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Kaderly, Robert Elton

POSTNATAL MATURATION OF THE MICROCIRCULATION IN THE FEMUR OF THE DOG

The Ohio State University

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POSTNATAL MATURATION OF THE MICROCIRCULATION
IN THE FEMUR OF THE DOG

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By
Robert Elton Kaderly, B.S., D.V.M., M.S.

*****

The Ohio State University
1984

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The microcirculation of long bones may be artificially subdivided into (1) arterial supply and venous drainage of the marrow, and (ii) arterial supply and venous drainage of cortical bone. The microvascular systems of marrow and cortical bone are not mutually exclusive. One relationship between the two systems is obvious: extraosseous arteries must traverse cortical bone through vascular channels to supply the marrow, and venous structures must leave the medullary cavity through vascular channels within the cortex to enter the extraosseous venous system.

Although the subject of venous drainage of long bones has not received as much investigative attention as arterial supply, maintaining adequate venous drainage could be much more important than arterial supply for normal microcirculation. The unyielding diameter of vascular channels passing through rigid cortical bone places a unique restriction on the capacity of venous structures to compensate for increased afferent flow. Impaired blood flow through the marrow would inhibit the entry of blood cells, platelets and tissue fluid into the systemic circulation, while also compromising the nutrition of the marrow tissue and cancellous bone. Poor venous drainage of bone may predispose to osteonecrosis\(^1, 2\) and possibly delay or prevent fracture healing in some instances.\(^3\) Stagnation of blood due to obstructed
venous outflow may be involved in the establishment of osteomyelitis
during bacteremic episodes, the sequential development of bone
sarcomas in multifocal areas of bone infarction, hematogenous
metastasis of various neoplasms to bony sites, the pathogenesis of
aneurysmal bone cysts, or the necrosis of supporting cancellous bone
in conditions such as Legg-Calve-Perthes' disease.

Venous drainage patterns and directional blood flow from marrow
and cortical bone remains a controversial issue. The difficulties of
studying minute vessels encased within an opaque, mineralized shell are
compounded when attempting to separate the microcirculatory vascular
structures into arterial and venous components. Selectively profusing
only venous structures is technically difficult. Complete filling of
all intraosseous vessels with a common material makes the
differentiation of arterial and venous vessels unclear. In addition,
the morphological characteristics of static vascular structures do not
always suggest the direction of blood flow. Various other techniques
(bone blood flow measurements, vascular pressure recordings) can be
helpful in interpreting anatomical information.

The following investigation was designed to further describe the
microcirculatory structures and vascular patterns in marrow and
cortical bone. Structural evidence supporting the hypothesis of
centrifugal and centripetal transcortical blood flow was sought. By
following to maturity the relatively simplified arterial and venous
systems present in the newborn puppy, the complex microcirculatory
patterns in the adult dog could be interpreted more accurately. An
emphasis was placed on investigating venous structures and patterns
because of the potential clinical relevance of impaired venous drainage and the current lack of a definitive study of the venous drainage of long bones. Attention was concentrated in three areas: (i) maturation of the marrow microcirculation, (ii) maturation of the microcirculation in cortical bone, and (iii) the communications of marrow and cortical bone microcirculation.
CHAPTER I

MATURATION OF THE MICROCIRCULATION IN THE MARROW
ABSTRACT

Proximal and distal epiphyseal, metaphyseal, and diaphyseal nutrient arteries entered the medullary cavity at their respective levels. Arteries within the medullary cavity branched to eventually form small arteries and arterioles. Small arteries gave rise to arteriolar capillaries which were characteristic in their acute angles of origin, abrupt narrowness, and thin walls. Arteriolar capillaries supplied sinusoids in areas of hematopoietic marrow. Arterioles terminated into capillaries which established capillary-venule beds in patchy areas of fatty marrow.

Sinusoids joined with other sinusoids through communicating venules, and emptied directly into the central medullary vein via drainage venules or indirectly into the central medullary vein via collecting sinuses and collecting veins. Transmural migration of marrow blood cells was demonstrated through migration pores in the sinusoids and collecting sinuses. The central medullary vein was (consistently) drained by cranial and caudal proximal metaphyseal and distal metaphyseal emissary veins and (inconsistently) by proximal and distal diaphyseal emissary veins.

Maturation of the microcirculation in the proximal and distal epiphyses was followed from the random cartilage vessels of newborn puppies, through the establishment and development of the microcirculation in secondary ossification centers of 2 and
10-week-old puppies, to obliteration of the physis and the joining of epiphyseal and metaphyseal microvascular systems of adult dogs. Transphyseal vessels were only demonstrated in the femurs of newborn puppies. Throughout femoral development, vessels in the ligament to the head of the femur did not contribute to the microcirculation in the femoral head.
INTRODUCTION

Unique vascular structures of marrow have been known to exist for many years. In 1901, Minot coined the term "sinusoid," and described its characteristic features by comparing it to a capillary. Vascular differences between hematopoietic and fatty marrow were recognized grossly by Trueta in 1953. Only recently, with the advent of transmission and scanning electron microscopic techniques, has ultrastructural detail revealed specific structural adaptations of the arterial and venous microvascular systems of marrow, which apparently are present to facilitate the function of bone marrow as an organ.

While the ultrastructural features of vessels within marrow have suggested certain physiological mechanisms, from a larger point of view, a description of the dog's arterial and venous marrow microvascular systems in complete continuity, is unavailable.

In general, arterial vessels within the medullary cavity supply both marrow and cortical bone microcirculations. More attention is devoted to Chapter I (Maturation of the Microcirculation in the Marrow) to appropriately "set the stage" for Chapters II and III.
MATERIALS AND METHODS

Vascular injections were performed on puppies and dogs of mixed breeding and of either sex. Twelve newborn puppies weighing 0.45-0.60 kg (2 litters), 6 two-week-old puppies weighing 1.6-1.8 kg (one litter), 6 ten-week-old puppies weighing 4.5-5.0 kg (one litter), and 17 adult dogs weighing 18-30 kg were used in this investigation. All subjects were anesthetized with intravenous or intracardiac injections of pentobarbital sodium (approximately 25 mg/kg to effect). Each animal was heparinized with heparin sodium (200 USP units plus 10 units/kg of body weight) and placed in dorsal recumbency.

In the puppies, a surgical approach was made to the caudal abdomen by a longitudinal incision through the linea alba, followed by a transverse abdominal incision at the cranial limit of the initial longitudinal incision. The left and right sides of the abdominal wall were reflected laterally to locate the common iliac vein and the external iliac artery just proximal to the internal inguinal rings. Segments of both the artery and vein on each side were isolated and 2 six-inch lengths of 2-0 surgical silk suture were passed around each vessel. In the adult dogs, a ventral approach to the coxofemoral joint was substituted for the abdominal celiotomy. The medial circumflex femoral artery (source vessel of the nutrient artery to the femur) and the femoral vein were isolated after removing the overlying pectineus muscle. Two lengths of 2-0 surgical silk suture were placed around each vessels. The common iliac vein in the puppies or the femoral vein in the adult dogs was ligated first, by tying the most proximal length of suture. Polyethylene male urinary catheters (sizes 3 1/2, 5, 8, or
10 Fr.) were incised at a 30° angle, and the distal length of suture was retracted gently to occlude the lumen of the vein. A small perforation was made through the wall of the vein between the two lengths of suture with a #11 scalpel blade. The appropriate sized catheter was passed into the vein and secured by ligating the distal suture. The same catheterization procedure was performed on the external iliac artery in the puppies and the medial circumflex femoral artery in the adult dogs. When all four catheters were in place and secured, the animals were euthanized by administering an intravenous overdose of pentobarbital sodium.

Sixty milliliter syringes of warm, heparinized 0.9% saline (7,000 USP units/250 ml) were connected to the arterial catheters and the vessels were slowly flushed until clear fluid flowed freely from the venous catheters. In 4 newborn puppies and 2 adult dogs, vascular saline flushing was followed immediately by perfusion with a 2% glutaraldehyde-2% paraformaldehyde solution (pH 7.4) to fix the tissues for future scanning electron microscopic (SEM) studies. Approximately 1 ml/kg of body weight of the glutaraldehyde-paraformaldehyde mixture was perfused antegrade through syringes attached to the arterial catheters, followed by retrograde perfusion of the glutaraldehyde-paraformaldehyde mixture (approximately 0.2 ml/kg of body weight) through syringes attached to the venous catheters. Microfil®, a colored liquid silicone mixture that polymerizes intravascularly after a catalyzing agent is added, was prepared for vascular injection. In general, white Microfil® (MV-112) was used for antegrade arterial injections, and orange Microfil® (MV-117) was used for retrograde venous injections.
The MV compound (pigmented component) was combined with MV diluent and curing agent at a ratio of 4.0:5.0:0.45 vol:vol:vol, and mixed thoroughly. Under constant gentle hand pressure, Microfil\textsuperscript{r} injections were promptly made via antegrade routes (through the external iliac or medial circumflex femoral arteries), retrograde routes (through the common iliac or femoral veins), or both antegrade and retrograde routes. Arterial microcirculation supplying the medullary cavity was to be demonstrated by the antegrade injections; venous microcirculation draining the medullary cavity was to be demonstrated by the retrograde injections. The volume of Microfil\textsuperscript{r} used for each injection varied greatly, depending on the size of the animal, the route of injection, and the intended specific vascular structures (arterial or venous) or areas (marrow or cortical bone) to be studied. A minimum of 6 hours post-injection at room temperature was allowed for the intravascular catalization process to occur.

The femurs were harvested, the surrounding soft tissues were removed, and the lateral or cranial surfaces were sectioned longitudinally to expose the marrow cavity for better penetration of the Spalteholz clearing solutions which were to follow. Multiple cross-sections of the mid-diaphysis were also made on one pair of glutaraldehyde-fixed adult femurs. A modified Spalteholz clearing technique\textsuperscript{4,5} was used to render transparent (clear) the osseous and soft tissues which permitted three-dimensional visualization of the opaque, Microfil\textsuperscript{r}-filled vascular structures. All specimens except the glutaraldehyde-fixed newborn femurs were thoroughly decalcified in 3% nitric acid.
The time required for complete decalcification to occur varied from several hours in the newborn femurs to over one week in the femurs of adult dogs. Nitric acid solutions were changed daily. Fatty marrow was removed by submerging the specimens in Triton X-100 (SEM specimens) or chloroform. The tissues were dehydrated by daily serial passage through successively increasing concentrations of alcohol (50%, 75%, 85%, 95%, absolute). The specimens were cleared and stored in water-free methyl salicylate. For microscopic examination, specimens were transferred to an optically correct glass viewing box containing methyl salicylate and illuminated by two fiber optics light sources. Photographs were taken through a stereoscopic dissecting microscope and an operating microscope using 35mm Zeiss cameras and ASA 50 tungsten color slide film. Scanning electron microscopy was performed on glutaraldehyde-fixed vessels in nondecalcified fragments of the newborn puppy femurs that had been previously defatted (Triton X-100) and dehydrated (Spalteholz alcohol sequence). Decalcified, defatted, and dehydrated pieces of femoral bone from two adult dogs were also prepared for scanning electron microscopic examination. The SEM specimens were critically point dried, mounted, sputter-coated with gold, evaluated under the electron microscope, and photographed with Polaroid type 55 positive/negative film.
RESULTS

The femurs of the newborn puppies measured approximately 3 mm in diameter at the mid-diaphysis, and 22 mm in length. Both epiphyses were entirely cartilaginous. Between the two epiphyses, a marrow cavity was present within a shell of periosteal woven bone. The proximal femoral physis was continuous between the femoral head and the greater trochanter. As the puppies became older, the configuration of the femurs changed by disproportional lengthening of the shaft and non-symmetrical growth at the proximal physis (Fig. 1.1). The increased rate of growth of the proximal physis at the femoral head caused elongation of the femoral neck and the eventual division (at two weeks of age) of the proximal physis into separate physes for the femoral head and the greater trochanter. The femurs of the adult dogs measured 12-14 mm in diameter (at the narrowest point on the diaphysis) and 165-220 mm in length. From birth to maturity, the femurs displayed a 4.6-fold increase in diameter and a 7.5-10-fold increase in length. There was a 40-50-fold increase in body weight.

Antegrade injections of white Microfil into the medial circumflex femoral artery of adult dogs resulted in the filling of arterial vessels and sinusoids within the marrow cavity (Fig. 1.2). Attempts at direct cannulation of the diaphyseal nutrient artery of the femur were abandoned due to the difficult location of the nutrient foramen on the caudal surface of the femur under the attachment of the adductor magnus
Figure 1.1

Comparative sizes and configurations of the femur in the newborn puppy (A), two-week-old puppy (B), ten-week-old puppy (C), and adult dog (D)
Figure 1.2

Caudal one-half, proximal left femur (cut surface); adult dog. Low magnification of the arterial vascular pattern within the medullary cavity. Arterial structures and sinusoids are filled with Microfil®.
et brevis muscle. Upon entering the marrow cavity, the diaphyseal nutrient artery divided promptly into ascending and descending medullary arteries. These tortuous main branches soon gave rise to several smaller, long, longitudinally directed arteries which traveled proximally and distally through the marrow toward the cancellous bone of the proximal and distal metaphyses (Fig. 1.3). Even though most venous structures were not filled by this injection route, a large concentration of arterial vessels and sinusoids were present in the adult marrow, making it extremely difficult to clearly identify the terminations of the arterial microcirculation. After following the maturation of the simplified arterial and venous marrow systems from birth, a retrospective examination of the marrow vessels in the adult dog was more enlightening.

By only partially filling arterial and venous marrow systems in the newborn puppy, several antegrade and retrograde injections revealed the generalized vascular patterns within the marrow cavity. The diaphyseal nutrient artery usually was single, entering the marrow cavity from the caudal surface of the proximal femur and branching into ascending and descending medullary arteries. When proximal and distal diaphyseal arteries were present (4 of 24 puppies), the proximal diaphyseal nutrient artery gave rise to the ascending medullary artery and the distal diaphyseal nutrient artery gave rise to the descending medullary artery. In the newborn puppy, thin branches arose from the medullary arteries at right angles.

The basic venous drainage system of the medullary cavity within the femoral shaft consisted of a central medullary vein which was
Figure 1.3

Caudal one-half, diaphysis of left femur (cut surface); adult dog. Low magnification of longitudinal branches arising from the descending medullary arteries and passing distally within the medullary cavity. Note where the nutrient artery enters the medullary cavity.
consistently drained through the cortex by proximal and distal emissary metaphyseal veins. The central medullary vein was also inconsistently drained by very small proximal diaphyseal emissary veins (all passing through the nutrient foramen) and a larger, single distal emissary diaphyseal vein (Fig. 1.4). By selective arterial and venous injections, close inspection of the nutrient canal in the femurs of adult dogs confirmed the absence (in most cases) of a large diaphyseal "nutrient" vein passing through the nutrient canal beside the diaphyseal nutrient artery. Nearly the entire diameter of the nutrient canal was occupied by the diaphyseal nutrient artery (Fig. 1.5). Several very flattened, narrow veins were demonstrated, however, in intimate contact with the diaphyseal nutrient artery as it passed through the nutrient canal. Occasionally wrapping around the diaphyseal nutrient artery were flattened venous plexuses that communicated with the narrow veins within the nutrient canal (Fig. 1.6).

As the newborn puppies matured, regional drainage patterns became better established in the proximal and distal metaphyses. The marrow of the proximal metaphysis was mainly drained by the large cranial proximal metaphyseal emissary vein (on the cranial surface of the proximal femur) and the large caudal proximal metaphyseal emissary vein, which emerged from the medullary cavity out of the trochanteric fossa. The marrow of the distal metaphysis was regionally drained by one to three distal metaphyseal emissary veins, all emerging from the cortex on the caudal surface of the femur (Figs. 1.7, 1.8). The venous anastomoses of the proximal and distal emissary metaphyseal veins (and the proximal and distal diaphyseal emissary veins, when present) with
Figure 1.4

Medial surface view, diaphysis of the left femur; newborn puppy. Only the main arterial and venous structures of the medullary cavity have been injected. CMV = central medullary vein, DMA = descending medullary artery, PDV = proximal diaphyseal emissary vein, DDV = distal diaphyseal emissary vein.
Figure 1.5

Medullary cavity and lateral cortex (C) at the level of the nutrient canal; adult dog. The nutrient artery occupies nearly the entire nutrient canal.

Figure 1.6

Longitudinal section through the cortex (C) near the nutrient canal (NC); adult dog. Several small proximal diaphyseal emissary veins (PDV) surround the transparent nutrient artery.
Figure 1.7

Craniolateral edge of (laterally sectioned) proximal left femur; two-week-old puppy. Cranial (crPMV) and caudal (caPMV) proximal metaphyseal emissary veins draining the proximal marrow cavity (M) and anastomosing with the central medullary vein.

Figure 1.8

Caudolateral edge of (laterally sectioned) distal right femur; two-week-old puppy. Distal metaphyseal emissary vein (DMV) passing obtusely through the cortex (C) and draining the distal medullary cavity.
the central medullary vein were retained throughout the development of the femur to serve as permanent collateral drainage routes from the marrow cavity in the femurs of the adult dogs (Fig. 1.9).

The level at which marrow blood flowed from the arterial microcirculation into the venous drainage system was best seen in the metaphyses of partially injected newborn puppy specimens. Because a large percentage of vascular structures were not filled in a few of these specimens, it was possible to trace individual vascular pathways continuously from the arterial system to the venous system in the areas of hematopoietic marrow. Increasingly narrower branches of the medullary arteries, destined to supply the hematopoietic marrow, ultimately terminated in very small arterioles or capillaries which supplied dilated, irregular vascular structures, the sinusoids. Developing sinusoids in the metaphyses emptied into collecting sinuses which in turn converged and left the marrow cavity as metaphyseal emissary veins (Figs. 1.10, 1.11).

Ultrastructural examination of vascular structures within bone marrow revealed characteristic differences between arterial and venous vessels. Arteries were smooth, nearly parallel-walled vessels of gradually changing caliber with numerous longitudinally oriented endothelial nuclei protruding into their lumen. Venous structures, particularly the sinusoids, exhibited irregular walls and abrupt variations in diameter (Fig. 1.12). Sinusoids appeared to develop by budding dilatations off of collecting sinuses and were very closely associated with the hematopoietic marrow in the interstices of cancellous bone (Figs. 1.13, 1.14). In the adult specimens, the narrow arteriolar
Figure 1.9

Drawing of the emissary venous drainage of the central medullary vein; adult dog

A = caudal proximal metaphyseal emissary vein

B = cranial proximal metaphyseal emissary vein

C = diaphyseal emissary vein accompanying diaphyseal nutrient artery

D = distal metaphyseal emissary vein

E = distal epiphyseal emissary vein
Figure 1.10

Lateral (cut) surface of distal metaphysis, right femur; newborn puppy. Fine branches from descending medullary arteries (DMA) supplying sinusoids (VS) just proximal to the distal physis.

Figure 1.11

Lateral (cut) surface of distal metaphysis, left femur; newborn puppy. Distal metaphyseal sinusoids (VS) converging on collecting sinuses) and draining through the caudal cortex via a distal metaphyseal emissary vein (DMV).
Figure 1.12

SEM of marrow cells and trabecular bone; newborn puppy. Comparison of a large smooth-walled artery (AR) and an irregular sinusoid (VS).
Figure 1.13

SEM of trabecular bone (TB) and marrow tissue; newborn puppy. Developing sinusoids (VS) and collecting sinuses.

Figure 1.14

SEM of decalcified trabecular bone (TB), marrow tissue, sinusoids (VS), and collecting sinuses (CS); adult dog. Several collecting sinuses converge on large collecting vein (CV).
capillaries supplying the sinusoids often appeared quite long and sometimes arose from surprisingly larger arteries at very acute angles (Figs. 1.15, 1.16). Frequently several sinusoids were supplied by a single capillary and more than one capillary would supply a single sinusoid. The relatively long arteriolar capillaries supplying sinusoids in the marrow of adult dogs appeared to be extensions of much shorter arteriolar capillary side branches from arteries in the marrow of newborn puppies, as seen under the scanning electron microscope. (By removing the arterial wall, numerous endothelial nuclear impressions in the Microfil identiﬁes this vessel as an artery.) (Figs. 1.17, 1.18.)

At high ultrastructural magnification, the outer surfaces of sinusoids and collecting sinuses were wrinkled and featured migration pores for the transmural passage of marrow cells from the hematopoietic marrow compartment into the blood stream. Migration pores were crater-like in appearance, exhibiting a variable degree of elevation of the sinusoidal wall around each pore (Figs. 1.19, 1.20). Bi-concave erythrocytes and leukocytes were randomly ﬁxed to the sinusoidal wall. Migration pores beneath the attached marrow blood cells were visible in various stages of development. A large surface area of individual marrow blood cells appeared to make initial contact with, and become ﬁxed to the sinusoidal wall. As cavitation of a migration pore beneath an attached cell became greater, the attached cell apparently began to separate from the sinusoidal wall. Concurrently, the sinusoidal wall appeared to be forming a smooth elevation around the periphery of the developing migration pore. When a single stalk was all
Figure 1.15

Arterial vessels of the distal diaphyseal marrow; adult dog.
Long side branches of a large medullary artery (DMA) continuing to divide into narrow arteriolar capillaries to supply well-defined sinusoids.

Figure 1.16

Arterial supply to the sinusoids (VS) through very narrow capillaries (cap); adult dog. Ar = arteriole.
Figure 1.17

SEM of bone marrow; newborn puppy.
Large artery (AR) lying adjacent to trabecular bone (and near a collecting vein, CV) and giving off acute, narrow arterioles (ar) to supply sinusoids (VS). CS = collecting sinus

Figure 1.18

SEM of bone marrow; newborn puppy.
Endothelial nuclear protrusions into the lumen of the artery have created impressions in the Microfil® material. VS = sinusoid, ar = arteriole
Figure 1.19

SEM of a branched collecting sinus (CS) within marrow tissue; newborn puppy.

Figure 1.20

SEM of migration pores (mp) within the walls of a collecting sinus; newborn puppy.
that remained of the attachment between the marrow blood cell and the elevated rim of the migration pore, the marrow blood cell began its transmural migration. Erythrocytes entering migration pores became slightly wedge-shaped by developing an elongation at their leading edge (Figs. 1.21., 1.22).

In addition to the arterial capillary-venous sinusoid communication found throughout the entire marrow cavity (but more heavily concentrated in the hematopoietic marrow of the metaphyses and around the endosteal surfaces), a second type of arterial venous communication was present. Patches of anastomotic capillary-venule beds were also identified throughout the marrow cavity of adult dogs, and were better developed in the mid-diaphyseal zone of fatty marrow. Very few capillary-venule beds were found in the puppy femur specimens because essentially all of the marrow cavity was filled with hematopoietic marrow, i.e., there were no zones of fatty marrow. The capillary-venule beds were composed of irregular hexagonal units that were supplied by delicate capillaries arising from the terminal branches of medullary arterioles. Venules draining the capillary-venule beds emptied into larger collecting veins and several collecting veins joined to empty into the central medullary vein (Figs. 1.23, 1.24). (Note that the term "collecting veins" is used instead of "collecting sinuses." The venous structures draining the capillary-venule beds were designated as "collecting veins" because they lacked the ultrastructural features of collecting sinuses and sinusoids.) Several small patches of capillary-venule beds were found between large clumps of hematopoietic marrow in the newborn puppy specimens.
Figure 1.21

SEM of a sinusoidal wall; newborn puppy. Erythrocytes (RBC) adhering to sinusoidal walls and passing through migration pores (mp).

Figure 1.22

SEM of the transmural migration of marrow erythrocytes (specimen has been rotated). Newborn puppy.
Figure 1.23

Vascular pattern of fatty marrow, mid-diaphysis; adult dog. Numerous venules drain patchy capillary beds. C = cortex

Figure 1.24

Capillary beds (cb) of fatty marrow; adult dog. Several collecting veins (CV) receive venules (ven) from capillary beds.
Ultrastructural examination further demonstrated the three-dimensional anastomotic arrangement of the vascular beds and the larger collecting veins. Venules of the capillary-venule beds lacked migration pores and exhibited a relatively smooth outer surface as compared to the sinusoids and collecting sinuses (Figs. 1.25, 1.26).

Structural interrelationships of the venous microcirculation within the marrow cavity were demonstrated by the retrograde venous injection route. Many sinusoids in the diaphyseal marrow cavity drained directly into the central medullary vein through thin, straight draining venules rather than the typically dilated, irregular metaphyseal collecting sinuses. Single sinusoids or small groups of sinusoids were drained by individual (often very long) drainage venules (Fig. 1.27). Nearby sinusoids were joined together by intersinusoidal communication vessels that were very similar in appearance to the sinusoid-central medullary vein drainage venules. These thin intersinusoidal communications appeared to frequently join sinusoids located around the periphery of the marrow cavity (endosteal surface) (Fig. 1.28). By electron microscopy, the marrow of newborn puppies displayed long and short intersinusoidal communicating venules passing between developing sinusoids (Figs. 1.29, 1.30). Communicating venules joined large dilated sinusoids with stringy masses of tortuous venules which drained patchy capillary-venule beds (Figs. 1.31). Occasionally, adjacent capillary-venule beds were also joined by individual communicating venules (Figs. 1.32, 1.33).

As the newborn puppy's microcirculation matured, significant changes occurred in the vasculature of the proximal and distal
Figure 1.25

SEM of a small capillary-venule bed in the marrow cavity; newborn puppy. CV = collecting vein.

Figure 1.26

SEM of anastomotic, three-dimensional venule pattern; newborn puppy. ven = venule.
Figure 1.27

Sinusoids (VS) draining directly into the central medullary vein (CMV) via long and short drainage venules; two-week-old puppy. C = cortex.

Figure 1.28

Transcortical view of intersinusoidal communicating venules (com) between several sinusoids (VS). Two-week-old puppy.
Figure 1.29

SEM of trabecular bone; newborn puppy. A long, thin intersinusoideal communicating venule (com) joining two sinusoids (VS). Developing sinusoids draining into a collecting sinus (CS).

Figure 1.30

SEM of collecting sinus (CS) receiving a branched sinusoid (VS); newborn puppy. TB = trabecular bone.
Figure 1.31

Venous structures within the marrow cavity; adult dog. Several capillary-venule beds (cvb) entering collecting veins (CV) beneath the cortex at the level of the nutrient canal. VS = sinusoid, C = cortex.
Figure 1.32

A large tuft of venules joined to a smaller venule tuft by a single communicating venule (com); adult dog. cvb = capillary-venule bed, CV = collecting vein

Figure 1.33

A single dimpled sinusoid (VS) with venules leading from the sinusoid to the central medullary vein (CMV) and a capillary-venule bed (cvb); adult dog.
epiphyses. At birth, both epiphyses were composed entirely of hyaline cartilage. Vascular loops consisting of an arteriole, a venule, and a small capillary anastomosis, entered the cartilaginous femoral head and greater trochanter from the peripheral margins of epiphyseal cartilage. The epiphyseal vessels of the femoral head were continuations of subsynovial arteries and veins which traveled along the surface of the developing femoral neck (Figs. 1.34, 1.35). Epiphyseal vessels which entered the cartilaginous distal femoral epiphysis were continuations of perichondral arteries and veins. The perichondral vessels passed over the lateral and medial surfaces of the femoral condyle and penetrated the hyaline cartilage at the trochlear ridge (Fig. 1.36). Vascular loops within the proximal and distal epiphyses were randomly distributed throughout the hyaline cartilage, and gave off a few coarse branches. At times, single vessels extended from the ends of the capillary loops and crossed the immature physis to anastomose with sinusoids within the marrow of the metaphysis (Figs. 1.37, 1.38). A scanning electron micrograph of the proximal femur of the newborn puppy demonstrated a large vessel traversing the physis, thereby establishing vascular communication between the developing femoral neck and the cartilaginous femoral head (Fig. 1.39). Within two weeks, branches from the randomly distributed epiphyseal vessels had begun to concentrate centrally to supply the rapidly establishing secondary centers of ossification. A majority of the blood volume of the secondary ossification center was contained within venous structures--venules, veins and a few early sinusoids. Venous drainage of the femoral head was facilitated by a significant increase in the
Figure 1.34

Craniolateral surface, left femoral head and neck; newborn puppy. Vessels on the surface of the femoral neck penetrating the cartilaginous femoral head to form random epiphyseal vascular loops (EP).

Figure 1.35

Branching vascular loops (EP) within the cartilaginous femoral head; newborn puppy. Synovial vascular network (SV) on the surface of the femoral neck.
Figure 1.36

Epiphyseal vascular loops (EP) of the cartilaginous femoral condyle, cranial surface; newborn puppy. Perichondrial vessels (PC) from the lateral and medial surfaces at the trochlear margin penetrating the distal epiphyseal cartilage.
Figure 1.37

Lateral (cut) surface, distal femoral epiphysis; newborn puppy. Random distribution of vascular loops within the cartilaginous femoral head.

Figure 1.38

Lateral (cut) surface, distal femoral physis; newborn puppy. Vessels from the ends of the epiphyseal vascular loops (EP) traversing the physis and communicating with distal metaphysial sinusoids (VS).
Figure 1.39

SEM of the proximal physis; new-born puppy. A large vein coursing from the proximal metaphysis, across the physis (PH) and through the proximal epiphysis (EP).
Figure 1.40

Cranial surface, right femoral head and neck; two-week-old puppy. Vascular supply to, and venous drainage from, the secondary center of ossification (SC). ac = articular cartilage.

Figure 1.41

Subsynovial veins (DV) on the cranial surface of the femoral neck descending from the secondary center of ossification (SC); two-week-old puppy.
number and diameter of subsynovial veins descending the femoral neck (Figs. 1.40, 1.41). As the puppies grew older, the secondary ossification centers enlarged. More and more of the random vascular loops within the remaining epiphyseal cartilage were incorporated into the microvasculature of the expanding epiphyseal marrow cavities. At ten weeks of age, proximal and distal physes were clearly defined and no vascular structures were seen crossing them. Small arterioles and capillaries advanced to the faces of the physes, only to turn back by joining sinusoids (usually) which drained away from the physes into metaphyseal or epiphyseal collecting sinuses. Vascular loops within the narrowing band of hyaline (articular) cartilage were still present in the ten-week-old specimens. Openings in the plate of subchondral bone allowed microcirculation to occur between the articular cartilage and the epiphyseal marrow cavity (Figs. 1.42, 1.43). No vessels remained in the relatively thin rim of articular cartilage in the femoral head and condyle of the adult dogs. It was difficult to identify the location of the former proximal physis due to the continuity of vascular structures between the femoral head and neck. In general, the marrow cavity of the femoral head had an even distribution of hematopoietic and fatty marrow vascular arrangements. Continuity of the microcirculation was best seen in the subchondral bone where arterial capillaries drained into sinusoids or venules (Figs. 1.44). At no time during the development of the femur was the epiphyseal vascular supply augmented by penetration of the articular cartilage from vessels within the ligament to the head of the femur. On the contrary, all of the numerous arterial vessels in the ligament formed blind ending loops with venous structures at the fovea of the femoral head (Fig. 1.45).
Figure 1.42

Lateral (cut) surface of distal femur; ten-week-old puppy. Developing secondary ossification center (SC) incorporating more epiphyseal cartilage and giving better definition to the physis (PH) and articular cartilage.

Figure 1.43

Vessels of the secondary ossification center; ten-week-old puppy. Residual vascular loops within the epiphyseal cartilage (EC) are continuous with the vessels of the expanding secondary ossification center across a plate of subchondral bone (SB). EA = distal epiphyseal nutrient artery, EV = distal epiphyseal emissary vein.
Figure 1.44

Caudal articular surface, femoral head; adult dog. Subchondral vascular continuity between arterial capillaries (cap), sinusoids (VS), and collecting sinuses (CS).

Figure 1.45

Vascular loops within the ligament to the head of the femur (LIG); adult dog. Ligament vessels are blocked from epiphyseal vessels (EP) by a plate of articular cartilage (ac).
Figure 1.46

Drawing of the arterial and venous marrow microcirculation; newborn puppy.

A = cranial proximal metaphyseal emissary vein
B = diaphyseal nutrient artery
C = central medullary vein
D = collecting sinus
E = distal metaphyseal emissary vein
F = arteriolar capillaries
G = distal epiphyseal vascular loops
Figure 1.47

Drawing of microvascular relationships at the proximal and distal physes; ten-week-old puppy.

Proximal femur:

A = vascular loops in the remaining epiphyseal cartilage

B = sinusoids and collecting sinuses in the secondary ossification center

C = superficial periosteum, reflected

D = cranial proximal metaphyseal emissary vein

E = diaphyseal nutrient artery

Distal femur:

A = central medullary vein

B = distal metaphyseal emissary veins

C = distal epiphyseal emissary vein

D = distal physis
DISCUSSION

Terminology. Different investigators have used various terms when referring to the vascular structures within the medullary cavity. This author chose to use descriptive terms which identified the type of vessel (arterial, venous), suggested its approximate size and character, and expressed its general location relative to the ends or shaft of a long bone.

The term "nutrient artery" commonly refers to the principal artery entering the medullary cavity. All arteries that pass through nutrient foramina are "nutrient" vessels, i.e., they nourish osseous and marrow tissues. In an attempt to be more specific, arterial vessels entering the medullary cavity at different levels were referred to as "epiphyseal," "metaphyseal," or "diaphyseal nutrient arteries." The common term "nutrient vein" is contradictory.6 "Epiphyseal," "metaphyseal," or "diaphyseal emissary veins" (referring to veins draining the medullary cavity by passing directly through the cortex) was preferred.

Rather than the usual single diaphyseal nutrient artery of the femur in the dog,7 in this investigation 4 of 24 puppies demonstrated dual diaphyseal nutrient arteries of nearly equal size located proximally and distally on the caudal aspect of the femoral diaphysis. Also, all long bones have an epiphysis, a physis (in growing bones) and a metaphysis at their proximal and distal ends. Therefore, the use of "proximal" and "distal" to further describe the location of vessels in these areas was considered appropriate.

Very narrow branches from medullary arterioles which supplied sinusoids have been previously referred to as "thin-walled arteries."8,9
As shown with transmission electron microscopy, the walls of "thin-walled arteries" are usually only two cell layers thick, an endothelial lining and a single layer of smooth muscle cells. In this investigation these vessels were considered to be arteriolar capillaries, because the tunics (intima, media, adventitia) of typical arteries are not present. Vessels of similar size and configuration to capillaries of soft tissues elsewhere were characteristically seen in fatty marrow areas and as side branches from radiating intracortical arterioles (see Chapter II, Results).

Narrow, straight vessels joining adjacent sinusoids or individual sinusoids to the central medullary vein were interpreted as small venous structures. Previous investigators have referred to the intersinusoidal vascular communications as "capillaries"—an unlikely situation, since the vessels are interposed between two venous structures. This author considered intersinusoidal "communicating venules" a more accurate designation. Vessels of similar morphology which drained blood from individual sinusoids directly into the central medullary venous system were called "drainage venules." The term "collecting sinuses" was reserved for irregular vascular structures which drained sinusoids and exhibited migration pores in their wrinkled, thin walls. Collecting sinuses had some features in common with sinusoids, but were not sufficiently dilated nor blind ending to justify the term "collecting sinusoids." "Collecting veins" differed from collecting sinuses by demonstrating no migration pores in their smoother, less irregular vascular walls. Blood from venule beds (fatty marrow) drained into collecting veins. Because transmural migration
also apparently does not occur in the principal venous structure within the marrow cavity, the use of "central medullary vein" rather than "central medullary sinus" or "central medullary sinusoid" was preferred.

**Vascular Structure and Function.** Most investigators now believe that tissues within the medullary cavity are exclusively supplied by epiphyseal, metaphyseal, and (particularly) diaphyseal nutrient arteries.\(^{13,14}\) Others have reported that marrow nutrition is augmented to a variable degree by periosteal vessels.\(^{9,15,16,17}\) Although vascular structures were shown to join the periosteal and marrow vascular systems (see Chapters II and III), evidence for centripetal transcortical blood flow from the periosteum to marrow tissue was not found. In newborn puppies only, arterial supply to the medullary cavity was minimally supplemented by perichondrial vessels at the synovial margins of the joints. The vessels penetrated proximal and distal epiphyseal cartilages as random vascular loops. Small capillaries from the ends of the vascular loops crossed the physis and anastomosed with metaphyseal sinusoids. The transphyseal vascular connections were transient, and could not be demonstrated in specimens two weeks of age and older. While apparently not a common clinical problem in newborn puppies, transphyseal vascular anastomoses represent a potential route of bone marrow infection from an infectious synovitis, as seen in the septic arthritis-osteomyelitis syndrome of neonate foals and children.\(^{18,19}\)

Arteriolar capillaries leading to sinusoids were unique in their narrowness (as compared to their parent arteries), acute angle of origin, and unusually long length. The abrupt decrease in arteriolar
capillary wall thickness has suggested significant vessel distensibility during systole, causing a pulsatile increase and decrease in adjacent marrow tissue fluid pressure. The alternations in marrow tissue fluid pressure are thought to aid in the transmural migration of marrow blood cells. Another possible function of the arteriolar capillaries is suggested by their narrowness, long length, and acute angle of origin. The hematocrit of intrasinusoidal blood is apparently lower than the hematocrit of extraosseous blood. A hypothetical explanation for this discrepancy involves the concept of "plasma skimming" by the arteriolar capillaries. Plasma is "skimmed off" of blood flowing through the large diameter parent arteries and directed through the arteriolar capillaries into the sinusoids. The right-angle origin of arteriolar capillaries may increase the efficiency of the skimming process. During a strong erythropoietic or granulopoietic stimulus, "showers" of cells may be released into the hypocellular intrasinusoidal blood, causing an increase in the hematocrit of the blood leaving the sinusoids.

Two investigators have described "occasional" arterio-venous shunts from the arteriolar capillaries to post-sinusoidal vessels. The shunts apparently by-pass sinusoids and capillary venule beds. Morphological evidence for arteriovenous shunting was not found in this investigation. The significance of arteriovenous shunts within the marrow—if they exist—remains speculative at this time.

Sinusoids are extremely thin-walled (one cell layer thick), large diameter vessels that are largely responsible for the preponderance of venous blood within the hematopoietic marrow tissue.
cross-sectional ratio of arterial:venous structures has been estimated
to be 1:30 in the long bones of guinea pigs, but the ratio of arte-
riolar:sinusoidal blood flow is 20:1. Undoubtedly, the site of entry
for fat and marrow emboli after a long bone fracture, or total hip re-
placement, is through tears in the thin-walled, large diameter sinus-
oids. The radiographic technique of intraosseous venography
developed by Steinback and others is possible because the major
portion of intramedullary blood volume is contained within venous
structures. Radiographic contrast material injected through the cortex
into hematopoietic marrow areas results in filling of the sinusoids
and, eventually, the remainder of the marrow venous system. Intersi-
nusoidal communicating venules probably help distribute the contrast
material throughout the medullary cavity.

Sinusoids appear to be vascular extensions of collecting sinuses
because both have a very similar wall structure. Both types of vessels
have simple endothelial linings which are capable of forming transient
migration pores for transmural cellular migration. The endo-
thelial cells of sinusoids and collecting sinuses are also capable of
phagocytosis.

Marrow collecting veins and the central medullary vein exhibited a
more structured vascular wall. These veins were still quite thin-
walled and distensible when compared to their arterial counterparts.11
Because marrow veins are readily distensible, changes in systemic ven-
ous pressure are rapidly transmitted to the marrow tissue. Marrow
venous pressure is therefore essentially the same as marrow tissue
fluid pressure.
Vascular Structure and Marrow Blood Flow. Investigating the dynamics of marrow blood flow by in vivo methods is technically difficult. Branemark and Kinoshita were able to observe blood flowing through the marrow sinusoids in the long bones of rabbits. Sinusoidal blood flow was characteristically irregular, with alternating periods of sluggish flow and stagnation. Sinusoids rhythmically dilate over a period of 1-2 minutes, followed by a slightly faster emptying period. Flow rates through the sinusoids were 0-0.2 mm/sec, as compared to arteriolar flow of 1.0-1.5 mm/sec and capillary flow of 0.5 mm/sec. With an overrepresentation of sinusoids in the metaphyseal regions of a long bone, a predilection for (hematogenous, septic) osteomyelitis and metastatic bone tumors at these sites is predictable. Bacteria or neoplastic cells could better establish themselves in areas of stagnant blood flow. Contact time would be prolonged and the circulating body defense mechanisms (antibodies, complement system factors, leukocytes, macrophages) would be decreased in these areas.

As described in Chapter I, Results, the basic venous marrow drainage system from emissary veins is well established at birth (Fig. 1.46). The volume of blood that can be drained by any individual emissary vein is severely limited by the incapacity of the vein to appreciably dilate within the rigid confines of the emissary canal. Marrow veins do not possess valves, so that blood entering the central medullary vein may be shunted proximally or distally, depending on regional pressure gradients. Muscular activity is suspected to increase extra-osseous vascular resistance, particularly along the diaphysis. If vascular resistance is increased along the shaft of a long bone,
increased venous outflow from metaphyseal emissary veins--within limits--could prevent vascular engorgement of the marrow microcirculation. In the adult, venous blood in the central medullary vein may also be drained by epiphyseal emissary veins due to the vascular continuity between the metaphyseal and epiphyseal marrow. From less than 2 weeks of age until skeletal maturity (during active endochondral bone formation) arterial and venous systems of the epiphysis and metaphysis are segregated above and below the physis (Fig. 1.47).

Marrow blood flow varies greatly in different locations within the medullary cavity. The variation is grossly related to the fatty or hematopoietic character of the marrow tissue. Blood flow is much greater in hematopoietic marrow than in fatty marrow. Since the medullary cavity of puppies is composed almost entirely of hematopoietic marrow, and hematopoietic marrow progressively changes to fatty marrow during the aging process, marrow blood flow is also an inverse function of age. Neural, humoral and metabolic factors also have an effect on regional blood flow. Vascular resistance has been shown to increase with exercise, hemorrhage, norepinephrine and sympathetic stimulation. Increased marrow blood flow may occur with increased vascular resistance when the limits of venous drainage from other emissary veins have been exceeded. Recent exercise experiments in conscious dogs have shown a 65% increase in marrow blood flow only after extended physical exercise. The marrow hyperemia persisted for one hour after exercised had ceased. Gross showed a similar slow response with prolonged exercise and unaltered perfusion rates during moderate exercise of short duration. These studies support the earlier belief
that metabolic factors causing an increase in pCO₂, and a decrease in pO₂ and pH are largely responsible for increased marrow blood flow.46,47

Blood flow in marrow has been difficult to accurately measure due to some of the conditions listed above. Different techniques of undoubtedly varying accuracies have been devised to investigate this subject.48 The most accurate technique to date appears to be the use of radio-labeled microspheres. In one study, blood flow was shown to be 19.6 ml/100 Gm/min in the femoral head, 50.3 ml/100 Gm/min in the femoral neck, and 29.0 ml/100 Gm/min in cancellous bone of the tibia.49

Transmural Migration. Early ultrastructural investigations of the sinusoidal wall suggested that the movement of blood cells from the extravascular marrow across the wall was facilitated by a separation of adjacent endothelial cells at contact points. The sinusoidal walls were described as "functionally incomplete" and in a state of "dynamic flux and readjustment."10 Weiss and DeBruyn have since shown that transmural migration is intracytoplasmic, i.e., through endothelial cells, rather than between them. Migration pores are ultrastructurally described as diaphragmed fenestrae which maintain the functional integrity of the sinusoidal wall during transmural cellular passage.42,50 With transmission electron microscopy, the sinusoidal wall has been shown to consist of a complete layer of lining (endothelial) cells, a discontinuous basal lamina, and a discontinuous layer of adventitial cells. No adventitial cells or basal lamina can be found at migration pore locations.34 The mechanism of migration pore formation is unknown.3 In this investigation, scanning electron micrographs of the sinusoid's marrow surface suggested a surface attraction and attachment
of mature marrow blood cells to the sinusoidal wall. Erythrocytes had already shed their nuclei before attaching to the sinusoidal wall, contrary to the observation of Weiss in which nuclear extrusion was said to occur as a result of erythrocytes squeezing through the very narrow migration pores. Subsequently, the concurrent formation of a migration pore beneath an attached erythrocyte and the sequential detachment of the erythrocyte appeared to occur. If migration pores do form in response to the attachment of mature marrow blood cells, empty migration pores would represent recent transmural cellular migrations or pores which have lost their marrow blood cells during tissue processing.

Cells that pass from hematopoietic marrow into the vascular compartment are described as "myelofugal." There is some evidence to suggest that a few intravascular lymphocytes attach to the luminal surface of the sinusoidal wall and pass through the wall into the extravascular marrow ("myelopetal" passage). Because these observations were made from static figures, the actual direction of movement of the "myelopetal" cells remains questionable.

The sinusoidal wall is apparently freely permeable in either direction to large plasma protein molecules and particulate matter. Since extravascular protein can be easily removed at the sinusoid level by the venous microcirculation, the absence of lymphatic vessels within bone marrow--while not conclusively proven--appears likely. Freely flowing marrow tissue fluid, termed "transparenchymal plasma flow" also decreases the need for a marrow lymphatic system and may aid in the transparenchymal migration of nonmotile marrow blood cells.
CHAPTER II

MATURATION OF THE MICROCIRCULATION IN CORTICAL BONE
ABSTRACT

Arterioles arising from medullary arteries traveled directly to the endosteal cortical surface and entered (individually or in multiples) penetrating canals. The cortical arterioles assumed a generalized radial course toward the periosteal surface, where an anastomosis with the deep periosteal plexus occurred. Venules arising from endosteal sinusoids of the marrow cavity also entered the endosteal cortical surface and followed a similar pattern through the cortex to the deep periosteum.

Within the cortex, arterioles gave off smaller arterioles and capillaries to supply longitudinally oriented osteons. Resorption cavities, developing, and mature osteons were identified by their intracortical vascular patterns. (Wavy transcortical vascular patterns of newborn puppy specimens reflected the irregular organization of woven bone. Longitudinal branches within the cortex did not arise until secondary bone formation began.) Arterioles supplying resorption cavities doubled back within the cavities as venules at the head of the "cutter cone".

The deep periosteal plexus received blood from radial cortical arterioles and venules, and emptied into veins of the superficial periosteum.
INTRODUCTION

For many years, most investigators have agreed that arterial supply to cortical bone is mostly or entirely supplied by arterioles within the marrow cavity.\(^1-5\) A small portion of the outer cortex may be supplied by periosteal arterioles, particularly in the areas of heavy fascial attachment. The direction of arterial flow is centrifugal, from the endosteal surface to the periosteum.\(^6-8\) The presence and source of venous structures within the cortex, the centrifugal or centripetal direction of venous blood flow, and the reversal of flow under certain circumstances are still controversial issues.\(^9-13\) These questions persist because of the technical difficulties encountered in studying the microcirculation of cortical bone, and the debatable interpretation of static vascular patterns relative to actual blood flow dynamics. Intracortical vessels are very small, and are confined to tiny vascular channels encased in a rigid, opaque matrix. To be visualized, the incarcerated vessels must be adequately filled with an identifiable injection material, and the surrounding opaque, mineralized tissue removed or rendered transparent by radiography or clearing techniques.

Adequate circulation through bone is necessary for osteogenesis, bone growth, maintenance and the satisfactory repair of fractures and other injuries to bone.\(^14\) The performance of some of these functions has been directly related to local metabolic factors: pH, pO\(_2\), and pCO\(_2\).\(^14-17\) Consequently, the arterial or venous nature of the blood and its direction of flow through the cortex becomes very relevant, both physiologically and clinically. Trueta has stated, "I firmly
believed and still do, that the vessels and the blood they carry are the main factors responsible for the normality as well as for the many pathological conditions affecting bone."18
MATERIALS AND METHODS

Twelve newborn puppies, 6 two-week-old puppies, 6 ten-week-old puppies, and 17 adult dogs were heparinized, anesthetized, catheterized, euthanized, and perfused with orange or white Microfil®. (For details of the procedures, see Chapter I, Materials and Methods.)

Retrograde venous perfusions through the proximal portion of the femoral vein (adult dogs) or external iliac vein (puppies) were intended to identify venous structures in the cortex arising from the marrow cavity. Venous communication between the outer cortex and periosteum, if present, would also be filled by the retrograde flow of Microfil®. Orange pigmented Microfil® was used for the venous studies.

Antegrade arterial injections were made through the external iliac artery (puppies) or medial circumflex femoral artery (adult dogs) using white pigmented Microfil®. Based on a previous study,12 filling of arterial structures within the cortex from medullary arterioles was expected to occur before the marrow venous system had filled.

After injections were completed, only partial decalcification of some of the specimens was permitted. Since the entire thickness of bone was not cleared, the superimposition of vessels out of the plane of focus was minimized. Certain aspects of the cortical microcirculation in the partially cleared cortex were more easily depicted photographically by this method.
RESULTS

Vascular supply to cortical bone essentially arose from arterial structures within the marrow cavity which traversed the cortex and eventually communicated with a periosteal vascular system. Certain venous structures within the marrow cavity likewise were continuous with the periosteal vascular system. Microvascular patterns within the cortex changed from the newborn puppy to the adult dog. The vascular changes were a reflection of the progressive conversion of weak, woven (primary) cortical bone of the newborn puppies' femurs, to much stronger secondary bone, characterized by longitudinally oriented systems of osteons and well represented in the femurs of adult dogs.

In the adult dog, some arterioles arising from arteries within the medullary cavity entered penetrating (Volkmann) canals at the endosteal surface of the cortex. (As previously described in Chapter I, Results, other arterioles arose from the medullary arteries and, by entering sinusoids and capillary beds, were responsible for arterial supply to the marrow microcirculation.) On cross-sectional examination, the cortical arterioles were somewhat radially oriented, particularly in outer and inner cortical zones which corresponded to the outer and inner circumferential lamellae. Within the middle zone of cortex, the radial arterioles gave off smaller side branches (smaller arterioles and capillaries) which were oriented longitudinally within the central (haversian) canals of individual osteons. Because of the longitudinal vascular branching in the middle cortical zone, an abrupt demarcation between osteonal bone and circumferential lamellar bone was easily demonstrated (Figs. 2.1, 2.2). Most of the medullary arterioles entered
penetrating canals on the endosteal cortical surface individually. Very frequently, however, multiple arteriolar branches from a small medullary artery would arise simultaneously near the endosteal surface and travel parallel with each other into the cortex through a single large endosteal foramen. The multiple arterioles would usually travel into the osteonal (middle) zone of the cortex before diverging into individual vascular channels (Fig. 2.3). At the endosteal surface, the multiple arterioles would occasionally become quite tortuous (glomerulus-like) and then straighten out again just before entering their common endosteal foramen (Fig. 2.4).

Venous structures within the cortex were best demonstrated in the newborn, two-week-old, and ten-week-old puppies by using only the retrograde venous injection route. Intracortical venules filled by retrograde flow from venous structures within the medullary cavity and the periosteal venous system. Sinusoids located near the endosteal surface gave rise to venules which also entered penetrating canals. (Venules that join endosteal sinusoids and vascular structures within the deep periosteal plexus have been termed "portal" vessels. The term is helpful in distinguishing transcortical venules arising from endosteal sinusoids from venules arising within the cortex which drain cortical capillaries and arterioles.) In the very young puppies, portal venules were comparatively large diameter vessels that gave off regular, very short, angular branches as they passed outward through the woven cortical bone. Outside the cortex the venules emptied into the periosteal venous system (Figs. 2.5, 2.6). In the adult dogs, endosteal sinusoids retained their transcortical venous communication with the periosteum.
Figure 2.1

Cross-section of mid-diaphysis; adult dog. Cortical vessels radiating outwardly from the endosteal surface to the periosteum.

Figure 2.2

Cross-section of cranial cortex, mid-diaphysis; adult dog. Demarcation of outer and inner circumferential lamellae from middle osteonal layer. C = cortex, M = marrow cavity.
Figure 2.3

Inner cortex and outer marrow cavity (cut surface); adult dog. Multiple arterioles entering a single penetrating canal at the endosteal surface. C = cortex.

Figure 2.4

Inner cortex and outer marrow cavity (cut surface); adult dog. Tortuosity of arteriolar branches at the endosteal surface. C = cortex.
Figure 2.5

Venous structures within the diaphyseal cortex; ten-week-old puppy. Endosteal sinusoids (EVS) giving rise to portal venules which traverse the cortex to the deep periosteum. C = cortex.

Figure 2.6

Diaphyseal cortex (C), cut surface; ten-week-old puppy. Cortical venules joining the deep periosteal plexus (DPP). C = cortex.
However, due to secondary bone formation, bone growth, and cortical remodeling, portal venules became less distinctive in their morphology, exhibiting a more delicate and smoother branching pattern (Fig. 2.7). Therefore, when both arterial and venous vascular injections were performed, it was frequently difficult to differentiate intracortical arterioles and capillaries from venules. Single venules arising from sinusoids or individual marrow arterioles were traced into and through the cortex by adjusting the focus of the stereoscopic dissecting microscope. (Unfortunately, available photographic methods used in this investigation limited the depth of focus to a very narrow plane. Much of the three-dimensional quality of the vascular patterns and the course of individual vessels as seen through the stereomicroscope have been lost in the photographs [Fig. 2.8]). Medullary arterioles usually accompanied venules from endosteal sinusoids into endosteal foramina, but there appeared to be many more arterioles entering the cortex alone.

In the adult dogs, resorption cavities indicative of bone remodeling were identified by characteristic intracortical vascular patterns. Very large diameter, longitudinally oriented vascular channels were usually located in the middle (osteonal) cortical zone (Fig. 2.9). Vessels within the cortex entered or left the resorption cavity at different levels. Multiple vessels traveled within the resorption cavity to the "cutter cone" apex (Fig. 2.10). Arterioles at the head of the "cutter cone" turned back within the resorption cavity as venules. Other narrower longitudinal vascular channels containing fewer vessels were regarded as maturing osteons (Fig. 2.11). Individual capillaries occupied very small central canals within mature osteons.
Figure 2.7

Cortex and endosteum (cut surface); adult dog. Portal venules from endosteal sinusoids (EVS) giving off longitudinally oriented side branches as they travel outward through the cortex (C).

Figure 2.8

Cortex (C), endosteum, and outer medullary cavity; adult dog. Cortical arterioles and venules communicating between the deep periosteum (DP) and the marrow cavity.
Figure 2.9

Cortex (C), endosteum, and outer medullary cavity (cut surface); adult dog. Evidence of cortical remodeling by vessels within several resorption cavities (rc).
Figure 2.10

Cortex (cut surface); adult dog.
Tuft of vessels at the "cutter zone" head (cc) of a resorption cavity.

Figure 2.11

Cortex (cut surface); adult dog.
Arteriole (art) bifurcating at the apex of a resorption cavity and forming two returning venules (ven).
A deep periosteal plexus of vessels located in the inner (cellular) layer of the periosteum received the intracortical venules and terminal branches of the radial arterioles. In the very young puppies, the deep periosteal plexus was highly developed, demonstrating a longitudinally oriented, irregularly rectangular system of vessels. Nearly all of the cortical vessels weaving through vascular channels in the woven bone appeared to anastomose with the deep periosteal plexus at regular intervals (Figs. 2.12, 2.13). Older puppy specimens reflected a progressive decrease in the extent and complexity of the deep periosteal plexus (Fig. 2.14). In the adult dog, the deep periosteal plexus was irregularly represented over the surface of the femur. Some longitudinally oriented outer cortical vessels appeared to have been incorporated from the deep periosteal plexus into the cortex by appositional (periosteal) bone formation. The overlying superficial (fibrous) layer of periosteum contained considerably fewer, but larger, vessels which originated from or drained toward the linea aspera of the femur. Vessels in the superficial layer of periosteum were transversely oriented as compared to the longitudinal orientation of the underlying deep periosteal vessels. Vascular connections between the deep periosteal plexus and the superficial vessels occurred periodically. In the superficial periosteal layer, two veins often traveled parallel to a centrally located artery. In the superficial periosteal veins, blood flow was apparently in a cranial to caudal direction. Systemic veins, located parallel to the linea aspera and within the femoral attachment of the adductor muscles, received blood from the superficial periosteal veins (Fig. 2.15).
Figure 2.12

Lateral (cut) surface, right femoral diaphysis; newborn puppy. Cortical vessels emanating from mid-diaphyseal focus. M = marrow cavity.

Figure 2.13

Periosteal surface (above) and cut cortical surface (below), mid-diaphysis; newborn puppy. Cortical vessels draining into the deep periosteal plexus (DPP). C = cortex.
Figure 2.14

Periosteal surface, mid-diaphysis; ten-week-old puppy. Superficial periosteal vessels (SP), deep periosteal plexus (DPP), and endosteal vessels.

Figure 2.15

Periosteal surface, mid-diaphysis; adult dog. Superficial periosteal vessels originating from the linea aspera. AM = adductor muscle.
DISCUSSION

From birth to skeletal maturity, the femur specimens showed a 4.6 fold increase in mid-diaphyseal diameter, and a 7.5 fold increase in length. The body weights of the adult dogs were 40 to 50 times greater than the body weights of the newborn puppies. The disproportional increase of body weight to femur diameter and length placed additional mechanical stress on the femurs. Bone failure under this increased load was prevented by the replacement of woven (primary) bone by the osteonal "pillars" in lamellar (secondary) bone. Wavy vascular patterns indicated the haphazard arrangement of woven bone spicules in the newborn puppies' femurs. Even in the newborn puppies, vascular patterns suggested that blood flowed through the cortical arterioles and venules from the endosteal surface to the periosteum. Vascular anastomoses between the numerous cortical vessels and an extensive deep periosteal plexus were quite regular and frequent (Fig. 2.16). Many of the early vascular pathways through the woven bone were apparently retained as radiating arterioles in secondary bone. During secondary bone formation, the pre-existing radiating arterioles and venules within the woven cortical bone gave rise to small capillaries and venules which supplied developing osteons. The relative concentration of large radiating arterioles and venules decreased as the volume of secondary cortical bone increased. The decrease in concentration of radiating intracortical vessels was accompanied by a relative decrease in the number of cortical-periosteal vascular anastomoses. Based on the observed differences in concentration of cortical vessels and the number of venous connections with the deep periosteal plexus, very
Figure 2.16

Drawing of the arterial and venous microcirculation in woven cortical bone; newborn puppy.

A = superficial periosteal vessels
B = deep periosteal plexus
C = cortical venules arising from endosteal sinusoids
D = cortical arterioles, from medullary arterioles
E = distal epiphyseal cartilage
young puppies would be expected to have much greater cortical blood flow rates than adult dogs. Indeed, measurements of cortical blood flow in immature and adult dogs have been found to be 7.0 ml/100 Gm/min and 2.5 ml/100 Gm/min, respectively.20 (Others have provided evidence for the greater concentration of vascular structures in primary bone than in secondary bone, and a shorter maximum distance between osteocytes and vessels in primary bone than in secondary bone.21,22) One study, using the antipyrine washout technique, suggested that 70 per cent of nutrient arterial blood passed into the cortex and 30 per cent into the marrow.23

In general, radially oriented cortical arterioles may be regarded as "conduit" vessels, and longitudinal vessels within central canals of osteons may be regarded as "nourishing" vessels.11 From transmission electron microscopic studies, vessels within central canals ultrastructurally resemble capillaries and are usually singular. (Interestingly, unmyelinated nerve fibers with a possible vasomotor function are present in the osteons of adult dogs but absent in the osteons of young puppies. Lymphatic vessels are not present in the osteons of adult dogs or puppies.24) When two vessels are present within the same central canal, one vessel is significantly larger and thinner walled than the other.25 Branemark observed blood flowing in opposite directions when two vessels were contained within the same central canal.26 The developing osteons containing an arteriolar capillary and returning venules identified in this investigation offered compatible anatomic evidence of bi-directional flow within vessels of individual osteons.
Osteons are not truly longitudinal in their orientation, but instead, spiral slightly as they pass down the shaft of the bone. Within the left femur, osteons spiral distally in a clockwise direction; in the right femur the spiral is counterclockwise. Spiral resorption cavities may represent a structural weakness in cortical bone, i.e., a point of failure when torsional forces are applied to the femur. Osteons often end blindly and exhibit branching patterns to form anastomosing systems. The osteonal branches appear to form from vascular buds which arise from central canal vessels during the course of bone remodeling. Vascular changes occur during the formation and development of new osteons. Multiple vessels within a resorption cavity "drop out" as successive lamellae are laid down along the walls of the central canal. In this investigation, several vessels were seen in resorption cavities, two or three vessels in maturing osteons, and single capillaries in mature osteons. (By morphometric analysis, the surface area of vessels within the central canal is also directly related to the rate of osteonal bone deposition and the size of osteoblasts.) With the successive deposition of lamellae within developing osteons and the decrease in number and size of vessels within the central canal, the cellular functions of peripheral osteocytes rely more heavily on diffusion of nutrients and waste products through the tissue fluid of the canalicular system. Some investigators have suggested that the progressive decrease in osteonal vascularity creates a less favorable local environment in peripheral lacunae, causing metabolic aberrations or cell death of their osteocytes. The micronecrotic area at the periphery of an old osteon
may initiate the bone remodeling process by stimulating vascular ingrowth and necrotic bone resorption as a new resorption cavity is formed.15

Capillaries within the central canals are surrounded by a continuous basal lamina. The endothelial cells comprising the capillary wall are fenestrated.24 The basal lamina apparently functions as a filtration structure during exchange between canicular tissue fluid and plasma. By isotope tracer and morphometric techniques in the adult dog, the central canals were shown to occupy 1.3 to 1.5% of cortical bone by volume. The total cellular volume of cortical bone (lacunar volume plus canicular volume) was 4.2%.28 (Baud and Vose have suggested a microcanalicular system which increases the canicular system volume by 100%, making the total cellular volume of cortical bone approximately 7%.29,30) In one investigation, blood flow through cortical bone in the adult dog's femur was 3.7 ml/100 Gm/min, as compared to 19.6 ml/100 Gm/min in the femoral head, and 50.3 ml/100 Gm/min in the femoral neck.31

Arterial blood flows through the cortex from the endosteam to the periosteum under the driving pressure in the medullary arterioles. Vascular patterns in this investigation and the studies of others 12,19 suggest that blood flow through venules arising from endosteal sinusoids and joining periosteal venules is also in the centrifugal direction under normal resting conditions. Most of the pulsatile driving force in marrow arterioles is probably dissipated by the distension of thin-walled arteriolar capillaries supplying endosteal sinusoids, and distension of the sinusoids themselves.6,32 Therefore,
a factor largely responsible for the direction and magnitude of venous flow through the cortex is probably the venous pressure difference between the endosteal sinusoids and the extraosseous periosteal veins. Under normal resting conditions, marrow venous pressure is two to three times greater than extraosseous venous pressure. The difference in pressures creates a centrifugal venous pressure gradient.

All marrow, cortical, and deep periosteal venous structures are valveless. The direction of venous blood flow through the cortex could easily be reversed (as Brookes, Rhinelander, and Weiland have suggested) if marrow venous pressure fell below periosteal venous pressure, or periosteal venous pressure became greater than marrow venous pressure. Muscular activity is believed to increase periosteal venous pressure. At these times cortical vessels may become engorged as venous outflow is impeded (or reversed) at the cortical bone-periosteal interface. Bone blood flow studies done in conscious dogs at rest and during exercise revealed a 50% increase in perfusion of femoral cortical bone after prolonged exercise. The flow response was slow in developing and increased cortical blood flow persisted for one hour after physical exercise was terminated. Cortical blood flow did not decrease initially as one would expect with an immediate increase in periosteal venous pressure. The slow response and persistent hyperemia, however, did suggest a metabolically induced stimulus (an increase in PCO₂ or decrease in PO₂ or pH). Cortical venous engorgement from impaired periosteal venous drainage would permit such alterations in the microenvironment. Increased vascular resistance in cortical venules leaving the endosteal sinusoids would
also cause more blood to enter the marrow venous system. A rise in extraosseous vascular pressure in diaphyseal emissary veins would increase venous drainage from the ends of the marrow cavity through metaphyseal and epiphyseal emissary veins. The dynamic effect adjacent muscles appear to have on periosteal vascular structures and cortical blood flow emphasizes the importance of existing alternate routes of venous drainage from the medullary cavity in maintaining adequate circulation in long bones.
CHAPTER III

COMMUNICATION OF THE MARROW AND CORTICAL BONE MICROCIRCULATION
ABSTRACT

Arterial supply to the marrow and cortical microvascular systems arose from separate arteriolar branches of medullary arteries. Communication between the marrow and cortical venous microcirculation routinely occurred where portal venules arising from endosteal sinusoids traveled outward through the cortex to the periosteum. In general, both arterial and venous blood flow appeared to be in a centrifugal direction through the cortex.

Examples of bidirectional vascular patterns were identified. Some resorption cavities of the inner cortex received a medullary arteriole and were drained by a venule which traveled back into an endosteal sinusoid. Infrequently, an inner cortical arteriolar branch would re-enter the marrow cavity and supply an endosteal sinusoid. In rare areas venule patterns within the cortex suggested some centripetal cortical venous drainage directly into the central medullary vein. These areas were interpreted as intracortical capillary-venule anastomoses.
INTRODUCTION

Chapters I and II have described the general microvascular patterns of marrow and cortical bone as separate systems, for the sake of simplicity. Whereas most of the marrow is drained via the marrow venous system (central medullary vein and emissary veins), intercommunication with the cortical venous system is also present. Similarly, most of the cortical arterioles and capillaries drain into the deep periosteal plexus. Within the cortex, however, occasional communication with the marrow venous system also occur. Branemark has suggested that cortical bone and marrow should be regarded as an anatomic and functional unit.¹ The degree of communication between the marrow and cortical microcirculations would support or discount the validity of this concept.

The direction and characteristics of flood flow cannot be unequivocally reported from static vascular studies alone. Information from two additional types of studies—blood pressure measurements and vital microscopy of marrow and cortical blood flow—has been used in this investigation to interpret observed vascular patterns. Blood pressure is greatest in medullary arterioles and capillaries, less in marrow venous structures, and least in periosteal veins.²,³ Blood has been observed to flow through arterioles at 1.0-1.5 mm/sec, capillaries at 0.5 mm/sec, venules at 0.1-0.3 mm/sec, and sinusoids at 0-0.2 mm/sec.
Twelve newborn puppies, 6 two-week-old puppies, 6 ten-week-old puppies, and 17 adult dogs were heparinized, anesthetized, catheterized, euthanized and perfused with orange or white pigmented Microfil®. (For details of the procedures, see Chapter I, Materials and Methods.)

Demonstration of the communication of marrow and cortical microvascular structures was accomplished most consistently by prolonged antegrade arterial perfusion and gentle retrograde venous perfusion. Antegrade injection of Microfil® was continued until only pure Microfil® flowed from the venous catheter. The arterial catheter was plugged and a small amount of Microfil® (determined solely by the amount of vascular resistance encountered) was injected retrograde, through the venous catheter. Specimens were harvested, processed, examined, and photographed as previously described.
RESULTS

The marrow and cortical microcirculatory systems were found to be related to each other "in-parallel" rather than "in-series." Specific arterioles within the medullary cavity were responsible for providing vascular supply to cortical bone. Other arterioles gave off thin arteriolar capillary branches that emptied into sinusoids. Arterioles supplying sinusoids were not found to continue on to supply cortical bone, i.e., an "in-series" relationship. When an "in-series" arrangement appeared to exist, close inspection revealed the arteriole passing behind the sinusoid into the cortex. Vascular structures traveling from sinusoids in the periphery of the marrow cavity (endosteal sinusoids) into the cortex were frequently seen. These structures, however, had the morphological characteristics of venules, and differed significantly from the arteriolar capillaries that entered the sinusoids (Fig. 3.1). The venules were regarded as alternate sinusoidal drainage routes. Blood flowing from an endosteal sinusoid could enter the marrow venous drainage system (collecting sinuses, central medullary vein and diaphyseal, metaphyseal, or epiphyseal emissary veins) or leave the sinusoid via the intracortical venules (Fig. 3.2).

When located in the periphery of the medullary cavity, capillary-venule beds also exhibited an alternate route of venous drainage. In addition to the well-developed marrow venous drainage system of venules, collecting veins, and the central medullary vein, a few venules left the endosteal aspect of the capillary-venule bed and passed outwardly through the cortex to join the periosteal venous system
Figure 3.1

Endosteal surface, mid-diaphysis; adult dog. Small arteriolar capillary (cap) supplying endosteal sinusoids from which a portal venule (ven) arises. art = arteriole.

Figure 3.2

Endosteal surface, mid-diaphysis; adult dog. Collecting sinuses and portal venules draining endosteal sinusoids.
(Figs. 3.3, 3.4). Arterial supply to the capillary-venules beds appeared to be restricted to marrow capillaries; no cortical capillaries entering the capillary-venule beds were identified.

In general, arterial and venous structures within cortical bone indicated a centrifugal, unidirectional route of blood flow. Several less frequently observed vascular patterns suggested a possible bi-directional route of blood flow between marrow and cortical bone microcirculatory systems. Arterioles within the medullary cavity entered cortical bone and returned again to the medullary cavity to join the marrow venous system.

Both unidirectional and bi-directional microvascular systems were apparently involved in the bone remodeling process. Arising from arteries within the medullary cavity, cortical arterioles provided vascular supply to developing resorption cavities. At the "cutter cone" head, arterioles branched and doubled back within the cavity as venules. At times the venules traveled outwardly through the cortex to link the marrow and periosteal microvascular systems. Bone remodeling in the outer cortex usually demonstrated this unidirectional vascular pattern (Figs. 3.5, 3.6). The venules from resorption cavities of the middle and inner cortex drained back into collecting veins or sinusoids within the medullary cavity (a bi-directional pattern of flow). Fewer and smaller vessels were seen in the central canals of maturing osteons, indicating a "dropping out" of vascular structures as lamellae of osteonal bone filled in the resorption cavity. Nevertheless, the arteriovenous circuit from the medullary cavity, through cortical bone, and back into the medullary cavity was still
Figure 3.3

Transcortical venous drainage of a large capillary-venule bed at the periphery of the marrow cavity; adult dog.

Figure 3.4

Venules leaving the capillary-venule bed and entering the endosteal cortical surface; adult dog.
Figure 3.5

Cortex (C) and endosteum (cut surface); adult dog. A resorption cavity (rc) being supplied by a cortical arteriole (art) from the medullary cavity, and drained by a cortical venule (ven) to the periosteum.

Figure 3.6

Cortex (cut surface); adult dog. Medullary supply and periosteal drainage of a resorption cavity. art = cortical arteriole, ven = cortical venule.
identifiable in some maturing osteons (Fig. 3.7).

Another type of inner cortical vascular circuitry was also identified. An arteriole or capillary, upon entering the endosteal cortical surface, branched within the cortex. One intracortical capillary branch occasionally returned to the medullary cavity and entered an endosteal sinusoid, while other capillary branches passed outwardly through the cortex. The endosteal sinusoid apparently received vascular supply from a cortical capillary, rather than from the arteriolar capillaries of the marrow microcirculation (Fig. 3.8).

In a few limited areas, intracortical venules drained directly into the central medullary vein. These venules did not appear to contact periosteal vessels and were interpreted as representing an intracortical capillary-venule anastomosis. In this instance, venous cortical blood flow apparently avoided sinusoidal structures upon reentry into the medullary cavity (Fig. 3.9).

Interestingly, several isolated examples of sinusoids entrapped within cortical bone were observed. The intracortical sinusoids were interposed between two or more venules. Since intracortical sinusoids were only seen on rare occasions and only when selective venous injections were used, the possibility of arteriolar capillary supply to these sinusoids could not be determined (Fig. 3.10).
Figure 3.7

Cortex (C) and endosteum (cut surface); adult dog. A resorption cavity being supplied by a cortical arteriole (art) and drained by a venule of an endosteal sinusoid (ven).

Figure 3.8

Cortex (C) and endosteum (cut surface); adult dog. A cortical arteriole (art) entering the cortex, branching and returning to medullary cavity to supply an endosteal sinusoid (EVS).
Figure 3.9

Cortex (cut surface); adult dog.
Venules of an intracortical capillary-venule anastomosis draining directly into the central medullary vein.

Figure 3.10

Cortex (cut surface); adult dog.
Isolated sinusoids entrapped within cortical bone.
DISCUSSION

Information from many vascular studies has begun to slowly resolve the question of whether separate microcirculations for marrow and cortical bone exist, or if circulation to marrow and cortical bone involves one "interdependent and communicating" vascular system, as Doan had suggested in 1921. From this investigation, both concepts appear to be partially correct.

In general, the marrow and cortical microvascular systems are supplied by separate arterioles (marrow arterioles and cortical arterioles) arising from common parent vessels, the medullary arteries. In general, marrow and cortical bone are each drained by separate venous systems (marrow via the central medullary and emissary veins, and cortical bone via the periosteal veins) (Fig. 3.11). The "in-parallel," rather than "in-series" concept of microcirculation in marrow and cortical bone has been supported by other anatomic and physiologic studies. This investigation, however, has shown that the marrow and cortical microvascular systems are not mutually exclusive.

The existence of intracortical communication of marrow and cortical microvascular structures has been questioned by some investigators. Intracortical communications which did not appear to join the periosteal vascular system were infrequently observed in this investigation. Under the driving force of the cortical arterioles and capillaries, arterial blood would flow into intracortical venules and venous blood would empty into the low pressure marrow venous system. Venules from intracortical intercommunications may join...
Figure 3.11

Schematic drawing of unidirectional and bi-directional vascular intercommunications between marrow and cortical bone microcirculatory systems.

A = cortical arterioles

B = intersinusoidal communicating venule; drainage venule; portal venule

C = capillary-venule bed; portal venule

D = intracortical capillary-venule anastomosis

E = sinusoidal system; collecting sinus

F = capillary-venule bed

G = deep periosteal venous plexus

H = superficial periosteum
endosteal sinusoids or pass directly to join the central medullary
vein. This vascular pattern would permit the bi-directional flow of
blood through cortical bone, as observed by Branemark in vivo.4

Communication between the marrow and cortical microcirculations
also occurs in the deep periosteal plexus. Portal venules arising from
endosteal sinusoids usually radiate through the entire thickness of the
cortex and become continuous with deep periosteal venules. Normal flow
through the portal venules is probably centrifugal since marrow venous
pressure is greater than periosteal venous pressure. In this author's
opinion, the portal venules represent the vascular structures
responsible for permitting reversal of intracortical blood flow
whenever a significant decrease in marrow venous pressure or increase
in periosteal venous pressure occurs. Similar portal venules joining
endosteal capillary-venule beds with the deep periosteal plexus were
also present (Fig. 3.11, C). Because fatty marrow was infrequently
seen around the periphery of the medullary cavity, these portal venules
(leading from endosteal capillary-venule beds) were rarely observed.
Flow through the capillary-venule bed portal structures may only be
centrifugal, since the driving force of capillary blood is greater than
the driving force of sinusoidal blood. In response to an appropriate
hematopoietic stimulus, conversion of the vascular structures of fatty
marrow into low pressure sinusoidal systems would enhance the
possibility of reversible flow within the portal venules.

Blood flowing from the medullary cavity, through cortical bone,
and into the medullary cavity again (bi-directional flow) may be a
means by which the hematopoietic activity of marrow tissue is
regulated. Marrow tissue must continuously respond to the ever changing demands of the body for erythrocytes, granulocytes and lymphocytes within a confined compartment. Increases in the volume of hematopoietic tissue require compensatory decreases in the volume of intramedullary vascular structures, cancellous bone, extracellular fluid or fatty marrow. Adipocytes constitute the most labile buffer. Under a strong hematopoietic stimulus, all intramedullary fat may be mobilized within 48 hours. Ionized calcium, mobilized from cortical bone within central canals by erythropoietin or parathyroid hormone and returned to the medullary cavity via bi-directional vascular routes, may be the specific stimulus for the hematopoietic response. Calcium, erythropoietin, and parathyroid hormone all markedly stimulate mitosis in hematopoietic marrow tissue in vitro and in vivo. The stimulatory effect of calcium would presumably be greatest at the endosteal surface, where blood calcium levels were highest. In fatty marrow areas, adipocytes characteristically occupy the central portions of the medullary cavity; hematopoietic tissue is dispersed around the periphery.

Communications between the marrow and cortical microvascular systems may prevent or decrease the amount of tissue necrosis during a temporary ischemic episode. Unfortunately, impaired circulation to the marrow often establishes a vicious cycle of ischemia, edema and fibrosis, increased marrow pressure, and increased vascular resistance. Increased vascular resistance worsens the ischemia, provoking further edema and ultimately results in the death of bone. In mature animals and man, obstruction to flow in
epiphyseal emissary veins appears to constitute the most serious threat
to marrow and cancellous bone viability. Hips placed in particular
positions of forced immobilization, and episodes of severe synovitis
have caused Legg-Calve-Perthes disease (ischemic necrosis of the
femoral head) in children.17,18,19 In an experimental study in young
puppies, intracapsular tamponade of the hip joint with simultaneous
blood flow measurements demonstrated an increase of 248% in femoral
head marrow venous pressure and a 60% decrease in femoral head marrow
blood flow.20 Also, osteonecrosis of the femoral head has been
experimentally produced in young pigs and puppies by ligation of
epiphyseal vessels.21,22 Obstruction of epiphyseal emissary veins may
cause less severe clinical problems in the adult because of the
continuity of epiphyseal and metaphyseal marrow venous systems.23,24
In addition to extraosseous venous factors, pathologic changes leading
to osteonecrosis may be caused by extraosseous arterial factors,
extraosseous arterial or venous factors, extraosseous extravascular
factors and cellular cytotoxic factors.24

Commonly employed orthopedic practices compromise the circulation
of cortical bone to varying degrees. Cortical bone ischemia occurs
beneath encircling Parham bands and along the contact surface of bone
plates due to the obstruction of cortical venous drainage.27 Damage to
medullary vessels from fracture trauma is compounded by the use of
intramedullary nails and pins. Intramedullary reaming and
methy1methacrylate packing destroys the medullary source of cortical
arterioles and the impermeable endosteal barrier of bone cement
prevents the re-establishment of transcortical blood flow. When the
vascularity of bone is reduced, bone's resistance to infection is reduced, and post-operative sepsis may result.28

In addition to the role circulation undoubtedly plays in the pathogenesis of certain orthopedic diseases, and the healing of fractures and other injuries to bone, circulation is intimately involved in the process of osteogenesis, the maintenance of bone vitality, the growth and remodeling of bone, and calcium-phosphorus metabolism. The necessity of adequate arterial supply and unrestricted venous drainage in accomplishing these diverse activities has made circulation in marrow and cortical bone a topic of sustained interest for many anatomists, physiologists, pathologists, and clinicians of radiology, internal medicine and surgery.
LIST OF REFERENCES

Preface


Chapter I


Chapter II


Chapter III


