A fundamental characteristic of blood vessels is the ability to change in caliber in response to neural and chemical stimuli. The effects of such changes on the architecture of the vessel wall cannot be appreciated in studies on physical models, such as soap bubbles and balloons, which have negligible wall thickness and uniform composition. The familiar Laplace relationship (T = PR) states that the tension in the wall of a cylinder is related to the product of the transmural pressure and the radius of the tube. This relationship is true, however, only when the wall thickness is negligible. Peterson et al. recently analyzed the importance of wall thickness in blood vessels and used the expression T = PR/8, where S is the wall thickness. Arterial walls are relatively thick in proportion to the diameter of the lumen and contain both active and passive elements having varying degrees of resistance to deformation. Any change in the caliber of arteries must necessarily be accompanied by an internal rearrangement of the components of their walls as well as by variations in their thickness. Most investigations of the architecture of blood vessels have not been concerned with the functional state of their walls. Many such studies have been conducted on specimens obtained from post-mortem material. Others have been carried out on arteries excised from living tissue but with loss of the distending blood pressure. Further, inadequate attention has been given to the effects of fixation on the various mural components; during preparation of routine microscopic sections by formalin fixation and embedding in paraffin, there is unequal shrinkage of cellular components and distortion of the architecture.

The purpose of this paper is to present a detailed histological analysis of arterial vasoconstriction and vasodilation. To study the changes in the architecture of arterial walls during changes in caliber, vasoconstriction and vasodilation were induced in local regions of small arteries in the dog mesentery. These vessels were then prepared for examination by quick freezing to preserve the normal architecture.

### Methods

Young mongrel dogs, weighing 6 to 9 Kg., were anesthetized with intravenous chloralose, 65 mg./Kg., and the mesentery of the small gut was exposed through a midline laparotomy. In each experiment, a vessel of about 1 mm. O.D. was selected to serve as a control; this vessel was excised and quick-frozen, as described below. In some experiments, a second vessel was perfused in situ with a saline solution containing acetylcholine (ACH), 1 µg./ml., to produce vasodilation. To produce vasoconstriction in other vessels, approximately 0.01 ml. of a saline solution containing 100 µg. of epinephrine/1 ml. was infiltrated into the mesentery adjacent to the artery with a 0.25-ml. syringe and a 27-gauge needle. In some experiments, a small amount of India ink suspension was added to the epinephrine solution to mark the site of injection in subsequent histological material. In all, 61 arterial radicles from 15 dogs were studied.

Each end of the arterial segment to be studied was attached to a rigid cardboard frame by means of a common office stapler. This stapling sealed the ends against loss of contents. The vessel was then quickly excised and dropped into a solution of liquid isopentane at −170 C. The entire procedure required less than 20 seconds. After the tissues had been fixed by freeze substitution with osmium tetroxide for 7 days at −70 C., they were mounted in paraffin blocks and serially sectioned at 5 µ thickness. Alternate...
sections were stained with hematoxylin and eosin, and a Weigert’s elastic procedure counterstained with van Gieson stain (EVG). Details of the methods involved here have been presented elsewhere.5,6

Results

In contrast to the appearance of formalin-fixed specimens, the walls of the control arteries in the present study were quite thin in relation to the size of their lumina (fig. 1). The ratio of wall thickness to luminal diameter was about 1:30, indicating that under control conditions these arteries are much more distended than would appear in routinely prepared sections. The organization of the components of the wall was also markedly different. The endothelial cells lining the lumen were flattened and quite thin in cross section, and their nuclei appeared elongated. The intima was not wrinkled, as it is in routine sections, but appeared as a thin circular ring without convolutions. The smooth muscle cells were long and thin, surrounding the intima in a narrow shell of uniform thickness. Their nuclei were 6 to 10 times longer than they were wide. The media presented as a narrow shell of uniform thickness surrounding the intima.

The arteries treated with ACH appeared to be even more dilated and had correspondingly thinner walls. The ratio of wall thickness to luminal diameter in these vessels was about 1:40 (fig. 1).

Although each of the arteries shown in figure 1 appeared to be approximately the same diameter prior to application of ACH or epinephrine, precise matching of their sizes was not possible. Thus, direct comparisons of different vessels could not be made to show the dimensional or architectural changes. With serial sections of a short length of the vasoconstricted area in a single vessel, however, it was possible to observe the entire sequence of histological changes, extending from the unconstricted area through the region of intense vasoconstriction (fig. 2).

Infusion of a droplet of epinephrine between layers of the mesentery adjacent to a small artery produced a localized progressive reduction of both the inside and the outside diameter of the vessel. A slight narrowing was apparent within 1 to 2 minutes, and after 4 to 5 minutes, a well-defined constriction about 5 mm. long was formed. The maximum reduction in caliber occurred within 8 to 10 minutes and commonly persisted over 30 minutes. The column of blood in the vessel was clearly visible under normal conditions, but became greatly narrowed in the constricted region and looked to be interrupted during the period of maximum constriction. When such vessels were transected distal to the constricted area, a few droplets of blood appeared at the proximal cut end for several minutes, but no significant outflow occurred.

The outside diameter of the vessel illustrated in figure 2 was progressively reduced from 0.92 to 0.38 mm. in the transition from its normal size to maximum constriction. Over this same region the diameter of the lumen was reduced from 0.86 to 0.18 mm., and the wall thickness increased from 0.03 to 0.10 mm. Thus, the outside diameter was reduced to less than one-half and the inside to less than one-fourth, while the wall thickness was increased over threefold. The ratio of wall thickness to luminal diameter was reduced from 0.03/0.86 (1:29) before constriction to 0.10/0.38 (1:2.6) during maximal vasoconstriction. The cross-sectional area of the lumen of this vessel was simultaneously reduced from 0.58 to 0.02 mm.2

Significant morphological changes may be correlated with these measurements. For example, the intima was progressively deformed. Apparently, it was incapable of shortening to the extent that the inner circumference was reduced, so that irregular indentations and longitudinal folds appeared during even mild vasoconstriction, usually when the diameter of the lumen was reduced by about 25 per cent. In maximal constriction, the intima appeared as a densely packed series of irregular convolutions. Although the intima was only slightly thickened during the process, the net effect of such folding contributed materially to reduction of the lumen (fig. 2).

Endothelial cells became progressively col-
Five arteries with outside diameters of about 1 mm. (ACH) Artery was perfused in situ with acetylcholine to produce vasodilation; the wall to lumen ratio is 1:40. (Control) Artery has a wall to lumen ratio of about 1:30. The intima is free of convolutions; smooth muscle cells and their nuclei are long and thin. (Slightly Constricted) Vessel was fixed two minutes after infusion of epinephrine; the wall is slightly thickened. (Moderately Constricted) Vessel was fixed four minutes after infusion of epinephrine; the wall is thicker and the intima is wrinkled. (Fully Constricted) Vessel was fixed after 10 minutes exposure to epinephrine; the wall is appreciably thickened and the lumen greatly reduced (ratio of wall to lumen 1:2). The intima
### TABLE 1

**Criteria of Vasconstriction in Small Arteries of Dog Mesentery**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumen</td>
<td>Packed with RBC's and plasma proteins</td>
</tr>
<tr>
<td>Lumen diameter</td>
<td>Reduced</td>
</tr>
<tr>
<td>Wall thickness</td>
<td>Increased</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>Assume columnar shape with round to oval nuclei</td>
</tr>
<tr>
<td>Internal elastic lamina</td>
<td>Project into lumen along crests of intimal folds</td>
</tr>
<tr>
<td>Smooth muscle cells</td>
<td>Markedly convoluted and compressed</td>
</tr>
<tr>
<td>Adventitia</td>
<td>Occasional focal spitting</td>
</tr>
<tr>
<td>Adventitia</td>
<td>Adjacent to elastic lamina; Compressed</td>
</tr>
<tr>
<td></td>
<td>Severe nuclear deformation</td>
</tr>
<tr>
<td></td>
<td>Appear short and blunted</td>
</tr>
<tr>
<td>Middle layer</td>
<td>Less severe than inner layer</td>
</tr>
<tr>
<td></td>
<td>Cells shortened</td>
</tr>
<tr>
<td></td>
<td>Nuclear Pleomorphism</td>
</tr>
<tr>
<td>Outer layer</td>
<td>Adjacent to adventitia</td>
</tr>
<tr>
<td></td>
<td>Minimal changes</td>
</tr>
<tr>
<td>Adventitia</td>
<td>Collagen and elastic fibers are not remarkable</td>
</tr>
</tbody>
</table>

**Umnar in shape with the long axis of the nucleus now at right angles to the basement membrane.** Because of the folding, nuclei appeared much closer to each other and often seemed perched atop the intimal convolutions. The cells projected into the lumen as an irregular series of short fingers. In very small arterioles, bulging of endothelial cells during vasocostriction may occlude the lumen. However, such closure was not observed in any of the vessels used in this study.

The major increase in wall thickness during vasocostriction occurred in the media. Smooth muscle cells appeared shortened and when lumen diameter reduction reached 25 per cent of its control size, the inner layers became distorted. Deformation of smooth muscle cells was most severe immediately adjacent to the elastic lamina, and was in direct proportion to the folding of the lamina. The markedly convoluted elasta trapped the underlying muscle cells twisting and compressing nuclei beyond normal recognition, as seen in figure 1 and figure 2 (D, E, and F). During intense vasocostriction, the entire media appeared disorganized, but a gradient of changes was suggested. Smooth muscle cells adjacent to the elastic membrane were most severely deformed, and there was a diminution in cytoarchitectural alterations as the adventitia was reached. In general, the muscle cells covered by adventitial connective tissue showed the least changes and often were normal. No significant connective tissue or ground substance changes were observed in the adventitia.

An increase in the ratio of wall thickness to lumen diameter is commonly employed as an indication of vascular wall hypertrophy in a variety of pathological states. Recent studies of small arteries in human pulmonary hypertension utilized this reasonable concept. However, this ratio is also increased in normal vessels during constriction and such arteries may be mistakenly identified as being hypertrophied. Histological characteristics of

---

*Circulation Research, Volume X, April 1962*
Sections through a single small mesenteric artery in which localized area of vasoconstriction was produced by topical application of epinephrine. Section A was taken proximal to the site of vasoconstriction. The ratio of wall to lumen is 1:30; intima is free of convolutions; smooth muscle cells are concentrically arranged, long and thin in cross section, and smooth muscle nuclei are 6 to 10 times as long as they are wide; Sections B, C, D, and E, taken successively through the tapered area of vasoconstriction, show progressive decrease in the diameter of the lumen and increase in wall thickness. The intima is compressed into folds; smooth muscle cells are shortened. Section F is through the area of intense vasoconstriction (ratio of wall to lumen is 1:2). Archi-
SMALL ARTERIAL CONSTRICTION

vasoconstricted vessels under the conditions of this study are listed in table 1. The degree of vasoconstriction may be inferred from the extent to which these changes occur. In the presence of such changes and in the absence of degenerative phenomena, an increase in the ratio of wall thickness to lumen may be interpreted as simple vasoconstriction rather than as hypertrophy.

Blood vessels are commonly considered to be distensible elastic cylinders with cross sections that are regular and circular. Also, vasoconstriction is thought to affect the circumference of the vessel uniformly, so that symmetrical reduction of the lumen results. However, application of discrete amounts of epinephrine to only one side of the vessel for a period of 1 to 2 minutes produced constriction of only a part of the wall, without affecting the region on the opposite side. Cross sections of these vessels were signet-shaped, with histological changes typical of unconstricted and severely constricted walls appearing on opposite sides of the same microscopic section (fig. 9).

Discussion

Although the procedures employed in this study have obvious advantages over other methods, the direct application of vasoactive substances is an unphysiological technique for producing changes in vessel dimensions. The local concentrations of epinephrine used in this study greatly exceeded those occurring under ordinary autonomic activity. Stapling of the vessel to cardboard holders maintained intraluminal pressure to the extent that no blood flowed from either cut end, and in the fixed sections the lumen was well packed with red cells. Undoubtedly some of the pressure head was lost at the time of excision through transection of numerous fine anastomotic channels in the mesentery. However, both normal and dilated vessels retained a cylindrical appearance in cross section without evidence of collapse. Attachment of the vessel to a rigid frame limited changes in overall length but did not rule out the possibility that the constricted region was lengthened or shortened at the expense of adjacent untreated areas. The technique of quick freezing and free substitution had the obvious advantage of reducing distortion due to shrinkage. By appropriate staining methods, it was possible to follow in a serial manner the cellular and fibrillar changes.

The data presented is applicable only to the dog mesenteric arterial bed under the specific conditions indicated. Allowing maximal vasoconstriction to continue beyond the time limits employed in this study introduces the variables of collateral circulation, increased vascular permeability, and the beginning of inflammatory and coagulative changes. Nevertheless, a striking uniformity of response can be elicited in different areas of the same mesentery and in different mesenteries.

During constriction of small arteries, the circumference of the vessel diminishes and, in accordance with the law of Laplace, the tension required to support a given pressure is reduced. However, such a relationship is valid only if the thickness of the vascular wall is negligible. In a thick-walled vessel, caliber can be reduced only through a progressive increase in the wall thickness. During vasoconstriction, the inner layers of the smooth muscle become compressed and distorted (fig. 2), and thus are no longer exerting tension. Indeed, tension must be exerted by the outer layers to produce the distortion of the inner layers, as well as to support the transmural pressure. The resistance to constriction offered by the inner distorted layers of the vessel is indicated by the fact that complete occlusion of the lumen was never seen in vessels with an apparent outside diameter of 1 mm. Since the outermost layers of smooth muscle can distort the inner layers of the vessel in addition to supporting the

Discussion

Although the procedures employed in this study have obvious advantages over other methods, the direct application of vasoactive substances is an unphysiological technique for producing changes in vessel dimensions. The local concentrations of epinephrine used in this study greatly exceeded those occurring under ordinary autonomic activity. Stapling of the vessel to cardboard holders maintained intraluminal pressure to the extent that no blood flowed from either cut end, and in the fixed sections the lumen was well packed with red cells. Undoubtedly some of the pressure head was lost at the time of excision through transection of numerous fine anastomotic channels in the mesentery. However, both normal and dilated vessels retained a cylindrical appearance in cross section without evidence of collapse. Attachment of the vessel to a rigid frame limited changes in overall length but did not rule out the possibility that the constricted region was lengthened or shortened at the expense of adjacent untreated areas. The technique of quick freezing and free substitution had the obvious advantage of reducing distortion due to shrinkage. By appropriate staining methods, it was possible to follow in a serial manner the cellular and fibrillar changes.

The data presented is applicable only to the dog mesenteric arterial bed under the specific conditions indicated. Allowing maximal vasoconstriction to continue beyond the time limits employed in this study introduces the variables of collateral circulation, increased vascular permeability, and the beginning of inflammatory and coagulative changes. Nevertheless, a striking uniformity of response can be elicited in different areas of the same mesentery and in different mesenteries.

During constriction of small arteries, the circumference of the vessel diminishes and, in accordance with the law of Laplace, the tension required to support a given pressure is reduced. However, such a relationship is valid only if the thickness of the vascular wall is negligible. In a thick-walled vessel, caliber can be reduced only through a progressive increase in the wall thickness. During vasoconstriction, the inner layers of the smooth muscle become compressed and distorted (fig. 2), and thus are no longer exerting tension. Indeed, tension must be exerted by the outer layers to produce the distortion of the inner layers, as well as to support the transmural pressure. The resistance to constriction offered by the inner distorted layers of the vessel is indicated by the fact that complete occlusion of the lumen was never seen in vessels with an apparent outside diameter of 1 mm. Since the outermost layers of smooth muscle can distort the inner layers of the vessel in addition to supporting the

Discussion

Although the procedures employed in this study have obvious advantages over other methods, the direct application of vasoactive substances is an unphysiological technique for producing changes in vessel dimensions. The local concentrations of epinephrine used in this study greatly exceeded those occurring under ordinary autonomic activity. Stapling of the vessel to cardboard holders maintained intraluminal pressure to the extent that no blood flowed from either cut end, and in the fixed sections the lumen was well packed with red cells. Undoubtedly some of the pressure head was lost at the time of excision through transection of numerous fine anastomotic channels in the mesentery. However, both normal and dilated vessels retained a cylindrical appearance in cross section without evidence of collapse. Attachment of the vessel to a rigid frame limited changes in overall length but did not rule out the possibility that the constricted region was lengthened or shortened at the expense of adjacent untreated areas. The technique of quick freezing and free substitution had the obvious advantage of reducing distortion due to shrinkage. By appropriate staining methods, it was possible to follow in a serial manner the cellular and fibrillar changes.

The data presented is applicable only to the dog mesenteric arterial bed under the specific conditions indicated. Allowing maximal vasoconstriction to continue beyond the time limits employed in this study introduces the variables of collateral circulation, increased vascular permeability, and the beginning of inflammatory and coagulative changes. Nevertheless, a striking uniformity of response can be elicited in different areas of the same mesentery and in different mesenteries.

During constriction of small arteries, the circumference of the vessel diminishes and, in accordance with the law of Laplace, the tension required to support a given pressure is reduced. However, such a relationship is valid only if the thickness of the vascular wall is negligible. In a thick-walled vessel, caliber can be reduced only through a progressive increase in the wall thickness. During vasoconstriction, the inner layers of the smooth muscle become compressed and distorted (fig. 2), and thus are no longer exerting tension. Indeed, tension must be exerted by the outer layers to produce the distortion of the inner layers, as well as to support the transmural pressure. The resistance to constriction offered by the inner distorted layers of the vessel is indicated by the fact that complete occlusion of the lumen was never seen in vessels with an apparent outside diameter of 1 mm. Since the outermost layers of smooth muscle can distort the inner layers of the vessel in addition to supporting the

Discussion

Although the procedures employed in this study have obvious advantages over other methods, the direct application of vasoactive substances is an unphysiological technique for producing changes in vessel dimensions. The local concentrations of epinephrine used in this study greatly exceeded those occurring under ordinary autonomic activity. Stapling of the vessel to cardboard holders maintained intraluminal pressure to the extent that no blood flowed from either cut end, and in the fixed sections the lumen was well packed with red cells. Undoubtedly some of the pressure head was lost at the time of excision through transection of numerous fine anastomotic channels in the mesentery. However, both normal and dilated vessels retained a cylindrical appearance in cross section without evidence of collapse. Attachment of the vessel to a rigid frame limited changes in overall length but did not rule out the possibility that the constricted region was lengthened or shortened at the expense of adjacent untreated areas. The technique of quick freezing and free substitution had the obvious advantage of reducing distortion due to shrinkage. By appropriate staining methods, it was possible to follow in a serial manner the cellular and fibrillar changes.

The data presented is applicable only to the dog mesenteric arterial bed under the specific conditions indicated. Allowing maximal vasoconstriction to continue beyond the time limits employed in this study introduces the variables of collateral circulation, increased vascular permeability, and the beginning of inflammatory and coagulative changes. Nevertheless, a striking uniformity of response can be elicited in different areas of the same mesentery and in different mesenteries.

During constriction of small arteries, the circumference of the vessel diminishes and, in accordance with the law of Laplace, the tension required to support a given pressure is reduced. However, such a relationship is valid only if the thickness of the vascular wall is negligible. In a thick-walled vessel, caliber can be reduced only through a progressive increase in the wall thickness. During vasoconstriction, the inner layers of the smooth muscle become compressed and distorted (fig. 2), and thus are no longer exerting tension. Indeed, tension must be exerted by the outer layers to produce the distortion of the inner layers, as well as to support the transmural pressure. The resistance to constriction offered by the inner distorted layers of the vessel is indicated by the fact that complete occlusion of the lumen was never seen in vessels with an apparent outside diameter of 1 mm. Since the outermost layers of smooth muscle can distort the inner layers of the vessel in addition to supporting the

Discussion

Although the procedures employed in this study have obvious advantages over other methods, the direct application of vasoactive substances is an unphysiological technique for producing changes in vessel dimensions. The local concentrations of epinephrine used in this study greatly exceeded those occurring under ordinary autonomic activity. Stapling of the vessel to cardboard holders maintained intraluminal pressure to the extent that no blood flowed from either cut end, and in the fixed sections the lumen was well packed with red cells. Undoubtedly some of the pressure head was lost at the time of excision through transection of numerous fine anastomotic channels in the mesentery. However, both normal and dilated vessels retained a cylindrical appearance in cross section without evidence of collapse. Attachment of the vessel to a rigid frame limited changes in overall length but did not rule out the possibility that the constricted region was lengthened or shortened at the expense of adjacent untreated areas. The technique of quick freezing and free substitution had the obvious advantage of reducing distortion due to shrinkage. By appropriate staining methods, it was possible to follow in a serial manner the cellular and fibrillar changes.

The data presented is applicable only to the dog mesenteric arterial bed under the specific conditions indicated. Allowing maximal vasoconstriction to continue beyond the time limits employed in this study introduces the variables of collateral circulation, increased vascular permeability, and the beginning of inflammatory and coagulative changes. Nevertheless, a striking uniformity of response can be elicited in different areas of the same mesentery and in different mesenteries.

During constriction of small arteries, the circumference of the vessel diminishes and, in accordance with the law of Laplace, the tension required to support a given pressure is reduced. However, such a relationship is valid only if the thickness of the vascular wall is negligible. In a thick-walled vessel, caliber can be reduced only through a progressive increase in the wall thickness. During vasoconstriction, the inner layers of the smooth muscle become compressed and distorted (fig. 2), and thus are no longer exerting tension. Indeed, tension must be exerted by the outer layers to produce the distortion of the inner layers, as well as to support the transmural pressure. The resistance to constriction offered by the inner distorted layers of the vessel is indicated by the fact that complete occlusion of the lumen was never seen in vessels with an apparent outside diameter of 1 mm. Since the outermost layers of smooth muscle can distort the inner layers of the vessel in addition to supporting the
transmural pressure, the functional need for hypertrophy of the media is doubtful. The concept that small arteries and sites of controlled resistance become hypertrophied in the presence of chronic hypertension is based on the finding that the walls are comparatively thick in relation to the size of the lumen. However, since the walls of arteries may be greatly thickened during vasoconstriction, the wall to lumen ratio per se cannot be a reliable index of hypertrophy. Further, quick frozen and freeze-substituted walls of normal vessels are considerably thinner than those handled in the routine fashion, suggest-
ing that the shrinkage due to decompression of vessels, routine fixation procedures, and mounting artifacts contributes to the increased thickness of the wall seen in many diagnostic and pathological slides.

A general increase in total peripheral resistance is usually accompanied by a very great increase in systemic arterial pressure. The fact that peripheral resistance remains high in spite of increased pressure indicates that the normal smooth muscle in the vascular wall can develop sufficient tension to maintain vasoconstriction without the need for hypertrophy. Hypertrophy of smooth muscle in vascular walls is presumably analogous to that of skeletal muscles performing increased work. Although the need for increased tension over long periods of time could possibly lead to proliferation of smooth muscle, the situation is quite different in two types of muscle, since smooth muscle actually performs very little work while sustaining very high tensions at a fixed caliber. From the functional point of view, a hypertrophied vessel must have a wall which is very thick in relation to the diameter of the lumen with no distortion of inner layers of smooth muscle or their nuclei. A definition of the criteria of hypertrophy similar to the list of criteria for vasoconstriction in table 1 would make more obvious the distinction between these two states.

Summary

The cytoarchitectural changes which take place in the walls of small arteries (about 1 mm. O.D.) during vasoconstriction and vasodilation have been studied. Vessels were fixed while in their functional state by immersion in liquid isopentane at —170 C. and prepared for microscopic examination by freeze substitution.

The walls of control vessels were thin in relation to the diameter of lumina (WT:L 1:30), indicating that they are more distended than they appear in routinely fixed sections. Vessels dilated with ACH had even thinner walls (WT:L 1:40). Vasoconstriction, induced by local application of epinephrine, increased the wall thickness and reduced the size of the lumen (WT:L 1:2) but in no case was the lumen obliterated in arteries of this size.

Although an increase in the WT:L ratio is commonly employed as evidence of vascular hypertrophy, normal vessels which are fix and sectioned while in a functional state of vasoconstriction may exhibit similar gross characteristics. Constricted vessels are characterized by progressive deformation of the internal elastic lamina, crowding of endothelial cells, and distortion of smooth muscle cells and their nuclei, particularly in the region immediately adjacent to the lumen. During intense vasoconstriction, the wall tension appears to be supported only by the outer layers of the vessel.

References

Architecture of Small Arteries during Vasoconstriction
Robert L. Van Citters, Bernard M. Wagner and Robert F. Rushmer

Circ Res. 1962;10:668-675
doi: 10.1161/01.RES.10.4.668
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1962 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/10/4/668

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/