Gangrene of Lower Extremity Secondary to Extensive Venous Occlusion

By James V. Ross, Jr., M.D., Archie H. Baggenstoss, M.D., and John L. Juergens, M.D.

Gangrene of an extremity caused by venous occlusion without associated arterial occlusion is uncommon. Haimovici noted that Fabricus Hildanus, in 1593, apparently recognized the possibility of gangrene of venous origin; it was not until 1859, however, that Heuter reported a case, giving an excellent account of the clinical and pathologic criteria of this type of gangrene. Grégoire, in 1938, coined the term "phlegmasia cerulea dolens" to denote extensive venous occlusion that is characterized by cyanosis, ischemia, woody edema, violaceous discoloration, ecchymosis, and transient loss or reduction of arterial pulsations. Like Trémolières and Véran, who described this condition in 1929, Grégoire attributed the ischemia to secondary arteriospasm.

Buerger, in a book published in 1924, mentioned only that complete obstruction of the chief veins of a part without occlusion of the arteries, may also lead to gangrene, although this is of rare occurrence. It was not until 1938 that Tilley made the first report of this condition in the American literature; in the same year, Pringle documented the first two cases in the English literature. In Tilley's three cases, clinical data are lacking, but careful dissection of the amputated limbs revealed "obstruction of all the veins; the arteries were grossly normal and no obstruction could be demonstrated."

Ten years later, Haimovici and Suffness reported a fourth case in the American literature and again brought the clinicopathologic characteristics to the attention of physicians in the United States. Although sporadic reports of phlegmasia cerulea dolens have appeared subsequently in the American literature, we have been able to collect records of only 13 cases with gangrene since Tilley's three cases in 1938. Although the possibility of gangrene owing to venous occlusion alone has been commented on by Homans, Samuel, and Allen and associates, other specific case reports have not appeared. This attests to the fact that gangrene caused by venous occlusion without associated arterial occlusion is indeed uncommon or is unrecognized by American physicians.

Methods and Materials

A study was made of the records of patients at the Mayo Clinic who had gangrene apparently produced by venous occlusion during the 31-year period from 1929 through 1959. A total of 16 patients appeared on a clinical basis to have this unusual type of gangrene. Two cases were discarded, however, because of associated diabetes mellitus and infection, one case was discarded because of a past history of embolic phenomena, and two cases were discarded because of arterial thrombosis; these associated findings cast some doubt on the cause of the gangrene. Among the 11 remaining cases, pathologic material was available for study in nine, and the two remaining cases were thought to have been subjected to adequate clinical investigation to warrant inclusion.

The clinical criteria for inclusion in the present study were (1) the clinical appearance of extensive venous thrombosis, (2) the evolution of gangrene in an edematous, cyanotic limb, and (3) palpable arterial pulsations in the affected extremity at the time of the appearance of gangrene.

The pathologic criteria were (1) thrombosis of the major venous channels of the affected limb, (2) patency of the major arteries of the same limb, and (3) gangrene of the limb. In three specimens, extensive pathologic examination of the major veins and arteries of the involved extremity was done. In an additional specimen, fluid was injected from the common iliac artery to the dorsalis pedis artery as further evidence of a patent arterial system.

From the Mayo Clinic and the Mayo Foundation, Rochester, Minnesota.
47.3 years, for females 57.5 years, and for both males and females 52.4 years.

Pathologic Aspects

A total of 13 gangrenous limbs were present; eight right lower extremities (in two males and six females) and five left lower extremities (in three males and two females) were affected. One male and one female had bilateral involvement.

The extent of the gangrene varied from splotchy superficial zones on the legs or on four or more toes to involvement of the lower extremity from the knee downward (table 1).

The underlying condition was neoplastic disease in six cases, chronic cardiac disease in two, thrombocytopenic purpura (with splenectomy) in one, congenital membranous valve of the urethra in one, and chronic cholecystitis and cholelithiasis in one (table 1).

The upper limit of the thrombus as shown by necropsy or postamputation pathologic examination was the iliofemoral vein in eight cases, with minimal extension into the inferior vena cava in three of these cases and moderately high extension in two; in the other three of these eight cases, the upper extent of the thrombus was in the femoral-popliteal venous system. One of the two instances of moderately high extension into the inferior vena cava occurred in a patient (case 5) who had an end-to-end Nylon prosthetic graft inserted after sacrifice of part of the inferior vena cava during excision of a rhabdomyosarcoma that did not involve the lumen of the vessel. The graft was not involved by the thrombus, which extended above and below the prosthesis at the level of the suture lines (fig. 1), with extension into the left iliofemoral vein. The other patient who had moderately high extension into the inferior vena cava was the only one to show involvement of the renal vein and histologic evidence of venous infarction of the kidney.

Of the three patients who had occlusion of the femoral-popliteal vein, two underwent surgical amputation of the affected limb. Both patients survived the operation only to die subsequently from pulmonary embolism. The

Figure 1
Case 5. Extensive thrombosis above and below Nylon graft.

The records were reviewed with particular regard to (1) underlying disease, (2) treatment with anticoagulant drugs and sympathetic-blocking agents, (3) the development of acute peripheral circulatory failure, and (4) the cause of death.

Results

The 11 patients satisfying the clinical and pathologic criteria for gangrene caused by venous occlusion without associated arterial occlusion included seven females and four males ranging in age from 7 months to 75 years. The one infant was a boy. Exclusive of this infant, the average age for males was
### Table 1

#### Data in 11 Cases of Gangrene of Lower Extremity due to Venous Occlusion

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Underlying disease process</th>
<th>Upper extent of thrombosis</th>
<th>Extent of gangrene</th>
<th>Cause of death</th>
<th>Palpable pulses with onset of gangrene</th>
<th>Extent of dissection or examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49</td>
<td>F</td>
<td>Thromboctopenic purpura (with splenectomy)</td>
<td>Bilateral iliofemoral and low inferior vena cava</td>
<td>Left foot and ankle, right midfoot and ankle</td>
<td>Peripheral vascular circulatory failure and shock</td>
<td>Femoral, popliteal, posterior tibial, and dorsalis pedis</td>
<td>To dorsalis pedis; arteries injected</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>F</td>
<td>Adenocarcinoma of pancreas</td>
<td>Bilateral iliofemoral and low inferior vena cava</td>
<td>Right distal third of foot</td>
<td>Uremia</td>
<td>Femoral, popliteal, and posterior tibial</td>
<td>Popliteal and below for several inches</td>
</tr>
<tr>
<td>3</td>
<td>7/12</td>
<td>M</td>
<td>Congenital membranous valve of urethra</td>
<td>Bilateral femoral and popliteal</td>
<td>Left to knee</td>
<td>Uremia</td>
<td>Femoral and popliteal; edema</td>
<td>Popliteal and below edema</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>F</td>
<td>Old and healed subacute bacterial endocarditis and rheumatic heart disease</td>
<td>Left femoral and popliteal</td>
<td>Left distal third of foot</td>
<td>Pulmonary embolism</td>
<td>Femoral, popliteal, posterior tibial, and dorsalis pedis</td>
<td>Surgical specimen: midfemoral to posterior tibial and dorsalis pedis</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>M</td>
<td>Retroperitoneal rhabdomyosarcoma</td>
<td>Bilateral iliofemoral and high inferior vena cava</td>
<td>Superficial blebs of left calf and foot</td>
<td>Peripheral vascular circulatory failure and shock</td>
<td>Femoral, popliteal, and posterior tibial</td>
<td>Midfemoral</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>M</td>
<td>Squamous-cell carcinoma of bronchus</td>
<td>Bilateral iliofemoral</td>
<td>Left distal half of foot, right to midcalf</td>
<td>Carcinomatosis</td>
<td>Femoral, popliteal, posterior tibial, and dorsalis pedis</td>
<td>Midfemoral</td>
</tr>
<tr>
<td>7</td>
<td>62</td>
<td>F</td>
<td>Adenocarcinoma of bile duct</td>
<td>Bilateral iliofemoral and low inferior vena cava</td>
<td>Right to below knee</td>
<td>Pulmonary embolism</td>
<td>Femoral, popliteal, posterior tibial, and dorsalis pedis</td>
<td>Midfemoral</td>
</tr>
<tr>
<td>8</td>
<td>75</td>
<td>F</td>
<td>Abdominal carcinomatosis, unknown cause</td>
<td>—</td>
<td>Right entire foot</td>
<td>Pulmonary embolism</td>
<td>Femoral, popliteal, and posterior tibial</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>43</td>
<td>F</td>
<td>Adenocarcinoma of pancreas</td>
<td>—</td>
<td>Right first four toes</td>
<td>—</td>
<td>Femoral, popliteal, posterior tibial, and dorsalis pedis</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>F</td>
<td>Arteriosclerotic hypertensive cardiovascular disease</td>
<td>Junction of popliteal and femoral</td>
<td>Right lower two thirds calf and entire foot</td>
<td>Pulmonary embolism</td>
<td>Transient loss of popliteal and posterior tibial</td>
<td>Surgical specimen: femoral, popliteal, and posterior tibial</td>
</tr>
<tr>
<td>11</td>
<td>36</td>
<td>M</td>
<td>Chronic cholecystitis and cholelithiasis</td>
<td>Bilateral iliofemoral and high inferior vena cava</td>
<td>Right distal two thirds foot</td>
<td>Uremia</td>
<td>Femoral, popliteal, posterior tibial, and dorsalis pedis</td>
<td>Lower femoral</td>
</tr>
</tbody>
</table>
cause of death in the 10 patients known to have died is shown in table 2. Only one patient, who had adenocarcinoma of the pancreas and gangrene of four toes, was reported to be living at the time of this study.

Clinical Aspects

Seven of the 11 patients received anticoagulant therapy. Six of them were given anticoagulants prior to the onset of gangrene, including one patient referred to the clinic with gangrene who had been started on anticoagulant therapy at home 7 days prior to admission. The drugs used were bishydroxy-coumarin (Dicumarol) in five patients, Warfarin (coumadin) sodium in two patients, and heparin by continuous intravenous drip in one patient who had received Dicumarol up to the time of the appearance of gangrene. Table 3 shows the prothrombin times in these six patients on the day prior to, the day of, or the day after the appearance of the gangrene. All prothrombin times were determined by the modified Quick one-stage method used at the clinic, in which the therapeutic range is considered to be between 27 and 60 seconds; in terms of prothrombin activity, this corresponds to 30 and 10 per cent, respectively. Four patients had prothrombin times of 30 seconds or more during this period. One patient may be presumed to have been in the therapeutic range of hypoprothrombinemia, with a prothrombin time of 69 seconds on the day of admission. The sixth patient, who had a prothrombin time of 27 seconds, was still in the therapeutic range at the lowest level acceptable.

One patient underwent a right lumbar sympathetic block with the use of piperocaine (Metycaine) hydrochloride but apparently was not helped and may have been harmed by the procedure; it was the clinical impression that the block may have contributed to the more rapid appearance of massive edema, extensive cyanosis, and shock.

There appeared to be nothing distinctive in the clinical picture early in the course of the disease to forewarn the physician that the venous occlusion might lead to gangrene. The fact that all six patients who had underlying neoplastic disease also had histories of previous episodes of thrombophlebitis may be significant. A similar history should alert the physician to the possibility of gangrene due to venous occlusion.

Three patients clinically presented the picture of peripheral circulatory failure and shock, which did not respond to the intravenous administration of fluids. In one of these patients, acute pulmonary embolism was the immediate cause of death.

Discussion

It is the absence of any significant occluding lesion within the major arteries of the affected limb that distinguishes the condition presently under consideration from the usual forms of gangrene and makes gangrene of venous origin a distinct clinicopathologic entity. Necropsy and postamputation pathologic findings of patent major arteries with extensive thrombosis of the veins in a gangrenous limb indicate the existence of this mechanism. Gangrene can be produced in dogs if the
occlusion of the venous system is complete. Veal and co-workers\textsuperscript{10} ligated the femoral vein in dogs and noted only transient edema and no gangrene. Fontaine and Pereira,\textsuperscript{23} in their extensive study of the formation and retention of edema in limbs in which the venous return was obstructed by ligation, resection or sclerosis of the veins and lymphatics, produced gangrene in this manner. They made a complete circular incision in the upper part of the thigh in dogs, incising skin, aponeurosis, and muscle, ligating and dividing all veins but sparing all major arteries, nerves, and bones. On the evening of the day of operation, massive edema of the lower limb appeared, followed by the onset of wet gangrene 2 days later. Arteriograms of the gangrenous limb showed a normal arterial system. Arteriograms also have proved the patency of the arterial system down to the size of digital arteries in patients with this type of gangrene.\textsuperscript{1}

The fact that the gangrene seen in this condition can be superficial and similar to that seen in frostbite or ergot poisoning raises the question of the status of the extremely small arteries and arterioles in the subcutaneous tissue. Neither in this study nor in the literature is there evidence to show that this portion of the arterial system is not occluded. Although such evidence is lacking, occlusion of these small arteries alone would not appear to be sufficient to explain the more extensive gangrene seen in some cases. Further study regarding this portion of the arterial system in this type of case is needed.

Arteriospasm, which apparently occurs in some cases,\textsuperscript{1, 3, 4} is not a constant clinical finding and probably cannot in itself be considered the basic cause. Thus, it would appear that arterial blood can reach the tissues but is prevented from returning by extensive venous obstruction primarily and perhaps the venospasm secondarily,\textsuperscript{24} causing stasis, hypoxia, and subsequent gangrene.\textsuperscript{1} Gangrene could develop in any case of venous obstruction that becomes so extensive as to prevent the return of arterial blood from the affected limb. Its prevalence in the lower extremity may be related in part to the more frequent occurrence of thrombophlebitis in the lower extremity.

Although the onset of this syndrome has been reported to occur suddenly and to mimic an arterial embolus (pseudoembolic type),\textsuperscript{1} it was primarily a complication of extensive thrombophlebitis in this study. From an analysis of our cases, underlying neoplastic disease with its tendency for recurrent episodes of thrombophlebitis is more prone to be accompanied by this dire complication.

The use of anticoagulant therapy early and continuously throughout the course of the disease does not necessarily prevent further extension of the thrombus or the development of gangrene. On the other hand, it is impossible to assess the number of patients who have received anticoagulant treatment and in whom such therapy has prevented the development of gangrene. The basic defect is presumably a thrombosing tendency or a state of
in the major venous system in the affected leg (fig. 4), often with extension into the inferior vena cava, thrombosis of the renal vein and renal infarction appear to be uncommon despite clinical evidence of some renal dysfunction or insufficiency in about a third of our cases.

Peripheral circulatory failure and shock should be anticipated in the event of unremitting and progressive massive edema. The onset of shock is an important sign of a poor prognosis. This coincides with the earlier experimental work of Perlow and associates\textsuperscript{28} and Katz and co-workers,\textsuperscript{29} which indicated that venous obstruction to the hind limb in a dog leads to intractable shock and death; these workers also showed that, if blood for transfusion is not available, the early use of saline, before capillary permeability is affected, combats shock and prolongs life. Administration of a solution of dextrose does not appear to prevent shock in the experimental animal.\textsuperscript{29} However, peripheral circulatory failure and shock do not always occur in this condition.

The management of phlegmasia cerulea dolens has not been satisfactory, as shown by the numerous regimens advanced and the controversy concerning all of them. Veal and associates\textsuperscript{10} advocated high elevation of the affected limb with regular passive flexion to express the entrapped blood, diminish venous engorgement, and allow fresh arterial blood to enter. This appears to be a reasonable approach, but the possibility of dislodging a portion of the thrombus and initiating pulmo-

<table>
<thead>
<tr>
<th>Case</th>
<th>Drugs used</th>
<th>Prothrombin time, seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day before</td>
</tr>
<tr>
<td>1</td>
<td>Dicumarol</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>Dicumarol</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>Dicumarol</td>
<td>41</td>
</tr>
<tr>
<td>7</td>
<td>Dicumarol</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>Coumadin</td>
<td>37</td>
</tr>
<tr>
<td>9</td>
<td>Coumadin</td>
<td>—</td>
</tr>
</tbody>
</table>

**Figure 4**

*Case 1. Extensive organizing venous thrombi, with patent arteries. a. Left iliac vein (hematoxylin and eosin). b. Left femoral vein (hematoxylin and eosin). c. Left posterior tibial vein and tributaries (hematoxylin and eosin).*

hypercoagulability, the mechanism of which is not completely understood despite the various theories advanced.\textsuperscript{17, 25–27} Further study and information regarding this aspect of the disease are imperative before prophylaxis or treatment can be considered adequate. Therefore, it is logical to give anticoagulants to these patients until specific information to the contrary is forthcoming. The condition has an extremely high rate of mortality either from pulmonary embolism or the serious underlying disease, such as neoplasms.

Either or both limbs may be involved by the gangrene, but unilateral involvement is the usual occurrence, and the gangrene is restricted more often to the region below the knee, more specifically, to the ankle and foot (figs. 2 and 3). It is a wet gangrene, frequently superficial, and it appears to develop more slowly in most cases as compared to that from arterial occlusion.

Although extensive thrombosis is present...
GANGRENE AFTER VENOUS OCCLUSION

Summary and Conclusions

Gangrene of the lower extremity caused by extensive venous occlusion is an uncommon entity. A study has been made of 11 such cases encountered at the Mayo Clinic during the 31-year period ending in 1959. Only one of the patients was alive at the time of the study.

Neoplastic disease was the most frequently observed underlying process in this series. Despite extensive venous occlusion, with involvement of the inferior vena cava in five cases, the renal vein was involved in only one. Peripheral circulatory failure with shock occurred in three patients and was a grave prognostic sign. The commonest cause of death was pulmonary embolism.

Complete obstruction to the venous return is probably the basic etiologic factor, but further study of the extremely small arteries and arterioles is necessary before the cause of this type of gangrene can be known with certainty.

The management of phlegmasia cerulea dolens and complicating peripheral circulatory failure is not satisfactory. Shock should be treated by the early use of blood.

References

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