

On Connecting Large Vessels to Small

The Meaning of Murray's Law

THOMAS F. SHERMAN

From the Department of Biology, Oberlin College, Oberlin, Ohio 44074

ABSTRACT A large part of the branching vasculature of the mammalian circulatory and respiratory systems obeys Murray's law, which states that the cube of the radius of a parent vessel equals the sum of the cubes of the radii of the daughters. Where this law is obeyed, a functional relationship exists between vessel radius and volumetric flow, average linear velocity of flow, velocity profile, vessel-wall shear stress, Reynolds number, and pressure gradient in individual vessels. In homogeneous, full-flow sets of vessels, a relation is also established between vessel radius and the conductance, resistance, and cross-sectional area of a full-flow set.

INTRODUCTION

The arrangement of vessels in the organism is influenced by general physical laws as well as by specific physiological requirements. In the physics of transport, dimension is of great importance, as is portrayed in the equations for steady-state flow and diffusion in tubes. If a given vascular volume within a given tissue space is divided into a small number of large vessels or a large number of small vessels (all in parallel along a given length), steady-state flow and diffusion are affected in opposite ways. For a given pressure difference along the tubes and a given concentration difference between the walls of the tubes and the spaces around them, the flow along the tubes and diffusion from the tubes are both dependent upon the second power of the tube radii, r , but oppositely so: flow is directly proportional to r^2 , whereas diffusion is inversely so. For a fluid transport system involving both translational flow and transmural diffusion, a compromise must be found between large and small vessels. In animals this has been done through arrangements of large and small vessels in series, the former to minimize the costs of bulk flow across relatively large distances, the latter to minimize diffusion distances and maximize diffusion surfaces.

For over a century now the physiologist has been working with the laws of Poiseuille and Fick, which have served him well at any particular level of a branching system of vessels. The pattern of the whole, however, has been more difficult to understand. How should large and small vessels be connected to one another? Refuge from such a general question can be taken in the great

diversity of anatomical structures and physiological functions. But the suspicion remains that in the "ideal" tissue there should be an optimum way to connect large and small vessels together to achieve the fastest transport for the least amount of work. If there is a general rule for such connections, even if imperfectly followed by "nonideal" tissues, the physiologist should know about it, for it would enable him to estimate such important variables as flow conductance and surface area at different stages of a branching system.

Such a problem was posed by Thomas Young in his Croonian Lecture in 1808 (Young, 1809) when he wished to estimate the resistance of an arterial system: "In order to calculate the magnitude of the resistance, it is necessary to determine the dimensions of the arterial system, and the velocity of the blood which flows through it." Starting with assumed dimensions for the aorta and for the capillaries, Young had to decide upon a probable branching pattern which would connect the one with the other. He chose a symmetrical, dichotomous system in which the diameter of each branch was "about 4/5 of that of the trunk, or more accurately 1:1.26." By assuming this geometric ratio between the diameters of daughter and parent vessels, Young calculated that twenty-nine bifurcations were necessary to diminish the aorta to the size of the capillaries. From estimates of the lengths of the aorta and capillaries, he constructed another geometric series for lengths of the thirty generations of vessels, and went on to calculate blood volumes, velocities of flow, and resistances in the different stages of the system. Young does not say why he chose a ratio of 1.26:1 for the relative diameters of parent and daughter vessels, nor does he remark upon its being $2^{1/3}:1$, but it seems certain that he was familiar with a rule—either empirical or theoretical—which favored this choice.

Young's rule can be expressed in terms either of a ratio of radii or of a ratio of areas, for if one vessel divides into two equal daughters, and if the radii (or diameters) of parent and daughters are related as $2^{1/3}:1$, the total cross-sectional areas of parent and daughter vessels are related as $1:2^{1/3}$:

	<u>Parent</u>	<u>Daughters</u>	<u>Parent:daughters ratio</u>
Radius	$2^{1/3}$	1	$2^{1/3}:1$
Area	$2^{2/3}\pi$	2π	$2^{2/3}:2 = 1:2^{1/3}$

That is, as the radii get smaller, the cross-sectional areas get bigger by the same geometric factor.

Expressed either as a ratio of radii or of areas, Young's rule has appeared many times in this century but, as Zamir (1977) has remarked, it has usually been "surrounded by an air of mystery," with little explanation of its basis. Weibel (1964) attributes the rule to D'Arcy Thompson, but Thompson (1942) says only that it is a principle "familiar to students of hydrodynamics." McDonald (1974) attributes the rule to Blum (1919), who in turn refers us to Hess (1917). Hess did in fact attempt to establish the rule by a theoretical argument. But the clearest and most general approach to the problem was made by Cecil D. Murray (1926*a*). Murray derived a relation, hereafter referred to as Murray's law, which applied to asymmetrical as well as symmetrical branching systems. For symmetrical, dichotomous systems such

as those of Young and Hess, Murray's law reduces to their $2^{1/3}$ rule.

Murray's law for connecting large vessels to small is as memorable as Pythagoras' edict on right triangles, for Murray states that the *cube* of the radius of a parent vessel should equal the sum of the cubes of the radii of the daughter vessels. An alternative statement (employed here) is that an optimum vascular system must have its vessels connected in such a way that the total flow of the system, wherever that flow is intercepted, is carried by a set of vessels whose radii cubed sum to a constant value. Murray derived his law using a biological consideration, but it can be derived for non-living optimum systems as well. Like the laws of Poiseuille and Fick, which also arose within a biological context, Murray's law is a general physical principle of great utility in the description of biological bulk transport systems.

Murray's ideas went almost unnoticed for nearly half a century. They have been rediscovered recently by many workers (Rosen, 1967; Kamiya and Togawa, 1972; Milsum and Roberge, 1973; Rashevsky, 1973; Kamiya et al., 1974; Hutchins et al., 1976; Zamir, 1976*a* and *b*, 1977, and 1978; Hooper, 1977; Uylings, 1977). The purpose of this paper is to show that Murray's law can be derived for nonliving as well as living systems; that it is validated by considerable biological data, including the classical data of Mall which has been frequently tabulated (in altered form) in physiology textbooks; that it has great utility in predicting physiological parameters in the circulation; and that it is related in interesting ways to the growth of organisms and to the scaling of vascular systems in animals of different size.

DERIVATION OF MURRAY'S LAW

Murray supposed that physiological vascular systems, subjected through evolution to natural selection, must have achieved an optimum arrangement such that in every segment of vessel, flow is achieved with the least possible biological work. He assumed that two energy terms contribute to the cost of maintaining blood flow in any section of any vessel: (a) the energy required to overcome viscous drag in a fluid obeying Poiseuille's law, and (b) the energy metabolically required to maintain the volume of blood and vessel tissue involved in the flow. These energy terms are related to the radius of the vessel, but in opposite ways: the larger the radius, the smaller is the power, P_f , required for flow, but the larger is the power, P_m , required for metabolic maintenance of the blood and vessel wall tissue. The vessel can be neither too large nor too small if the total power, $P_t = P_f + P_m$, is to be minimized.

If gravitational and kinetic energy terms can be neglected, a Newtonian fluid exhibits a volumetric flow rate, f , which is linearly proportional to the pressure difference, p , to which it is subjected:

$$f = cp,$$

where c is a conductance coefficient. In cylindrical tubes, the conductance is proportional (from Poiseuille's law) to r^4 , the fourth power of the radius of the tube:

$$c = \frac{\pi r^4}{8\eta l},$$

where η is the viscosity of the fluid and l is the length of the tube. For a tube of unit length, and letting $a = 8\eta/\pi$,

$$af = pr^4$$

$$p = af^{-4}r^4.$$

The power required to maintain flow is

$$P_f = pf = af^2r^{-4}.$$

Hence, the power required to maintain a given flow is dramatically reduced by small increases in the radius of a vessel. Offsetting this, however, is a metabolic power requirement, P_m , which increases linearly with the volume of the blood and vessel

$$P_m = m \cdot \text{volume} = mr^2l,$$

where m is a metabolic coefficient. For unit length of vessel, and letting $b = \pi m$:

$$P_m = br^2.$$

The total power required is then

$$P_t = P_f + P_m = af^2r^{-4} + br^2.$$

Of the two coefficients in this expression, a depends upon the viscosity of the flowing fluid, and b upon the metabolism of blood and vessel tissue. For given values of a and b , the power required for flow in a unit segment of vessel depends only upon f , the flow, and r , the radius of the vessel. For a specified value of f , the power, P_t , depends only upon r , and P_t as a function of r will be minimized by that value of r where $dP_t/dr = 0$ and $d^2P_t/dr^2 > 0$. To find this optimum value of r :

$$\frac{dP_t}{dr} = \frac{d(af^2r^{-4} + br^2)}{dr} = -4af^2r^{-5} + 2br = 0$$

$$\frac{d^2P_t}{dr^2} = \frac{d(-4af^2r^{-5} + 2br)}{dr} = 20af^2r^{-6} + 2b.$$

Since a , b , f , and r are always positive, $d^2P_t/dr^2 = 20af^2r^{-6} + 2b$ is positive, and any point for which $dP_t/dr = 0$ is a minimum (rather than a maximum). Hence a minimum for P_t exists where

$$-4af^2r^{-5} + 2br = 0$$

$$2af^2r^{-5} = br$$

$$f^2 = \frac{b}{2a}r^6$$

$$f = kr^3; \quad k = \left(\frac{b}{2a}\right)^{1/2} \quad (1)$$

The new coefficient k depends only upon a and b (which, in turn, depend only upon viscosity and metabolic rate), so that if viscosity of the fluid and the metabolism of the blood and vessel tissue remain constant throughout all parts of a vascular system, k remains constant as well. Then Eq. 1 expresses, for any vessel that is minimizing energy requirements, a constant relation between flow and vessel radius. As Murray put it, "We see one of the simplest requirements for maximum efficiency in the circulation—namely that the flow of blood past any section shall everywhere bear the same relation to the cube of the radius of the vessel at that point."

If Eq. 1 applies to every vessel in a branching system (e.g., to all the arterial vessels of an organ), then it can be applied to a sum of such vessels. We have only to add the flows on one side and the cubes of the radii on the other side. In general,

$$\Sigma f = \Sigma kr^3 = k\Sigma r^3.$$

In particular, if we add together a group of vessels whose flows add up to the total flow, f_t , through the organ, we have

$$\begin{aligned} f_t &= k(\Sigma r^3)_t \\ (\Sigma r^3)_t &= \frac{f_t}{k} = \text{a constant}, \end{aligned} \quad (2)$$

where $(\Sigma r^3)_t$ is the sum of the cubes of the radii of any set of vessels which carry the full flow of fluid. For any such set (hereafter referred to as a full-flow set), the cubes of the radii add up to f_t/k , and hence the sums of the cubes of the radii for all such sets are equal.

Murray himself concentrated upon the application of his equation (Eq. 1) to individual branchings of parent to daughter vessels. Because flow is conserved at any branching, $f_0 = f_1 + f_2$, where f_0 is the flow in the parent vessel and f_1 and f_2 are the flows in the daughters, hence

$$\begin{aligned} kr_0^3 &= kr_1^3 + kr_2^3 \\ r_0^3 &= r_1^3 + r_2^3, \end{aligned} \quad (3)$$

where r_0 is the radius of the parent vessel and r_1 and r_2 are the radii of the daughters. Eq. 3 was used by Murray (1926*b*) to derive expressions for the optimum branching angles of vessels of different size. But if Eq. 3 applies to every branching, it can be applied to a series of branching, with the result that every set of subsequent daughter vessels that accommodates without duplication the full flow of the original parent vessel has a $(\Sigma r^3)_t$ equal to $r_0^3 = f_t/k$ (Eq. 2).

Eqs. 1–3 are alternative expressions of Murray's law. Eq. 2, which does not seem to have been used previously, will be employed below in the empirical testing of Murray's law, and in the discussion of its significance.

Murray derived his law without any assumptions regarding the form of the branching system: whether it was symmetrical or not, dichotomous or not. It

is therefore a general law which, within the confines of its assumptions, applies to branching systems of all forms. Applied to symmetrical dichotomous systems, it reduces to Young's $2^{1/3}$ rule:

$$r_0^3 = r_1^3 + r_2^3 = 2r_1^3,$$

when $r_1 = r_2$, so that

$$r_0 = 2^{1/3}r_1 \quad \text{or} \quad r_1 = 2^{-1/3}r_0.$$

For repeated bifurcations within a symmetrical system

$$r_z = 2^{-z/3}r_0,$$

where r_z is the radius of a vessel which is z bifurcations removed from a parent vessel of radius r_0 . (Weibel [1964], taking Young's rule from Thompson, tested his data on the airways of the lung against equations of this form.) Since the number of daughter vessels after z bifurcations is 2^z , the sum of the cubes of their radii is $\sum r_z^3 = 2^z r_z^3 = 2^z (2^{-z/3} r_0)^3 = 2^z (2^{-z} r_0^3) = r_0^3$, which is Murray's law expressed as Eq. 2.

In the derivation of Murray's law, a question arises about the vessel radius, r . The power required for laminar flow depends upon the internal radius only, whereas the metabolic requirement depends more nearly upon the external radius (because it depends upon the volume of vessel as well as the volume of contained fluid). In the expressions above, the same radius has been used in both terms, which suggests that the derived law is appropriate only for thin vessels whose internal and external radii are nearly the same. However, the thickness of a vessel wall tends to be a linear function of internal radius—because of Laplace's relation that states that for a given transmural pressure, the tension in the wall is proportional to r —so that wall thickness increases with r to counteract that tension. If wall thickness is wr , where w is a constant and r is internal radius, the external radius of the vessel, R , is also a linear function of r , since $R = r + wr = (1 + w)r$. For a unit length of vessel, the volume of the contained fluid is πr^2 and that of the vessel tissue is $\pi R^2 - \pi r^2 = \pi(1 + w)^2 r^2 - \pi r^2 = \pi r^2(2w + w^2)$, so that the volume of vessel wall is proportional to r^2 , as is the volume of contained fluid. If vessel and contained fluid have the same metabolic energy cost, they can be joined as a single term with volume πR^2 and energy requirement $m\pi R^2 = bR^2 = br^2(1 + w)^2 = b'r^2$, where $b' = b(1 + w)^2$. Under these conditions, only the coefficient b changes by inclusion of the vessel wall; the overall derivation remains the same, and Murray's law still holds. In addition, the law can be expressed for external as well as internal radii, because if $r_0^3 = r_1^3 + r_2^3$, then $r_0^3(1 + w)^3 = r_1^3(1 + w)^3 + r_2^3(1 + w)^3$ and $R_0^3 = R_1^3 + R_2^3$. This, of course, is not to claim that vessel walls are invariably proportional to internal radius: as transmural pressures decrease in the circulatory system, the walls tend to become thinner, as they need to sustain less tension (witness the difference between arteries and veins). Further, changes in vessel muscle tone (vasoconstriction and dilation) cause changes in internal radius without a corresponding change in wall thickness.

Murray's law will not always hold exactly, but it is far less approximate than might, at first sight, seem to be the case.

If the volume of vessel tissue is proportional to the square of the internal radius (as when wall thickness is proportional to r), then Murray's derivation can hold for a biological vasculature even when the flowing fluid itself is inert and nonliving, as in the airways of the lungs, where the vessels are filled with air (of no metabolic cost) rather than with blood. For Murray's law derives from the assumption that the total power requirement of the system is the sum of two factors, which are proportional to $f^2 r^{-4}$ and to r^2 , respectively. A factor proportional to r^2 can be given by the volume (per unit length of tube) of (a) the flowing fluid alone, if the vessels are very thin-walled; (b) the vessels alone, if the fluid has no power cost associated with its maintenance; or (c) the fluid and vessel combined.

The derivation of Murray's law involves two assumptions of a biological nature: (a) that optimality (a minimum energy condition) is sought, as by the action of natural selection, and (b) that a maintenance energy term is required for the volume of some material involved. The derivation could of course be applied also to nonliving optimum vasculatures formed from a material that had an initial power cost associated with it, a cost to be amortized over a given period of operation even if no further maintenance was to be required. Thus Murray's law would hold for civil engineering projects involving pipes of iron or concrete as well as for vasculatures of living tissue. Thus D'Arcy Thompson's "students of hydrodynamics" may well have derived the $2^{1/3}$ rule from assumptions similar to Murray's, but Murray seems in any case to have been the first to derive it for asymmetrical as well as symmetrical systems.

In Murray's optimum system, flow and vessel radius are functionally related: an optimum radius is found for a given flow. For a given metabolic coefficient, m , the volume of a vascular system in an organ or organism will depend upon the flow required of it: an optimum vasculature for high flows will have larger vessels than one for low flows, the cubes of the vessel radii being proportional to the flows required.

An interesting alternative system is one that is to be optimum within the confines of a given total volume of vascular tissue. If, for example, an organism has grown to a fixed adult size, with a vasculature that is optimum for some average flow that is required of it, does that vasculature remain for its volume the optimum one for other flows as well, or would some other arrangement be better for conditions of increased or decreased flow? Considering the great changes in flow required in an organism of fixed size moving from rest to maximum activity, etc., such a question is an important one. The answer (as shown below) is that the system obeying Murray's law is the optimum one, for its volume, at all levels of total flow.

One way to demonstrate that this is so is to characterize a branching system that has, for a given total volume, the least resistance to flow. If the resistance is minimum at one rate of flow, it will be so at all flow rates, and so too will be the power required for any given flow. We seek then a rule for branching

in a system of given volume of material, M , such that the resistance to flow will be minimal. Such a system has been studied in detail by Cohn (1954 and 1955), by Rashevsky (1960), and by Horsfield and Cumming (1967), but only for symmetrical branchings. A simple demonstration is given here that applies to asymmetrical branchings as well.

Let us look at any branching in a system of fixed volume. We will neglect the precise geometric form of the junction itself and consider unit lengths of a parent vessel and two daughters, without stipulating whether the daughters are of equal radii or not, where

r_0 radius of parent vessel

r_1 radius of daughter vessel 1

r_2 radius of daughter vessel 2

M volume of the system (where "system" denotes the sum of unit lengths of parent and daughter vessels, neglecting the region of junction itself)

R_1 resistance to flow in the parent vessel

R_2 resistance to flow in the parallel daughter vessels

R total resistance of the system (parent and daughters).

Then

$$R_1 = \left(\frac{8\eta}{\pi}\right)\left(\frac{1}{r_0^4}\right) = \frac{a}{r_0^4} = ar_0^{-4},$$

where $a = 8\eta/\pi$

$$R_2 = \left(\frac{8\eta}{\pi}\right)\left(\frac{1}{r_1^4 + r_2^4}\right) = \frac{a}{r_1^4 + r_2^4} = \frac{ar_1^{-4}r_2^{-4}}{r_1^{-4} + r_2^{-4}}$$

$$R = a\left(r_0^{-4} + \frac{r_1^{-4}r_2^{-4}}{r_1^{-4} + r_2^{-4}}\right) = a\left(x + \frac{yz}{y+z}\right) = a\left(\frac{xy + xz + yz}{y+z}\right)$$

where $x = r_0^{-4}$, $y = r_1^{-4}$, $z = r_2^{-4}$. Also

$$M = \pi(r_0^2 + r_1^2 + r_2^2) = \pi(x^{-1/2} + y^{-1/2} + z^{-1/2}).$$

Since a and π are constants, for convenience we seek to minimize a normalized resistance $R' = R/a = (xy + xz + yz)/(y + z)$ subject to the condition that a normalized amount of material $M' = M/\pi$ is fixed and is equal to $x^{-1/2} + y^{-1/2} + z^{-1/2}$.

Using the method of Lagrangian multipliers, we seek to minimize

$$(F) = \frac{xy + xz + yz}{y + z} + \lambda(x^{-1/2} + y^{-1/2} + z^{-1/2} - M'),$$

where λ is an arbitrary, non-zero constant. For this function to be a minimum, its derivatives with respect to x , y , z , and λ must be zero. The differentiation of $(x^{-1/2} + y^{-1/2} + z^{-1/2} - M')$ is straightforward. The differentiation of $(xy + xz + yz)/(y + z)$ is facilitated by setting $u = xy + xz + yz$ and $v = y + z$, and noting that $du/dx = y + z$, $du/dy = x + z$, $du/dz = x + y$, $dv/dx = 0$,

$$dv/dy = 1, dv/dz = 1.$$

Since $d(u/v)/dx = (v \cdot du/dx - u \cdot dv/dx)/v^2$, this leads to:

$$\begin{aligned} \frac{\partial F}{\partial x} &= \frac{(y+z)(y+z) - (xy+xz+yz)(0)}{(y+z)^2} - \frac{1}{2}\lambda x^{-3/2} \\ &= 1 - \frac{1}{2}\lambda x^{-3/2} = 0 \text{ at minimum} \end{aligned}$$

$$\begin{aligned} \frac{\partial F}{\partial y} &= \frac{(y+z)(x+z) - (xy+xz+yz)(1)}{(y+z)^2} - \frac{1}{2}\lambda y^{-3/2} = \frac{z^2}{(y+z)^2} - \frac{1}{2}\lambda y^{-3/2} \\ &= 0 \text{ at minimum} \end{aligned}$$

$$\begin{aligned} \frac{\partial F}{\partial z} &= \frac{(y+z)(x+y) - (xy+xz+yz)(1)}{(y+z)^2} - \frac{1}{2}\lambda z^{-3/2} = \frac{y^2}{(y+z)^2} - \frac{1}{2}\lambda z^{-3/2} \\ &= 0 \text{ at minimum} \end{aligned}$$

$$\frac{\partial F}{\partial \lambda} = x^{-1/2} + y^{-1/2} + z^{-1/2} - M' = 0 \text{ at minimum}$$

From the first three of these equations

$$\begin{aligned} \frac{1}{2}\lambda x^{-3/2} &= 1, \quad x^{-3/2} = \frac{2}{\lambda}, \quad x^{-3/4} = \left(\frac{2}{\lambda}\right)^{1/2} \\ \frac{1}{2}\lambda y^{-3/2} &= \frac{z^2}{(y+z)^2}, \quad y^{-3/4} = \left(\frac{2}{\lambda}\right)^{1/2} \left(\frac{z}{y+z}\right) \\ \frac{1}{2}\lambda z^{-3/2} &= \frac{y^2}{(y+z)^2}, \quad z^{-3/4} = \left(\frac{2}{\lambda}\right)^{1/2} \left(\frac{y}{y+z}\right). \end{aligned}$$

Hence, $x^{-3/4} = y^{-3/4} + z^{-3/4}$. Minima for the function $(xy + xz + yz)/(y + z)$ subject to the condition that $x^{-1/2} + y^{-1/2} + z^{-1/2} = M'$ therefore exist where $x^{-3/4} = y^{-3/4} + z^{-3/4}$ or (replacing $x, y,$ and z by $r_0, r_1,$ and r_2) where $r_0^3 = r_1^3 + r_2^3$.

If in the above derivation we start with vessel segments not of unit length but rather of similar shape to one another (i.e., with lengths proportional to their radii), minimal resistance is again achieved when $r_0^3 = r_1^3 + r_2^3$.

When the parent vessel is assumed to divide into three daughter vessels instead of two, minimal resistance can be shown to occur where $r_0^3 = r_1^3 + r_2^3 + r_3^3$ (r_3 being the radius of the third daughter vessel). Likewise, with four daughter vessels resistance is minimized when the sum of the cubes of the radii is conserved. Conservation of the sum of the cubes of the radii is the condition for minimal resistance whether the parent vessel divides symmetrically or asymmetrically, and whether it divides into two, three, four, or, presumably, any number of daughter vessels.

Hence, Murray's law seems to hold for a system of fixed volume seeking minimum resistance just as it holds for a system seeking, within a flexible volume, an optimum compromise between volume and resistance (i.e., between work associated with volume and that associated with flow itself). A system obeying Murray's law during growth, when vessel size is increased to meet increased flows, will continue to be optimum when, having achieved a fixed size, the system is subjected to variable flows. Since there is nothing in this derivation that assumes that the vasculature is living, Murray's law will hold for any branching vascular system that, within a given volume, requires minimum flow resistance. For symmetrical, dichotomous systems, this leads again to the $2^{1/3}$ rule.

VALIDATION OF MURRAY'S LAW

Do biological vessels actually conform to Murray's law? Quantitative studies of the vessels of whole organs have been conducted by Mall (1888) on the small intestine of the dog, by Miller (1893 and 1937) on the dog lung, and by Weibel and Gomez (1962), Weibel (1963 and 1964), Horsfield and Cumming (1968), and Horsfield (1978) on the human lung.

Mall's histological study was inspired by the physiologist Carl Ludwig, and he aimed to estimate, for different parts of the circulation, such physical characteristics as the total cross-sectional area of vessels. His data are still the basis of tables found in most present-day physiology textbooks, but the tables appearing today have passed through modifications made by Schleier (1919) or by Green (1944). Whereas Schleier merely edited the data, leaving out the inconvenient categories of vessels, Green drastically altered them by extrapolating from the dog intestine to the whole human body. Zamir (1977) attempted to compare Murray's law with Green's extrapolation. A valid comparison can only be made by means of a statistical test applied to the complete original data. For this purpose, Mall's original data are reproduced in Table I.

Mall himself noted that his data were approximate. Although he could directly count the number of large vessels over the entire organ, smaller vessel numbers were estimates based upon small samples, so that the number of capillaries, for example, might be in error by 30–50% or more (Mall sometimes employed far too many significant figures in tabulating his data). Vessel radii, which presumably are external radii, are also approximate, and there is probably a systematic distortion in the sizes of some of the small arteries, since the dogs were killed by bleeding with the result that vasoconstriction was probably pronounced.

Nevertheless, Table I displays in an approximate way how the blood brought in by the superior mesenteric artery is carried throughout the intestine. Five capillary beds are supplied: in the villi of the mucosa, around the crypts of the mucosa, in the circular muscle, in the longitudinal muscle, and in the peritoneum. Schleier (and subsequent textbooks) tabulated only those vessels involved with the circulation to the villi, because only by eliminating the other beds can a uniform progression from large vessels to small be

TABLE I
DATA OF F. P. MALL (1888)

Description of vessel	Number	Radius μm	Probable rank
Superior mesenteric artery	1	1,500	0
Main branches of mesenteric art.	15	500	1
Final branches of mesenteric art.	45	300	2
Short intestinal arteries (s.i.a.)	1,440	40	3
Long intestinal arteries (l.i.a.)	459	96	3
Last branches of s.i.a.	8,640	25	4
Last branches of l.i.a.	18,000	26.5	4
Branches to crypts	4,000,000	4	5, 6, 7
Branches to villi	328,500	15.5	5
Arteries of the villi	1,051,000	11.25	6
Capillaries of the villi (upper 2/3)	31,536,000	4	7
Capillaries of the villi (lower 1/3)	15,768,000	2.5	x
Veins at base of villi	2,102,400	13.25	6'
Veins between villi & submucosa	131,400	37.5	5'
Last branches of submucosal veins	18,000	64	4'
Anastomoses of submucosal veins	2,500,000	16	xx
Last branches of s.i.v.	28,800	32	4'
Long intestinal veins	459	220	3'
Short intestinal veins (s.i.v.)	1,440	56	3'
Last branches of mesenteric veins	45	750	2'
Branches of mesenteric vein	15	1,200	1'
Mesenteric vein	1	3,000	0'
Muscle layers			
Direct muscle arteries	1,800	15	3, 4, 5, 6
Indirect muscle arteries	3,600	20	3, 4, 5, 6
Capillaries of circular muscle	27,000,000	1.5	7
Capillaries of longitudinal muscle	9,000,000	1.5	7
Veins	3,600	56	3', 4', 5', 6'
Peritoneum			
Arteries	360	24	3, 4, 5, 6
Capillaries	36,000	9	7
Veins	360	40	3', 4', 5', 6'

Data of F. P. Mall (1888). Most of the data is also available in English in a later article by Mall (1905-06). The vessels are tabulated exactly as Mall presented them, except for the following changes: (a) names are translated from German, (b) vessel radii are given in μm instead of vessel diameters in cm, (c) a printer's error in assigning the decimal point in the size of the capillaries of the circular muscle has been corrected. In addition, the vessels are assigned to a probable rank (see text). Each rank is a group of vessels carrying the full flow of blood originating in the superior mesenteric artery. Two groups of vessels have not been assigned a rank: x, capillaries of the villi (lower one-third) represent a partial channel intermediate between ranks 7 and 6'; xx, anastomoses of submucosal veins represent cross channels within rank 4'.

displayed. Although the capillary bed of the villi is more extensive than the other four beds combined, all must be included if the total carriage of blood is to be portrayed. In addition, Schleier combined the upper capillaries of the villi with the lower. These channels are probably in series rather than in parallel, so that they should be regarded as separate stages of the system.

In analyzing these data, we seek to establish sets of vessels that carry, without duplication, the full flow of blood brought in by the superior mesenteric artery. These full flow sets have been tabulated as ranks in Table I. In passing from the superior mesenteric vein, a particle of blood must flow through the following sequence of ranks: arteries 0, 1, 2, 3, 4, 5, 6, capillaries 7, veins 6', 5', 4', 3', 2', 1', 0'. In some cases a vessel must be assigned to more than one rank. The branches to the crypts, for example, carry blood from arteries of rank 4 directly into veins of rank 6', so that these vessels achieve the same connection that vessels of ranks 5, 6, and 7 do in the villi. The ranks also represent the number of major branching processes that Mall detected downstream from the superior mesenteric artery (or upstream from the mesenteric vein). The actual number of dichotomous branchings is obviously far higher than the number of ranks.

The ranks have been brought together in Table II, where each vessel listed

TABLE II
VESSELS IN TABLE I GROUPED ACCORDING TO RANK

Vessel rank	Σr^2	Σr^3	Σr^4
	mm^2	mm^3	mm^4
0	2.2	3.4	5.1
1	3.8	1.9	0.94
2	4.0	1.2	0.36
3	8.6	0.54	0.043
4	20	0.51	0.013
5	140	1.5	0.021
6	200	1.8	0.019
7	650	2.4	0.0095
6'	380	5.5	0.10
5'	200	7.6	0.30
4'	120	6.3	0.37
3'	39	5.8	1.1
2'	25	19	14
1'	22	26	31
0'	9	27	81

The vessels of Table I have been grouped according to rank and the sums of r^2 , r^3 , and r^4 have been calculated for each rank.

in Table I has been assigned to its appropriate rank or ranks. For each rank, a sum of radii squared (Σr^2), of radii cubed (Σr^3), and of radii to the fourth power (Σr^4) have been calculated. For homogeneous ranks (ranks with only one set of similar vessels), Σr^2 , Σr^3 , and Σr^4 are nr^2 , nr^3 , and nr^4 , respectively, where n is the number of vessels of radius r .

It is evident from Table II that in moving from rank 0 (the superior mesenteric artery) to rank 7 (the capillaries), Σr^2 increases dramatically and Σr^4 decreases to a similar degree. Since Σr^2 is proportional to cross-sectional area of the vessels and Σr^4 is proportional to their conductance to flow, Table II displays the striking manner in which area increases as conductance decreases in moving from the larger to the smaller vessels. It was this sort of

insight that Mall hoped to gain from his studies, and although he (and later authors) failed to group the vessels together correctly, the general trend of his findings has been well known to physiologists since.

Unlike Σr^2 and Σr^4 , Σr^3 has no obvious physiological significance and has therefore been ignored. However, it is this quantity that, according to Murray's law, should be conserved. Table II shows that it remains fairly constant throughout the arterial system (from ranks 0 to 7) and even through the first one-half of the venous system as well (ranks 6' to 3'). In the larger veins Σr^3 tends to increase somewhat, though the changes in Σr^3 are far less than those for Σr^4 and about the same as those for Σr^2 .

If Σr^2 , Σr^3 , and Σr^4 are plotted against rank, it becomes evident that the values for ranks 3 and 4 are altogether too low. The deviations of these ranks from a line of best fit for the other ranks is greatest for Σr^4 values, and least for Σr^2 . If the mean value of r is raised by a factor of 1.5 for ranks 3 and 4, not only are the aberrant points for Σr^3 brought close to their line, but the corresponding points for Σr^2 and Σr^4 are restored to their lines as well. This suggests that there is a systematic underestimation of the value of r for these ranks, an error that might easily arise as a result of the preparation of the dog by bleeding, with the resultant vasoconstriction of the arteries of these ranks. There is reason therefore to suppose that Σr^3 is normally conserved even better than portrayed in Table II.

If Σr^3 is constant for ranks (full-flow sets) of the arterial system and much of the venous system, then for any homogeneous, full-flow set of this region where $\Sigma r^3 = nr^3$, we have a functional relation between n and r , namely, $nr^3 = K$, or $n = Kr^{-3}$, where K is a constant. If the vessels of every rank were homogeneous (i.e., had the same radius), we could check the $nr^3 = K$ rule by fitting a power curve of the form $nr^m = K$ to the data (or by finding the regression line for $\ln n = -m \ln r + \ln K$). A value of $m \approx 3$ would support the rule. Because ranks 3, 4, 5, 6, 7, 6', 5', 4', and 3' are not homogeneous, the test cannot be done without first converting these ranks to equivalent homogeneous ranks. To do this, the radius of the vessels that contribute the largest nr^3 component to the rank is taken as the radius of the rank, and the number of those vessels is recorded. To this number is added a calculated number of vessels of that radius needed to give an nr^3 value equal to that of the lesser groups of vessels in the rank. Table III shows the radii and numbers of vessels for homogeneous ranks created from Mall's data in this way. The conversion introduces a bias in favor of the nr^3 rule, since this rule has been used in the transformation of the ranks from nonhomogeneous to homogeneous. However, because the original ranks are only slightly nonhomogeneous, the bias is very small; it can be eliminated to any degree required by making successive approximations in the determination of the regression line.

When the data for ranks 0-3' in Table III are fitted to a regression line, a value of 2.984 is found for the exponent, m , with a coefficient of determination of 0.971. If the questionable ranks 3 and 4 are eliminated, m is found to be 3.006, with a coefficient of determination of 0.987. If only the arterial data (ranks 0 to 7) are fitted, the exponent is 2.947 (coefficient of determination

0.988) or, without ranks 3 and 4, the exponent is 2.972 (coefficient of determination 0.998). In any case, throughout the vascular system of the intestine—until the large veins are reached—the classical data for Mall falls very close to the line predicted by Murray's law.

The data of Miller (1893) for the dog lung also conform fairly closely to Murray's law, though not so closely as Mall's data for the small intestine. The exponent m is 2.61 for the arteries and 2.76 for the veins. For all the veins except the final four large pulmonary veins, however, the exponent is 3.01.

Weibel and Gomez (1962) in their study of the human lung fitted their data for arteries to an equation of the form $r_z = r_0 2^{-z/3}$, where z is the number of bifurcations, assumed in their model to be symmetrical. This equation is

TABLE III
DATA OF F. P. MALL (1888) MODIFIED TO FORM HOMOGENEOUS RANKS OF VESSELS

Vessel rank	Radius of predominant vessels of rank (r) μm	Equivalent number of vessels for homogeneous rank (n)
0 (parent artery)	1,500	1
1	500	15
2	300	45
3	96	608
4	26	27,400
5	16	408,000
6	11	1,260,000
7 (capillaries)	4	37,800,000
6'	13	2,380,000
5'	37	144,000
4'	64	24,100
3'	220	544
2'	750	45
1'	1,200	15
0' (end vein)	3,000	1

The vessels of Table I have been grouped according to rank, the radius of the predominant group has been taken as the radius of the rank, and the number of vessels for the rank has been calculated to give a value of nr^3 (for the homogeneous rank) equal to the original Σr^3 .

derived from Thompson's $2^{1/3}$ rule, and hence, the line of best fit of Weibel and Gomez (1962) has the slope predicted by Murray's law.

Horsfield and Cumming (1968), Singhal et al. (1973), and Horsfield (1978) do not assume a symmetrical branching pattern in their studies of the lung, but order the lung vessels by a modification of methods introduced by Horton (1945) and Strahler (1953 and 1957) for analyses of river systems. Since the Horsfield orders do not necessarily correspond to full-flow sets of vessels, however, they do not lend themselves easily to the present analysis.

Suwa et al. (1963) concluded that human arteries, over a wide range of sizes, preserve a constancy of $\Sigma r^{2.7}$ for full-flow sets, but that in the largest arteries Σr^2 is nearly constant in such sets. Patel et al. (1963) and Mall (1905–

06) also found that the largest vessels tend to maintain a constant total cross-sectional area, so that Murray's law is not followed in the most immediate branchings of the aorta, the pulmonary trunk, the venae cavae, and the pulmonary veins. Iberall (1967) concluded from a study of the data of Mall (1905–06), Patel et al. (1963), and Suwa et al. (1963) that “the cross-sectional data does not change much until arterial diameters of the order of 1/2 mm are reached; then an approximately uniform increase in area per level for arterial sizes down to about 20–30 μm occurs, after which a large increase in area down to capillary sizes of the order of 8 μm takes place.” Iberall thus divides the arterial tree into three regions; the most extensive (middle) region shows, in his view, a linear relation of some sort between Σr^2 and r^x . An inspection of Iberall's graph shows that he has chosen to make Σr^2 proportional to $r^{-0.7}$, and, hence, has accepted the conclusion of Suwa et al. that $r^{2.7}$ is constant in this middle region.

Blum (1919) estimated cross-sectional area ratios for a great many arterial branchings. He concluded that his results were scattered around a mean of 1.26, a result which, for symmetrical branching, is that predicted by Murray's law.

Hutchins et al. (1976) found a constancy of Σr^3 for branch points in normal coronary arteries. In diseased arteries they found the exponents to be <3 .

In summary, arteries and veins, excluding only the largest, follow Murray's law very well. Estimates of exponents, m , for a relation $nr^m = K$, fall mostly in the range of 2.7–3.0. The capillaries of the small intestine seem also to obey the relationship, but capillaries of many tissues cannot be expected to do so (see below).

There is evidence that the larger airways of the lungs also follow Murray's law. A test of the data of Miller (1893) gives an exponent of 2.71 for all the airways down to the alveolar sacs. Weibel and Gomez (1962) found a difference between the first ten generations of airways (starting with the trachea) and the finer airways beyond. The first ten generations followed the $2^{1/3}$ rule (and hence Murray's law), whereas those beyond deviated increasingly from the theoretical line. Wilson (1967) also noted the correspondence between the data of Weibel and Gomez and the $2^{1/3}$ rule, and independently gave a theoretical argument, very similar to Murray's, for the optimality of such a rule. Hooper (1977), realizing that the lung branches asymmetrically (not symmetrically, as Weibel and Gomez's model assumes), made resin casts of the airways and, cutting the casts, compared the weight distal to a cut with the radius of the airway at the cut. From a regression line fitted to 79 observations, he found that the weight was proportional to $r^{2.98}$. Using an argument adopted from a study of trees by Murray (1927)—that the weight supported by a parent branch is the sum of the weights supported by its daughters, Hooper concluded that for his airways (which were of fairly large size), $r_0^{2.98} = r_1^{2.98} + r_2^{2.98}$. This confirms Murray's law for the larger airways in a more direct way than do the earlier studies, because it does not require that data from an asymmetrical branching system first be fitted to a symmetrical model.

LIMITATIONS OF MURRAY'S LAW

Murray's law will usually apply only to branching systems for which the original assumptions leading to the law are valid. These assumptions are: (a) that the system is arranged to minimize energy output, and (b) that the energy output is that which results from two terms associated with (i) Poiseuille flow, where energy output is proportional to $f^2 r^{-4}$; and (ii) volume of the system, where maintenance energy is proportional to r^2 . Alternatively, the law applies to a system of given volume that is arranged to minimize resistance, where resistance is proportional to r^{-4} .

An electrical conduit system would be expected to obey some other law, for resistance in such a system is proportional not to r^{-4} but to r^{-2} . It is easy to show that the "Murray's law" for branching electrical systems is $r_0^2 = r_1^2 + r_2^2$. A branching system of wires, made from a given amount of material that is to minimize resistance, should have a constant Σr^2 for all full-current sets of wires. Throughout the system the current, I , in any segment of wire of radius r , should be $I = Kr^2$, where K is a constant. Since current is proportional to voltage gradient times conductance, and since conductance in a wire is proportional to r^2 , this means that the optimum electrical system has a constant voltage gradient (proportional to r^0). In contrast, the optimum flow system has a pressure gradient that is not constant with changes in vessel size, but is proportional to r^{-1} (see below).

A diffusion conduit system would follow the same law as the electrical system, for diffusion, like electrical current, has a conduction proportional to r^2 for a given cylindrical segment, or to Σr^2 for a sum of parallel segments. Although diffusion in a biological conduit system requires no work from the organism (the work is supplied by the free energy gradient), the minimization of resistance within a given volume will lead to the same result as for the electrical system, namely $\Sigma r^2 = K$. Krogh (1920, also described in Krogh [1941]) has studied terrestrial insect larvae that show no respiratory movements and hence rely upon diffusion to supply oxygen through their tracheal systems. In *Cossus* (goat moth) larvae, Krogh found that the tracheal system maintained a constant cross-sectional area ($\sim 6.7 \text{ mm}^2$) in branching from larger to smaller vessels. This curious fact, recently described by Schmidt-Nielsen (1979), is now seen to be predicted by a model analogous to Murray's.

The fundamental limitation of Murray's law itself ($\Sigma r^3 = K$) is that it applies only to branching conduction systems in which conduction is proportional to r^4 . Analogous laws, however (such as $\Sigma r^2 = K$ for the electrical or diffusion systems) apply to other cases. That the diffusion system of insects follows an analogue of Murray's law supports the appropriateness of Murray's approach.

Should Murray's law hold for fluid flow systems in which the work required to drive the flow is only partially accounted for by the frictional drag in the tubes themselves? In the lung, for example, the work used in overcoming frictional resistance in the airways is, in quiet breathing, only one-fourth to one-third of the total work of breathing, the balance being required to overcome the elasticity of the lungs and thoracic wall (Comroe, Jr. 1974).

Such factors may influence the total volume of the vessel system, but they do not affect the optimal branching rule for the system; Murray's law would still hold as the result of minimizing resistance in whatever volume was available for the branching system.

On the other hand, a system would not be expected to obey Murray's law where flow is turbulent instead of laminar, so that the work for propelling the fluid in the tubes is not proportional to $f^2 r^{-4}$. Uylings (1977) showed that optimality for a turbulent system requires that $r_0^{7/3} = r_1^{7/3} + r_2^{7/3}$. The turbulence of flow in the aorta and pulmonary trunk may help to explain why the immediate branchings of these vessels seem to conserve Σr^2 more nearly than Σr^3 . The occurrence of pulsatile plug flow in the aorta would also tend to limit Murray's law to the lesser arteries.

In the smallest blood vessels, Murray's law might be limited by the changes in blood viscosity noted by Fahraeus and Lindqvist (1931), since the derivation of Murray's law assumes a constant viscosity coefficient. The decrease in blood viscosity in the small vessels, although important in decreasing circulatory energy requirements, is nevertheless small compared with the decrease in vessel radius required to bring it about. If blood viscosity, η , were to be approximated by a single-power term in vessel radius, r , the relation would be no stronger than $\eta = k r^{1/6}$ (Fahraeus and Lindqvist, 1931; Haynes, 1960). If Murray's assumption that η is independent of r , that is, that $\eta = k r^0$, is changed to $\eta = k r^{1/6}$, then his law is altered only to $\Sigma r^{35/12} = \Sigma r^{2.92} = K$ from $\Sigma r^3 = K$. The Fahraeus-Lindqvist effect has therefore rather little effect upon the Murray system.

Various specific physiological requirements may be expected to limit adherence to Murray's law. The capillary beds of certain tissues may require vascular surface areas (and numbers of capillaries) unusually large compared with the dimensions of the arteries supplying them. Such arrangements allow rates of transmural diffusion to be unusually rapid, as at the alveoli of the lungs. In skeletal muscle the capillaries are arranged so as to allow large changes in the conductance of the system, so that greatly varying flows can be driven by a relatively constant pressure gradient. In the resting muscle only a minority of the capillaries are utilized at any given moment, so that the Σr^3 for the total capillary bed could be expected to exceed the Σr^3 for a full-flow set of arterial vessels supplying the bed.

In any vessel segment (of unit length) obeying Poiseuille's law, the flow through the segment is proportional to the pressure difference and to the fourth power of the vessel radius. If that vessel segment is part of an optimum system (obeying Murray's law as well as Poiseuille's law), the flow through the segment is still proportional to the pressure difference and to the fourth power of the radius, but, because the pressure difference in the segment (given a constant overall pressure difference for the system) is proportional to the vessel radius (see below), these two factors combine to give a flow in the segment that is proportional to the cube of the vessel radius. Of the total flow of a system, the portion that flows through a given segment is given by $r_i^3 / \Sigma r^3$, where r_i is the radius of the segment and Σr^3 refers to the whole system.

If the portion flowing to a given region is to be changed, the value of r_i^3 must be changed. If the system is to remain optimal, the radii of all vessels upstream that carry flow to that segment must also change, as must some of the vessels downstream from the segment. In the end the maintenance of optimality for all the physiological patterns of distribution would require vasomotor control of nearly all the arterial vessels. Since this is unlikely to be the case, Murray's law can be expected to hold only for the most common distribution patterns.

In vessels of the body where functions other than bulk flow become significant, Murray's law again may not hold. That the large veins act as blood reservoirs as well as flow channels may explain why they are somewhat larger than Murray's law would predict. The small airways of the lung tend also to be larger than predicted, and this is probably because, as noted by Weibel and Gomez (1962) and West (1979), diffusion becomes more important than bulk flow in the transport of gases in the terminal airways.

MEANING OF MURRAY'S LAW

By establishing a relation between flow and vessel radius in a vascular system, Murray's law enables one to predict a number of other interesting features of the system. The following characteristics hold for a system obeying Murray's law:

Volumetric Flow

In every vessel of a Murray system, flow is proportional to r^3 (Murray's law).

Velocity of Flow

Because the flow is proportional to r^3 and because the cross-sectional area of a vessel is proportional to r^2 , the average velocity of flow in any segment must be proportional to r (Murray, 1926*a*). Since the maximum velocity (at the center of the tube) is twice the average velocity in laminar flow, the maximum velocity of flow is also proportional to the vessel radius.

Velocity Profile

Since the maximum velocity of flow (at the center) is proportional to the vessel radius in every vessel of a Murray system, it is evident that the parabolas describing velocity profiles in all the vessels are similar to one another. In this sense the flow has a similar shape in every vessel of a Murray system.

Vessel-Wall Shear Stress

Since the velocity-profile parabolas are all similar to one another, the rate of change (at the vessel wall) of velocity with distance from the wall (dv/dx) is the same for all vessels. This can also be seen because in laminar flow in tubes

$$v = v_m \left[1 - \frac{(r-x)^2}{r^2} \right] = v_m \left(\frac{2rx - x^2}{r^2} \right),$$

where v is the velocity at a distance x from the wall, v_m is the maximum

velocity at center of the tube, and r is the radius of the tube. Then

$$\frac{dv}{dx} = v_m \left(\frac{2}{r} - \frac{2x}{r^2} \right) = 4\bar{v} \left(\frac{1}{r} - \frac{x}{r^2} \right),$$

where \bar{v} is the average velocity ($v_m/2$).

At the wall ($x = 0$), $dv/dx = 4\bar{v}/r$. Since \bar{v} is proportional to r , dv/dx is independent of r and hence the same for vessels of all sizes. The shear stress on the vessel wall, $T = \eta dv/dx$, where η is the viscosity of the fluid. Hence, the vessel-wall shear stress is constant throughout an optimum vascular system. Rodbard (1975) proposed that shear stress detected by the vessel endothelium leads to vessel growth or contraction, and Zamir (1977) suggested that this leads to the development of the Murray system as vessels maintain a constant shear stress.

Reynolds Number

Since the average velocity is proportional to r in a Murray system, and since the Reynolds number is proportional to velocity of flow times vessel radius, the average Reynolds number is proportional to the square of the radius for vessels in an optimum system. Caro et al. (1978) give estimates of the Reynolds numbers for flow in arteries of different sizes; their values closely conform to an r^2 proportionality.

Pressure Gradient

In a vessel segment where flow obeys Poiseuille's law, the flow is proportional to the pressure gradient (the pressure difference per unit length) times the fourth power of the vessel radius. If Murray's law also holds, the flow is proportional to the cube of the vessel radius, and the pressure gradient must therefore be proportional to r^{-1} (neglecting the small effects from changes in kinetic energy of the fluid). Zweifach (1974) has measured pressure gradients in small arterioles, capillaries, and venules of the cat mesentery. The pressure gradients reported by Zweifach are very nearly proportional to r^{-1} , suggesting that the smallest vessels of the cat mesentery conform closely to Murray's law even though the flow in such vessels is not completely laminar.

Conductance and Resistance

The conductance of a full-flow set of vessels is proportional to Σr^4 . If the full-flow set is homogeneous, the conductance is proportional to nr^4 . Since nr^3 is constant (in an optimum system), nr^4 must be proportional to r . Hence, conductance is proportional to r for homogeneous, full-flow sets in a Murray system. Resistance (the reciprocal of conductance) is proportional to r^{-1} , which agrees with the long-established fact that the greatest part of the resistance of the arterial tree is in the smallest vessels.

Cross-sectional Area

The cross-sectional area of a full-flow set of vessels is proportional to Σr^2 . If the full-flow set is homogeneous, the cross-sectional area is proportional to nr^2 .

If nr^3 is constant, then nr^2 is proportional to r^{-1} . Therefore, the cross-sectional area is proportional to r^{-1} for homogeneous full-flow sets in a Murray system. For similarly shaped vessels (where length is proportional to r) the wall surface of a homogeneous, full-flow set is also proportional to r^{-1} . A Murray system therefore gives (as do actual vascular trees) much greater total surface areas in the small vessels (where transmural diffusion occurs) than in the large vessels.

Murray's law is therefore very useful in providing a functional relation between vessel radius and volume flow (αr^3), velocity of flow (αr), and vessel-wall shear stress (αr^0) for all vessels of an optimum system. Where vessels comprise homogeneous, full-flow sets, Murray's law also provides a functional relation between vessel radius and conductance (αr), resistance (αr^{-1}), and cross-sectional area (αr^{-1}). These relations can serve to predict, at least in an approximate manner, properties of a vascular system at all its various levels.

Murray's law also provides an interesting perspective on the scaling of vascular systems in animals growing or evolving to different sizes. If capillary densities and dimensions are to remain constant as an organ increases in size, the number of capillaries must increase linearly with the mass or volume of the organ. That is, the number of capillaries, n , must be proportional to L^3 , where L is the linear dimension of the organ. As an organ grows in size, its blood flow (increasing with L^2 to L^3) could be accommodated by increasing the radius of its parent artery to various degrees. There is only one increase, however, that will supply the organ at minimum cost: the increase that will keep the value of nr^3 for the parent artery equal to nr^3 for the capillaries it is supplying. Since the number of capillaries increases with L^3 and the capillary radius is assumed to remain constant, nr^3 for the capillaries increases with L^3 . The radius of the parent artery must then increase with L , so that nr^3 for the artery increases with L^3 and remains equal to that for the capillaries. Thus, minimum energy cost is maintained by having the artery grow in radius proportionally to the linear dimension of the organ. If the organ is growing at the same rate as the animal itself, the radius of the artery should increase with the linear dimension of the whole animal. The proportion of space occupied by the blood vessels need not change therefore as the animal grows larger. It is well known that blood volume (unlike bone volume) remains a fairly constant percentage of body volume as animals increase in size (Sjöstrand, 1962).

If minimum energy cost required any other than the inverse cubic relation between the radius and the number of arterial vessels (for example, a constancy of nr^2 or nr^4), then the radii of supplying arteries would have to vary with some power of L other than unity if optimum conditions were to be maintained. Conversely, if a group of various-sized animals (or one individual at different stages of its growth) was to maintain a linear relation between r and L , and the $nr^3 = K$ relation did not hold, then only one size or stage could maintain optimum energy conditions. The $nr^3 = K$ relation permits all sizes and stages to operate at minimum cost while maintaining a constant proportion between vessel and organ size.

The constructs of the human mind are no doubt always imperfect idealizations of nature, in physiology perhaps even more than in the purer realms of physics and chemistry. Poiseuille's law of flow is not obeyed by non-Newtonian fluids, or fluids in turbulence, or fluids in noncylindrical vessels, nor by red blood cells undergoing tank-track roller motion in small capillaries. Fick's law of diffusion requires amendment even in some very dilute nonliving molecular matrices (as in hyaluronic acid gels; see Ogston and Sherman [1961]), as well as in cellular barriers with selective pores and solubilities and active transport systems. But Poiseuille's law and Fick's law have been useful idealizations nevertheless. We may find that Murray's law has considerable utility as well.

Received for publication 3 January 1981.

REFERENCES

- BLUM, E. 1919. Die Querschnittsbeziehungen zwischen Stamm und Asten im Arteriensystem. *Pflugers Archiv Gesamte Physiol. Menschen Tiere.* **175**:1-19.
- CARO, C. G., T. J. PEDLEY, R. C. SCHROTER, and W. A. SEED. 1978. *The Mechanics of the Circulation.* Oxford University Press, Oxford.
- COHN, D. L. 1954. Optimal systems. I. The vascular system. *Bull. Math. Biophys.* **16**:59-74.
- COHN, D. L. 1955. Optimal systems. II. The vascular system. *Bull. Math. Biophys.* **17**:219-227.
- COMROE, J. H., JR. 1974. *Physiology of Respiration.* Year Book Medical Publishers, Inc., Chicago. 2nd ed. 78; 120.
- FAHRAEUS, R., and T. LINDQVIST. 1931. The viscosity of the blood in narrow capillary tubes. *Am. J. Physiol.* **96**:562-568.
- GREEN, H. D. 1944. Circulation: physical principles. In *Medical Physics.* O. Grasser, editor. Year Book Publishers, Chicago. 210.
- HAYNES, R. H. 1960. Physical basis of the dependence of blood viscosity on tube radius. *Am. J. Physiol.* **198**:1193-1200.
- HESS, W. R. 1917. Uber die periphere Regulierung der Blutzirkulation. *Pflugers Archiv Gesamte Physiol. Menschen Tiere.* **168**:439-490.
- HOOPER, G. 1977. Diameters of bronchi and asymmetrical divisions. *Respir. Physiol.* **31**:291-294.
- HORSFIELD, K. 1978. Morphometry of the small pulmonary arteries in man. *Circ. Res.* **42**:593-597.
- HORSFIELD, K., and G. CUMMING. 1967. Angles of branching and diameters of branches in the human bronchial tree. *Bull. Math. Biophys.* **29**:245-259.
- HORSFIELD, K., and G. CUMMING. 1968. Morphology of the bronchial tree in man. *J. Appl. Physiol.* **24**:373-383.
- HORTON, R. E. 1945. Erosional development of streams and their drainage basins: hydrophysical approach to quantitative morphology. *Bull. Geol. Soc. Am.* **56**:275-370.
- HUTCHINS, G. M., M. A. MINER, and J. K. BOITNOTT. 1976. Vessel calibre and branch-angle of human coronary artery branch points. *Circ. Res.* **38**:572-576.
- IBERALL, A. S. 1967. Anatomy and steady flow characteristics of the arterial system with an introduction to its pulsatile characteristics. *Math. Biosci.* **1**:375-395.
- KAMIYA, A., and T. TOGAWA. 1972. Optimal branching structure of the vascular tree. *Bull. Math. Biophys.* **34**:431-438.

- KAMIYA, A., T. TOGAWA, and A. YAMAMOTA. 1974. Theoretical relationship between the optimal models of the vascular tree. *Bull. Math. Biol.* **36**:311-326.
- KROGH, A. 1920. Studien über Tracheenrespiration. 2. Über Gasdiffusion in den Tracheen. *Pflugers Archiv Gesamte Physiol. Menschen Tiere.* **179**:95-112.
- KROGH, A. 1941. The Comparative Physiology of Respiratory Mechanisms. University of Pennsylvania Press, Philadelphia. 116-117.
- MALL, F. P. 1888. Die Blut und Lymphwege in Dunndarm des Hundes. Abhandlungen der Mathematisch-Physischen Classe der Königlich Sachsischen Gessellschaft der Wissenschaften **14**:151-200. (Mall's initials are incorrectly given as J. P. in the original article.)
- MALL, F. P. 1905-06. A study of the structural unit of the liver. *Am. J. Anat.* **5**:227-308.
- MCDONALD, D. A. 1974. Blood Flow in Arteries. Edward Arnold (Publishers) Ltd., London, 2nd ed.
- MILLER, W. S. 1893. The structure of the lung. *J. Morphol.* **8**:165-188.
- MILLER, W. S. 1937. The Lung. Baillière Tindall. London.
- MILSUM, J. H., and F. A. ROBERGE. 1973. Physiological regulation and control. In Foundations of Mathematical Biology. R. Rosen, editor. Academic Press, Inc., New York. Vol. 3, 74-84.
- MURRAY, C. D. 1926*a*. The physiological principle of minimum work. I. The vascular system and the cost of blood volume. *Proc. Natl. Acad. Sci. U. S. A.* **12**:207-214.
- MURRAY, C. D. 1926*b*. The physiological principle of minimum work applied to the angle of branching of arteries. *J. Gen. Physiol.* **9**:835-841.
- MURRAY, C. D. 1927. A relationship between circumference and weight in trees and its bearing on branching angles. *J. Gen. Physiol.* **10**:725-729.
- OGSTON, A. G., and T. F. SHERMAN. 1961. Effects of Hyaluronic acid upon diffusion of solutes and flow of solvent. *J. Physiol. (Lond.)*. **156**:67-74.
- PATEL, D. J., F. M. DE FREITAS, J. C. GREENFIELD, and D. L. FRY. 1963. Relationship of radius to pressure along the aorta in living dogs. *J. Appl. Physiol.* **18**:1111-1117.
- RASHEVSKY, N. 1960. Mathematical Biophysics. Physico-Mathematical Foundations of Biology, Dover Publications, New York. Vol. 2, 3rd ed. 292-305.
- RASHEVSKY, N. 1973. The principle of adequate design. In Foundations of Mathematical Biology, R. Rosen, editor. Academic Press, Inc. New York. Vol. 3. 158-167.
- RODBARD, S. 1975. Vascular caliber. *Cardiology.* **60**:4-49.
- ROSEN, R. 1967. Optimality Principles in Biology. Plenum Publishing Corp., New York. 40-52.
- SCHLEIER, J. 1919. Der Energieverbrauch in der Blutbahn. *Pflugers Archiv Gesamte Physiol. Menschen Tiere.* **173**:172-204.
- SCHMIDT-NIELSEN, K. 1979. Animal Physiology. Adaptation and Environment. Cambridge University Press, Cambridge. 2nd ed. 52.
- SINGHAL, S., R. HENDERSON, K. HORSFIELD, K. HARDING, and G. CUMMING. 1973. Morphometry of the human pulmonary arterial tree. *Circ. Res.* **33**:190-197.
- SJÖSTRAND, T. 1962. Blood volume. In *Handb. Physiol.* **1** (sect. 2):51-62.
- STRAHLER, A. N. 1953. Revisions of Horton's quantitative factors in erosional terrain. *Trans. Am. Geophys. Union.* **34**:345.
- STRAHLER, A. N. 1957. Quantitative analysis of watershed geomorphology. *Trans. Am. Geophys. Union.* **38**:913-920.
- SUWA, N., T. NIWA, H. FUKASUWA, and Y. SASAKI. 1963. Estimation of intravascular blood pressure gradient by mathematical analysis of arterial casts. *Tohoku J. Exp. Med.* **79**:168-198.
- THOMPSON, D. W. 1942. On Growth and Form. Cambridge University Press, Cambridge. 2nd ed. 948-957.

- UYLINGS, H. B. M. 1977. Optimization of diameters and bifurcation angles in lung and vascular tree structures. *Bull. Math. Biol.* **39**:509-519.
- WEIBEL, E. R. 1963. *Morphometry of the Human Lung*. Academic Press, Inc., New York.
- WEIBEL, E. R. 1964. Morphometrics of the lung. *Handb. Physiology* 1(sect. 3):285-307.
- WEIBEL, E. R., and D. M. GOMEZ. 1962. Architecture of the human lung. *Science (Wash. D. C.)*. **137**:577-582.
- WEST, J. B. 1979. *Respiratory Physiology—The Essentials*. Williams and Wilkins, Baltimore, 2nd ed. p. 6.
- WILSON, T. A. 1967. Design of the bronchial tree. *Nature (Lond.)*. **213**:668-669.
- YOUNG, T. 1809. On the functions of the heart and arteries. *Philos. Trans. Royal Soc. Lond.* 1-31.
- ZAMIR, M. 1976 *a*. Optimality principles in arterial branching. *J. Theor. Biol.* **62**:227-251.
- ZAMIR, M. 1976 *b*. The role of shear forces in arterial branching. *J. Gen. Physiol.* **67**:213-222.
- ZAMIR, M. 1977. Shear forces and blood vessel radii in the cardiovascular system. *J. Gen. Physiol.* **69**:449-461.
- ZAMIR, M. 1978. Nonsymmetrical bifurcations in arterial branching. *J. Gen. Physiol.* **72**:837-845.
- ZWEIFACH, B. W. 1974. Quantitative studies of microcirculatory structure and function. I. Analysis of pressure distribution in the terminal vascular bed in cat mesentery. *Circ. Res.* **34**: 843-857.