent of more highly purified compounds the development of lytic agents may be approaching the stage of practical clinical trial. When used alone or combined with anticoagulants, lytic agents may eventually form the ideal therapy for acute arterial occlusion. However, the use of these drugs must also be viewed with caution until it has been demonstrated in man that fibrin can be dissolved without precipitating hemorrhage through induced afibrinogenemia or alterations in other clotting components.

After Care Following Acute Peripheral Arterial Occlusion. When the maximum improvement afforded by normal compensatory mechanisms has been achieved and the general condition of the patient has become stable, reconstructive arterial surgery has a place in the treatment of residual disabling ischemia secondary to acute arterial occlusion. However, the indications for arterial grafting in patients who recover from acute arterial occlusion should be decided on an individual basis: the overriding considerations will be the degree of residual ischemia, the technical feasibility of the surgical procedure as indicated by arteriography, and the general health of the patient.

In a large majority of patients subjected to sympathectomy, sympathetic tone returns within months of the operative procedure, even though the foot may remain warm. These observations tend to invalidate the claim that sympathectomy has any "prophylactic" value in the prevention of further ischemia.

Prolonged anticoagulant therapy can be expected to be of value in preventing the deposition of further clot. In view of the high recurrence rate of acute peripheral arterial occlusions in our series as well as the high incidence of serious cardiovascular disease, the use of ambulatory anticoagulant therapy for the prevention of further clotting in the leg and elsewhere in the circulation would appear to be justified.

Finally, it will be appreciated that acute leg artery occlusion usually represents but 1 episode punctuating a progressive or recurrent process having its origin in the heart. Thus, in addition to prophylactic anticoagulant therapy and bypass arterial grafts, the long-term management of some patients with acute arterial occlusion may encompass a medical and surgical attack on the diseased heart itself. On the assumption that the high incidence of atrial arrhythmias may have a causal relation to embolic phenomena, it appears justified to attempt to maintain a normal sinus rhythm in patients with paroxysmal arrhythmias by the use of digitalis and quinidine. Despite the attendant hazards, it may be desirable when patients are on anticoagulant therapy to attempt to convert fixed arrhythmias by the use of quinidine. The value of radioactive iodine for this purpose in selected patients will require further trial. Although not yet adequately evaluated for this purpose, mitral valve surgery has already been attempted as prophylaxis against recurrent systemic embolization.

**SUMMARY**

This study of acute peripheral arterial occlusion was based on material obtained from 5 sources: (1) clinical information from 75 patients hospitalized with acute arterial occlusion of a lower extremity; (2) pathologic examination by a special injection and dissection technic of 105 legs amputated for vascular or nonvascular disease; (3) arteriographic observations on the lower limbs of 52 cadavers; (4) necropsy examination of 9 patients
who died in the hospital following acute occlusion of a leg artery; and (5) data from an experimental investigation of acute femoral artery embolism in 30 dogs.

At the first hospitalization these patients sustained 43 fresh arterial occlusions in the left leg, 28 in the right leg, and 8 at the aortic bifurcation. No clinical differentiation was attempted between embolism and thrombosis. Eighty-eight per cent of the patients had clinically recognized heart disease. The therapeutic procedures were applied with no over-all predetermined plan.

During the initial hospitalization 64 per cent of the patients survived without major amputation, 15 per cent survived with a major amputation, and 21 per cent died (almost one third in the first 24 hours).

Among the 56 survivors for whom follow-up information was available, the expected 5-year survival rate was 46 per cent compared with 82 per cent in a New England population of comparable age, sex, and race. The expected 5-year rate of initial recurrence of an acute occlusion of a leg artery was 25 per cent, and the expected incidence of thromboembolic visceral complications was of a similar order of magnitude.

Fresh occlusions were found in one half of all legs amputated for arterial insufficiency and studied by the injection and dissection technic. In each amputated limb in which fresh arterial occlusions were found, propagation of clot was observed either distal to the most proximal clot in the extremity or distal to old occlusions or narrowing; in 70 per cent of the legs with fresh occlusions the clots were multiple. Fresh arterial occlusion alone rarely caused amputation. In only 5 per cent of the legs amputated for arterial insufficiency were fresh occlusions present without concomitant old occlusion and in each such instance the fresh occlusion was more than 22 cm. in length and was present at the level of amputation.

The clinical diagnosis of acute arterial occlusion was suspected in less than half of the patients in whose amputated legs fresh occlusions were demonstrated after injection and dissection of the extremity. The clinical diagnosis of acute peripheral arterial occlusion was related to the total length of the fresh occlusions. If the fresh occlusions exceeded 10 cm. in length in the resected specimen, the diagnosis was made in 94 per cent of instances; if the fresh occlusions were less than 5 cm. in length, the diagnosis was made in only 10 per cent of instances.

Evidence was obtained from clinical, pathologic, and experimental observations that clot fragmentation, clot lysis, and preformed interarterial anastomoses can compensate immediately for an acute arterial occlusion. Further increase in blood flow can occur within days to weeks after an acute occlusion through the gradual hypertrophy of anastomotic vessels that specifically bypass occluded arteries.

The necropsy material confirmed the clinical observations, indicating the high incidence of cardiac disease and recurrent thromboembolism among the patients in this study.

CONCLUSIONS

The pathogenesis and course of acute peripheral arterial occlusion outlined in this study provides a basis for the evaluation of procedures recommended for the prophylaxis and treatment of acute ischemia.

Acute occlusion of a leg artery usually reflects but 1 episode punctuating a progressive or recurrent process having its origin in the heart. It represents, in essence, a medical emergency in which the threat to life is at least as great as the threat to limb. Thus, any diagnostic or therapeutic procedure that is designed to save a limb but that increases the risk to life is not justified. This is particularly true during the first 24 hours of symptoms.

It is neither feasible nor necessary to distinguish between acute arterial embolism and thrombosis. Many acute occlusions, although not recognized clinically because of their small size, may nevertheless contribute to ischemia by their strategic location or by serving as a nidus for the propagation of clot.

Embolectomy, when considered in relation to the total clinical problem, is not recom-
mended as the treatment of choice in the acute phase of the occlusive process, although its efficacy in individual cases is well documented. In contrast, the evidence is entirely inadequate to justify medical or surgical alterations in autonomic tone in the treatment of any phase of organic arterial obstruction.

Fibrinolytic agents may in time have a place in the early treatment of acute arterial occlusion, and bypass grafting may be of value in the management of residual ischemia. The role of drugs in preserving or producing a normal sinus rhythm and of remedial cardiac surgery in diminishing the recurrence of systemic arterial emboli remains to be evaluated.

Anticoagulant therapy, although not ideal, appears to offer promise of the greatest overall benefit with the least risk. This is particularly true for the prevention of recurrent thromboembolic episodes in the leg or elsewhere in the circulation.

**SUMMARIO IN INTERLINGUA**

Iste studio de acute occlusion de arterias peripheric esseva basate super materiales obtenite ab 5 differente fontes: (1) Information clinique pro 75 patientes hospitalizate con occlusion arterial de un extremite inferior. (2) Examine pathologic, per medio de un technica special de injection e dissection, de 105 gambas amputate a causa de morbos vascular e non-vascular. (3) Observationes arteriographie in le extremitates inferior de 52 cadaveres. (4) Necropsias de 9 patientes qui moriva al hospital post occlusion acute de un arteria del gamba. E (5) le investigation experimental de acute embolismos del arteria femoral in 30 canes.

A lor prime hospitalisation le patientes includite in le materiales del studio suffrava 43 fresce occlusiones arterial in le gamba sinistre, 28 in le gamba dextere, e 8 al puncto del bifurcation aortic. Nulle differentiation clinique inter embolismo e thrombosis esseva tentate. Octanta-octo pro cento del patientes habeva morbo cardiac de recognition clinique. Le regimes therapeutic esseva applicate sin predetermine plano general.

Durante le prime hospitalisation, 64 pro cento del patientes superviveva sin amputa- tion major, e 21 pro cento moriva (quasi un tertio durante le prime 24 horas).

Inter le 56 superviventes pro qui informationes in re le curso posterior esseva disponibile, le superviventia quintenne amontava a 46 pro cento, in comparison con 82 pro cento constatate pro un population de Nove Anglaterra con etate, sexo, e racia comparabile. Le quintenne prime recurrentia de un acute occlusion de un arteria del gamba amontava a 25 pro cento. Le expectate incidentia de thromboembolic complicationes visceral esseva de un simile ordine de magnitude.

Fresce occlusiones esseva trovate in un mediate de omne le gambas amputate a causa de insufficientia arterial e studiate per le technica de injection e dissection. In omne extremitate amputate in que fresce occlusiones arterial esseva constatate, propagation de coagulo esseva observate (1) distal con respecto al plus proxime coagulo in le extremitate o (2) distal con respecto a ancian occlusiones o restrictiones. In 70 pro cento del gambas con fresce occlusiones, le coagulos esseva multiple. Fresce occlusion arterial esseva rarmente le causa exclusive del amputation. Solmente 5 pro cento del gambas amputate a causa de insufficientia arterial monstrava fresce occlusiones sin concomitante ancian occlusiones, e in omne iste casos le occlusion fresce mesurava plus que 22 cm in longor e esseva presente al nivello del amputation.

Le diagnose clinique de acute occlusion arterial esseva suspicite in minus que un mediate del patientes pro qui fresce occlusiones esseva demonstrate in le gambas amputate post application del technica a injection e dissection. Le diagnose clinique de occlusion acute de arterias peripheric esseva relationate al longor total del occlusiones fresce. Si le fresce occlusiones excedeva 10 cm in longor in le specimen resecate, le diagnose habeva essite facite in 94 pro cento del casos; si le occlusiones esseva minus que 5 cm in longor, le diagnose habeva essite facite in solmente 10 pro cento del casos.
Observationes clinicae, pathologicae, e experimentalium supportaua le conclusione que le fragmentation del coagulo, le lyse del coagulo, e le preformation de anastomoses interarterial es capace a compensar immeditamente un acute occlusion arterial. Augmento additional del fluxo de sanguine pote resultar intra dies o septimanae post un occlusion acute, in consequentia del hypertrophia gradual de vasos anastomatic que specificamente circun- fere un arteria oclusida.

Le materiales necroptic confirmava le observationes clinicae, signalante un alte incidencia de morbo cardiaca e de thromboembolismo recurrente inter le patientes in iste studio.

Le pathogenese e le causo de acute occlusion de arterias peripheric delineate in iste studio provide un base pro le evaluation de mesuras recommendate in le prophylaxe e le tractamento de acute ischemia.

Oclusion acute de un arteria de gamba reflecte usualmente non plus que un episodio in un processo progressive o recurrente que ha su origine in le corde. Illo representa, in essentia, un situation de urgentia medical in que le vita del patiente es al minus tanto impericulate como le extremitate afficite. Assi, omne mensura diagnostic o terapeutica que visa a salvar un gamba sed que augmenta le risco pro le vita del patiente non es justifi- cate. Iste observation es specialmente applicable durante le prime 24 horas post declaration del symptomata.

Il es impossible e non necessari distinguin inter acute embolismo e thrombosis arterial. Multe occlusiones acute, ben que clinicamente non recognoscite a causa de lor micre dimensiones, es nonobstante potentialmente capace a contribuir al disveloppamento de ischemia a causa de lor sito strategic o proque illos servi de nido in le propagation de coagulo.

Embolectomia, vidite in relation al total problema clinic, non es recommendate como tractamento de election durante le phase acute del processo occlusive, ben que su efficacia in casos individual es ben documentate. Del altere latere, il existe solmente un inadequatissime documentation in supporto de alterationes medical o chirurgic in le tono autonomic como tractamento de non importa qual phase de organic obstructiones arterial.

Agentes fibrinolytic ha possibilemente a vices un placi in le tractamento initial de acute occlusion arterial, e graffos circumfer- ente es forsanc de valor in le tractamento de ischemia residue. Le rolo de drogas in le preservation o restitutio de un normal rhythmio sinusal e de chirurgia cardiaca remedial pro reduce le numero del recurrentias de systemic embolos arterial debe esser evaluate in le futuro.

Therapia a anticoagulantes non es ideal sed pare offerer promissas del plus grande beneficio general con le plus basse risco. Isto vale specialmente con respecto al prevention de recurrente episodios thromboembolique in le gamba o alterubi in le circulation.

REFERENCES
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