Handbook of Physiology

a critical, comprehensive presentation of physiological knowledge and concepts

SECTION 2:

The Cardiovascular System

Formerly SECTION 2: Circulation

VOLUME IV.
MICROCIRCULATION, PART 1

Volume Editors: *EUGENE M. RENKIN*
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Preface

Three hundred and fifty years ago, the microcirculation was a hypothesis, a necessary link between the arteries and veins in Harvey's theory of the circulation of the blood. Although capillaries were observed by Malpighi three years after Harvey's death, two centuries elapsed before the cellular nature of the capillary wall was conclusively demonstrated. Since the middle of the nineteenth century, knowledge of the structure and function of small blood vessels has steadily increased, and the pioneering work of Müller, Poiseuille, Ludwig, Cohnheim, Starling, and Krogh has been sustained and developed by their many notable successors.

Although hemodynamics and transport in the minute blood vessels have always been recognized as topics of major importance, it is only recently that large numbers of investigators have been attracted to work on the microcirculation. Since publication of the first edition of the *Handbook of Physiology* on circulation more than twenty years ago, societies and journals dedicated to the microcirculation have proliferated, and the subject has become one of the most active and challenging areas of cardiovascular research.

Modern study of the microcirculation is an interdisciplinary exercise. It has long been a field where physical principles have been broadly and fruitfully applied, and at times the search for physical explanations of observed phenomena has led to the discovery of new physical relationships. For example, Poiseuille discovered a law that forms the basis of our understanding not only of microvascular flow but also of transport through porous membranes such as the capillary wall. Until twenty years ago, physical principles had been successfully applied to the microcirculation by only a few outstanding physiologists. In the mid-1960s, however, an influx of engineers and mathematically inclined biologists imparted a strong biophysical character to the field. This did much to enhance theoretical developments, particularly in the areas of rheology and transport. Somewhat earlier, electron microscopists had turned their attention to the microcirculation, and their contributions continue to increase. The early advances are admirably described by Majno in volume III of the first edition of the *Handbook* on circulation, but subsequent developments have drastically altered our ideas about the relationships between structure and function. Most recently there has been an upsurge of interest in the cellular biology of endothelium, and this promises to be one of the most important stimuli for further advancement.

Preparation of this edition of the *Handbook of Physiology* on the cardiovascular system has provided an opportunity for consolidation of essential concepts and new developments of microvascular physiology. Each chapter introduces the scope and principles of the topic it describes and offers to more experienced investigators a critical assessment of the status of current ideas and techniques. It is also hoped that this volume will help cardiovascular physiologists to correlate phenomena at the macrocirculatory and microcirculatory levels.

The volume begins with a historical review of the contributions of Poiseuille to our understanding of microvascular flow. This is followed by two chapters on the structure of the microcirculation, a chapter on endothelial cell biology, and one on microvascular growth and adaptation. The next two chapters are devoted to microcirculatory dynamics of blood and lymph. Six chapters on material transport in and around the microcirculation cover the mechanics and thermodynamics of transport, movement of fluid, movements of small solutes and of macromolecules, transport in the interstitium, and transport modeling. A chapter on control of the microcirculation and exchange forms a bridge between these chapters and the rest of the volume. The next eight chapters describe microcirculation and exchange in selected organs and organ systems: liver and spleen, heart, gastrointestinal system, lungs, synovial joints, adipose tissue, brain, and eye. Finally there are chapters on capillary portal circulations and on disseminated intravascular coagulation. We have not covered all the topics that might have been included, nor have we covered certain topics to the extent that some readers and authors might desire. However, this volume is larger than we originally expected, and an end had to be made somewhere.

We are grateful to the many contributors to this volume for their time and effort.

EUGENE M. RENKIN
C. CHARLES MICHEL

Contents

Part 1

Part 2

Contributions to microvascular research of Jean Léonard Marie Poiseuille

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CHAPTER CONTENTS

POISEUILLE'S LAW of viscous flow through cylindrical tubes is included in almost every introductory course in physics or medical physiology, but few scientists are aware of the meticulous experimental measurements that underlie the basic law and its application to hydrodynamics, physical chemistry, regulation of circulation, and capillary permeability. Nor is it generally known that Poiseuille was the first to use a mercury manometer for the measurement of blood pressure, to describe axial flow of red cells in the microcirculation, and to measure and correctly interpret the changes in central venous pressure that occur during breathing. These fundamental contributions to the physiology of the peripheral circulation were made between 1828 and 1841, and Poiseuille may well be considered the first major contributor to the modern field of microvascular research. It seems appropriate to introduce this *Handbook* volume on microcirculation with a historical essay bringing some of the most interesting and significant aspects of Poiseuille's work to the attention of contemporary students of the cardiovascular system.

Jean Léonard Marie Poiseuille (Fig. 1) was born in Paris on April 22, 1797; he was the son of Jean Baptiste Poiseuille, a carpenter, and Anne Victoire Caumont. Little is known of Poiseuille's personal life or even of his professional career. From 1815 to 1816 he studied at the École Polytechnique, where he presumably trained as an engineer. Subsequently he transferred to medicine, but we are ignorant of the reasons that led him to study medicine and experimental physiology. His doctoral thesis on arterial pressure (see Fig. 2) was a landmark in the history of cardiovascular physiology, and from then until 1868 Poiseuille continued to publish original work. Much of his work was conducted on animals, including horses and dogs as well as fish and Amphibia. However, we do not know where the work was done or what position, if any, he held at the university. The apparatus he constructed for experimental work was elaborate and expensive (see Fig. 4), and his work on large animals must have required considerable space and technical assistance. There are no records, however, that reveal the source of his financial support. According to Joly (18), Poiseuille maintained interests in medicine, particularly in diseases of the lung. Sachaile's book of 1845, *The Physicians of Paris* (42), lists Poiseuille's office hours as 7–10, but a note dated 1867 in Poiseuille's dossier at the department of primary schools states that he did not practice medicine after 1844. The question remains, therefore, as to how Poiseuille could afford to pursue his elaborate, expensive, and time-consuming research. In 1829 he married the daughter of M. Panay de Lorette, Chief Engineer of Roads and Bridges, and it may be that this alliance made it possible for Poiseuille to devote so much time to experimental work.

Poiseuille presented most of his work in the form of oral communications to the Academy of Sciences, followed by summaries in the Academy's *Comptes Rendus*. He presented the laws of flow through cylindrical tubes in three such communications during the winter of 1840–1841 and was awarded many prizes for both his physiological and physical studies. In 1842 he was elected to the Academy of Medicine, and he was also an active member of the Société Philomatique. Yet despite public acclaim for his work on hydrodynamics and the esteem with which Magendie and other noted physiologists regarded Poiseuille's physiological studies, he was never elected to the Academy of Sciences.

FIG. 1. Jean Léonard Marie Poiseuille (1797–1869). Original of this photograph is in the library of the Academy of Medicine in Paris and has been reproduced previously (4, 18). A drawing based on this photograph graces the Poiseuille Gold Medal Award of the International Biorheological Society (6, 7).

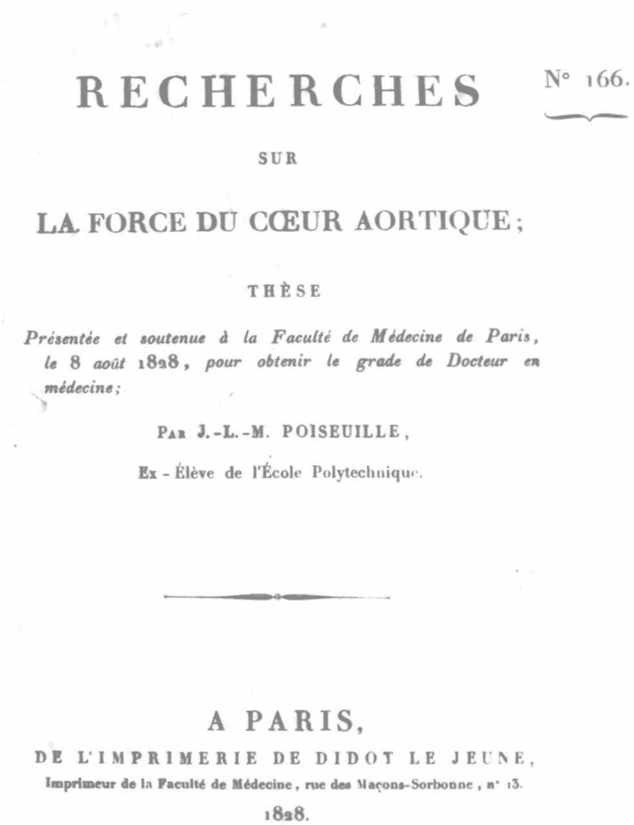
Poiseuille's most important contributions may be considered under four main headings.

1. 1828: Mercury manometer and measurement of pressure in the arteries (*Recherches sur la force du coeur aortique*).
2. 1830: Pressures and flows in the venous system (Les causes du mouvement du sang dans les veines).
3. 1833–1835: Microcirculation (Les causes du mouvement du sang dans les vaisseaux capillaires).
4. 1840–1846: Poiseuille's law (Le mouvement des liquides dans les tubes de très-petits diamètres).

RECHERCHES SUR LA FORCE DU COEUR AORTIQUE

In 1733 Hales published his famous *Essay on Hemastaticks* (14) in which he described the first measurements of arterial blood pressure. Considering the importance of these measurements, it may seem surprising that no further observations of blood pressure were made until Poiseuille took up the problem almost 100 years later. However, as Poiseuille points out in his thesis, the methods used by Hales were not suited to systematic investigations. In Hales's experiments the carotid arteries of horses and dogs were cannulated with brass pipes, the free ends of which were connected by flexible tubing (the trachea of a goose) to a vertical glass tube. It took time and loss of blood to fill the glass tube, and the blood clotted before systematic studies could be made in any one animal. Moreover there were large oscillations in the level of blood in the tube because of the respiratory movements of the struggling animals.

Poiseuille devised the U-tube mercury manometer to avoid dealing with a column of blood 10–12 ft high. He solved the clotting problem by using saturated $NaHCO_3$ to connect the artery with the mercury; presumably the carbonate precipitated the Ca^{2+} in blood, thus preventing coagulation. The U-tube mercury manometer is taken for granted by physiologists today, but the physical principles involved were by no means obvious to Poiseuille's contemporaries. He had to explain the physics of the instrument, including corrections for the varying column of bicarbonate-blood mixture in one limb of the U tube, the effects of



RECHERCHES N° 166.

SUR

LA FORCE DU CŒUR AORTIQUE;

THÈSE

Présentée et soutenue à la Faculté de Médecine de Paris, le 8 août 1828, pour obtenir le grade de Docteur en médecine;

PAR J.-L.-M. POISEUILLE,

Ex-Élève de l'École Polytechnique.

A PARIS,

DE L'IMPRIMERIE DE DIDOT LE JEUNE,

Imprimeur de la Faculté de Médecine, rue des Maçons-Sorbonne, n° 13.

1828.

FIG. 2. Title page of Poiseuille's doctoral thesis containing the first description of the mercury manometer and its application to the measurement of pressure in large and small arteries. [From Poiseuille (28).]

temperature on the density of mercury, the effects of slight inequalities in the diameters of the two limbs of the U tube, and the importance of maintaining the manometer in a vertical position. Poiseuille called his instrument the hemodynamometer, but it must be said that he failed to consider its dynamic properties and some of his reported oscillatory pressures must have reflected the inertial characteristics of the system. Addition of a float and recording stylus to the Poiseuille mercury manometer was first described by Ludwig in 1847 (22), and a detailed description of the recording hemodynamometer, with full credit to Poiseuille, is given in the 1861 edition of Ludwig's textbook (23). In the ensuing 100 years, until the 1960s, the Poiseuille-Ludwig hemodynamometer was used by hundreds of thousands of medical students and scientists. In recent years, however, the mercury manometer has been largely replaced by the electrical strain gauge even in the teaching laboratory. Today's students, adjusting the sensitivity of electrical pressure transducers, are unlikely to appreciate, as did Poiseuille, the physical meaning of force per unit area.

Poiseuille first used his hemodynamometer to investigate pressure gradients in the arterial circulation. It seemed obvious a priori that the pressure of blood would diminish with distance from the heart. However, Poiseuille's very first experiments to test this hypothesis (ref. 28, p. 23) "showed, to our astonishment, that two tubes (hemodynamometers) applied simultaneously to two arteries at different distances from the heart gave perfectly equal readings." Thus the average of nine successive readings of mean pressure in the carotid artery of an unanesthetized horse was 146.7 mmHg, whereas the mean pressure measured simultaneously in a small artery of the leg was also 146.7 mmHg. Yet the cross-sectional area of the leg artery was only 1/50 that of the carotid. Similarly precise comparisons were made between the mean pressures in many different arteries in dogs and horses, leading Poiseuille to generalize that *the mean pressure of blood is the same throughout the arterial system.*

Where, then, was the pressure drop in the circulation? In order to investigate this problem Poiseuille turned first to a study of pressures in the venous system and subsequently to a study of the microcirculation.

RECHERCHES SUR LES CAUSES DU MOUVEMENT DU SANG DANS LES VEINES

Hales (14) had already measured positive pressures in the external jugular veins of horses, sheep, and dogs, but Poiseuille was the first to insert tubes from the external jugular into the chest and so to record negative pressures with his U-tube manometers. For quiet breathing he found pressures ranging from −8 cmH_2O (saturated $NaHCO_3$ anticoagulant) during inspiration to −1.4 cmH_2O during expiration. When respiratory efforts were intensified, pressures ranged from −25 cmH_2O to +20 cmH_2O. In contrast, pressures measured in the abdominal vena cava or in peripheral veins were always positive and there were no respiratory fluctuations at locations protected from reflux of blood by valves. When the chest was opened and the lungs were artificially ventilated, pressures in the thoracic veins were always positive with respect to atmosphere.

Although these facts seem elementary and obvious today, it must be remembered that many of Poiseuille's contemporaries thought that blood was normally aspirated into the heart by suction caused by inspiratory muscles or by dilatation of the heart itself (3). Poiseuille established beyond doubt that the respiratory pump is only an accessory aid to venous return of blood and that the primary and most important force is the arterial pressure driving blood through the capillaries to the veins and heart. The above pioneer measurements and Poiseuille's clear interpretation of their significance were communicated to the Academy on September 27, 1830, and they were subsequently published in detail (29).

RECHERCHES SUR LES CAUSES DU MOUVEMENT DU SANG DANS LES VAISSEAUX CAPILLAIRES[1]

Under the conditions of Poiseuille's experiments the mean blood pressure in the arterial tree from the aorta to vessels 2 mm in diameter was about 150 mmHg, whereas peripheral venous pressures were only 5–10 mmHg. Thus the main pressure drop occurs in small blood vessels. Although Poiseuille did not state this explicitly, one may surmise that this conclusion led him to a study of the microcirculation. To this end he made microscopic observations of arterioles, capillaries, and venules in fish, amphibians, reptiles, birds, and small mammals. It was during the course of this work that Poiseuille noted the axial velocity gradient of red cells in arterioles and venules. He writes (30):

> at the center the speed is at its maximum; it diminishes as one approaches the walls: very near the walls one can distinguish a transparent space which is ordinarily occupied only by serum; this space has a width of about 1/8th to 1/10th that of the diameter of the vessel.

Poiseuille gives credit to Haller and to Spallanzini for prior descriptions of the clear layer of plasma at the walls of small blood vessels, but unlike Poiseuille, neither of his two distinguished predecessors under-

[1] The original paper of this title was communicated to the Academy of Sciences on December 28, 1835, but it was not published in detail in *Memoires des Savants Étrangers* (30) until 1841. The Section on Medicine and Surgery of the Academy awarded Poiseuille an emolument of 700 francs for this work.

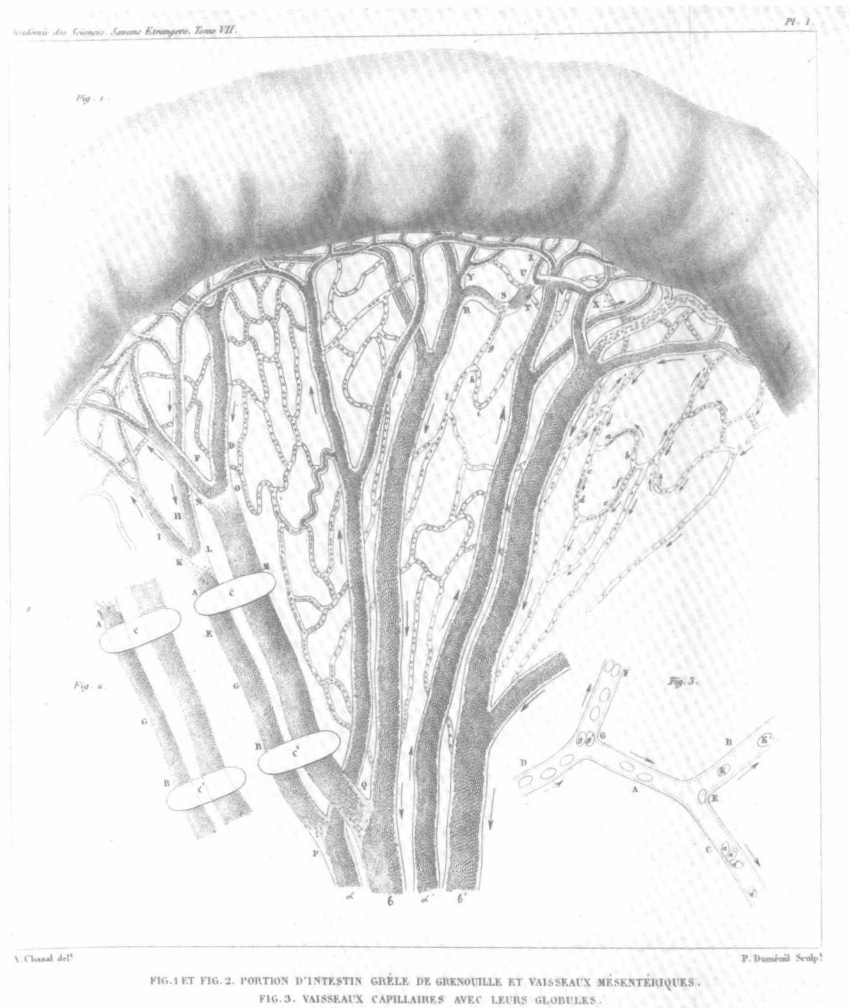


FIG. 3. Poiseuille's illustration of the microcirculation in frog mesentery. The *couche claire*, or plasma layer, is clearly seen at the walls of arterioles and venules. Occlusion of vessels by platinum weights at c and c′ prevented flow-dependent axial concentration of red cells. *Inset at right,* plasma skimming at branching junctions of arterioles and capillaries. [From Poiseuille (30).]

stood that this was a manifestation of an axial velocity gradient.

Figure 3 reproduces Poiseuille's illustration of the microcirculation in the mesentery of a frog. The clear layer of plasma is shown in pairs of arterioles and venules. Platinum weights were placed on a pair of vessels, and it is apparent that the plasma layer disappeared in the absence of flow. Plasma skimming at branching junctions of arterioles and capillaries is shown clearly in the inset at the right. The tendency of white cells to stick to the walls in the stagnant layer is also described in Poiseuille's paper (30).

Poiseuille subsequently performed an ingenious experiment to show that there is a sleeve of stagnant fluid at the walls during the flow of pure liquids through glass tubes (4). For this purpose he coated the walls of a glass tube with a thin layer of rough varnish and then measured the hydrodynamic resistance to flow of water through the tube. The rough coat of varnish was then polished by gentle heating but the resistance to flow was unaltered within the accuracy of measurement (better than 0.1%). This led to the conclusion that, in general, fluids flow on a thin, immobile layer of fluid at the walls of the tube.

Poiseuille's observations on axial flow of blood in arterioles and venules were of seminal importance to the field of hemorheology, being the forerunner of such classic contributions as those of Hess (16), Krogh (19), Fåhraeus and Lindqvist (9), and Whittaker and Winton (43). Modern hemorheology (see the chapter by Chien et al. in this *Handbook*) has its roots in this pioneer paper of 1841. Nevertheless Poiseuille's observations of the microcirculation failed to reveal the site of the main resistance to flow in the circulation, and it was not until the direct micropuncture studies of Landis (20, 21) that the main pressure drop was localized and attributed to the arterioles. Yet it was Poiseuille's failure to solve the problem in vivo that led him to study the flow of liquids in glass tubes of dimensions approximating those of blood vessels in the microcirculation.

RECHERCHES SUR LE MOUVEMENT DES LIQUIDES DANS LES TUBES DE TRÈS-PETITS DIAMÈTRES

The hydraulic engineers can perhaps afford to neglect the flow of liquids through tubes of small diameter but

> this is not true of the physiologists who have to consider the passage of liquids through tubes of about 0.01 mm in diameter.

With these words Poiseuille introduced his first paper on the laws of viscous flow to the French Academy of Sciences in 1840. During 1840–1841 he communicated four papers on this subject to the Academy. The first dealt with the flow of water through glass tubes as a function of pressures of up to 8 atm, and subsequent papers considered the effects on flow of tube length, tube diameter, and temperature. Each of these communications was published in the form of a short paper in the *Comptes Rendus de l'Académie des Sciences*, but for purposes of assigning priority it is important to note that they were deposited in a sealed packet with the Academy in 1839 and that preliminary results on the effects of pressure and of tube length had been reported orally to the Société Philomatique as early as 1838 (31). Full experimental details were not reported in communications to the Academy, but the stated results were considered so important that the Academy appointed a commission to investigate the validity of Poiseuille's claims. The commission members met during 1842 and actually repeated some of Poiseuille's experiments by using his basic apparatus fitted with different tubes. In 1843 they published their report in *Annales de Chimie et Physique* (5), fully confirming Poiseuille's claims: "en conséquence la Commission a l'honneur de proposer a l'Académie de donner son approbation au travail du M. Poiseuille et d'ordonner que son Mémoir soit inserrée parmi ceux des Savants Étrangers." Publication in extenso finally occurred in 1846 (35). It is indeed interesting that full publication of Poiseuille's great work should have been delayed in this way for several years until an elite committee of the Academy could approve the work.[2]

Poiseuille established his law of flow within a standard error of 0.1% in glass tubes ranging from 0.65 to 0.013 mm in diameter and over a pressure range of a few millimeters of water to 8 atm. This required meticulous experimental techniques and the wit to identify and incorporate a great many second-order correction factors. Indeed the historical interest in this phase of Poiseuille's work resides as much in contemplation of his exemplary experimental measurements as in his enunciation of Poiseuille's law, especially since the latter can be derived theoretically from first principles as was first done by Hagenbach in 1860 (13). In the words of Millikan (24), Poiseuille's papers of 1840–1846 "constitute one of the classics of experimental science. They are frequently quoted as a model of careful analysis of sources of error and painstaking investigation of the effects of separate variables."

The apparatus utilized by Poiseuille is shown in Figure 4. The heart of the apparatus, the viscometer bulb and tubing, are barely visible within the water bath CDEF and are therefore shown separately in Figure 5. The viscometer bulb and related "protective" gadgetry are connected via stopcock and four-way junction to a force pump capable of generating 10 atm of air pressure, a 60-liter buffer air reservoir capable of withstanding 20 atm of pressure, and mercury or water manometers via lead tubing. All scales and menisci were equipped with either optical magnifiers and/or vernier scales. The first 27 pages of the 1844 treatise are devoted mainly to the second-order corrections that eventually gave an accuracy of better than 0.2% in the prediction of flow rates as a function of pressure drop, tube dimensions, and temperature. Some of these factors are described briefly here.

Variations in Tube Diameter and Ellipticity

Since flow rate turned out to be a function of the fourth power of tube diameter, it was necessary to determine dimensions with great accuracy. Hundreds of tubes were examined and discarded in search of those having unusually uniform dimensions. Dimensions were measured both optically and from the weight of mercury as a function of length along the tube. After measurements of flow were completed on selected tubes, the tubes were sectioned, the ends ground flat, and the diameters of the hole in each section measured at high magnification to the nearest 0.5 μm. For example, in a tube of length 4.9375 cm, the maximum and minimum diameters at one end of the tube were listed as 0.01145 and 0.01125 cm; at the opposite end the diameters were 0.01142 and 0.01122 cm.

Similarly, precise measurements were made on many tubes of different lengths and diameters. To correct for ellipticity Poiseuille assumed that the equivalent tube radius would be that of a circle of cross-sectional area equal to the area of the measured ellipse, which in the above example is not significantly different from the algebraic mean of 0.01135 cm at the large end and 0.01132 cm at the small end of the tube. The equivalent radius was then taken as 0.011335 cm for this tube. This method of correcting for ellipticity and for changes in diameter with length is theoretically incorrect (see ref. 1 for laws of flow through elliptical tubes), but it sufficed to yield values for viscosity of water that did not vary by more than 0.15% over a wide range of tube sizes.

Temperature

Poiseuille determined the viscosity of water at temperatures ranging from 0°C–45°C, but most of his measurements were carried out at 10°C. At this temperature, viscosity varies 2.8%/°C, and in order to

[2] An earlier preprint of this paper was published in its entirety in 1844. The origin of this preprint is unknown, but it appears to be identical with the official 1846 edition except for the title page and the pagination. The 1846 edition is generally cited (see refs. 1, 2, 21), but Poiseuille himself in 1868 (39) refers to pagination of the 1844 preprint. A copy of this rare preprint is available in the rare books collection of the Health Sciences Library of the College of Physicians and Surgeons, Columbia University, New York.

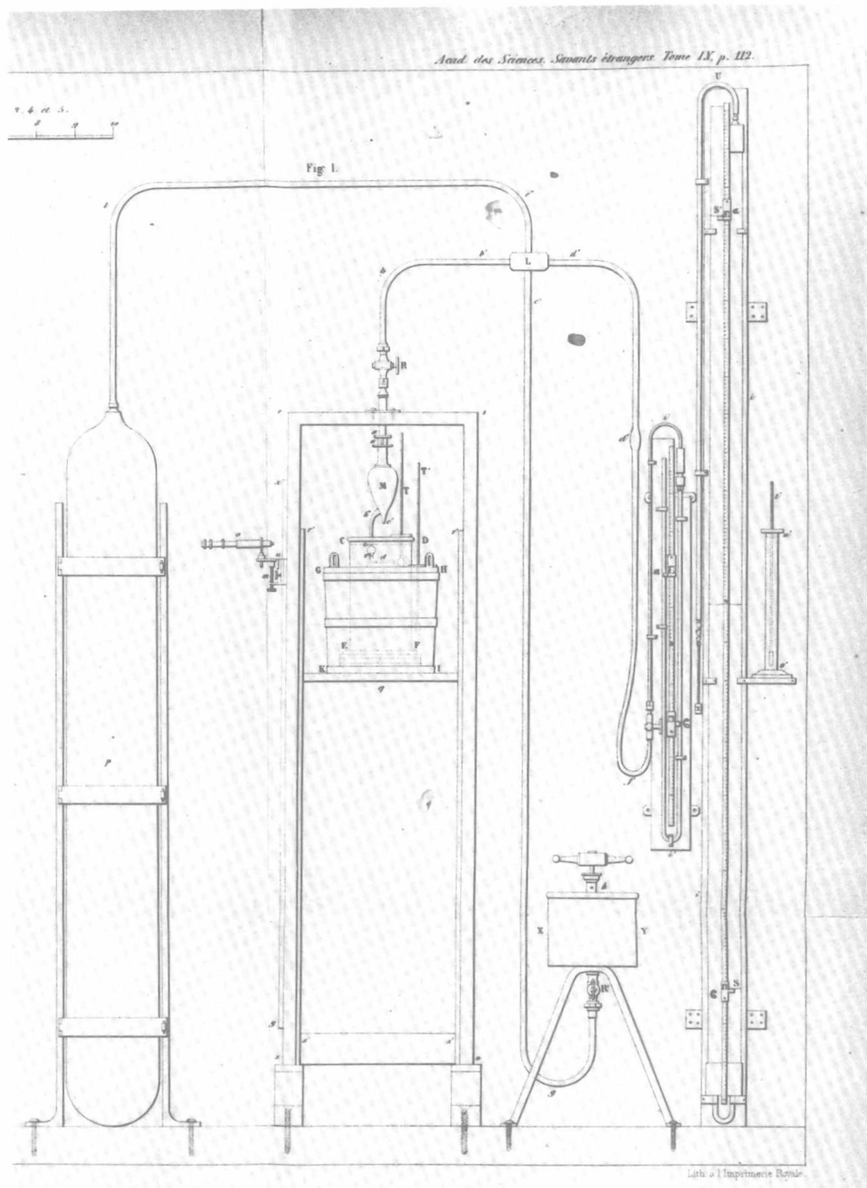


FIG. 4. Poiseuille's apparatus for measuring flow in glass capillary tubes as a function of pressure and temperature. The viscometer itself is barely visible in the water bath (CDEF) and so is shown separately in Fig. 5. The viscometer is connected via a particle separator (M) and stopcock (R) to a 4-way joint (L) leading to *1*) a force pump (XY) capable of generating 10 atm air pressure, *2*) a 60-liter buffer air reservoir (P) capable of withstanding 20 atm, and *3*) mercury or water manometers [via lead tubing (df)]. [From Plate I of Poiseuille's 1844 treatise (35).]

achieve consistency of results within 0.2% it was therefore necessary to set and control the temperature of the flow system within 0.1°C. This level of accuracy must have been exceedingly difficult to achieve in 1840 without the benefit of electrical methods for heating, cooling, stirring, and automatic thermostating. Poiseuille does not explain how he was able to cool and maintain the water bath at 10°C ± 0.05°C; he merely states that he took care to measure the temperature within 0.05°C and to make second-order corrections for temperature variations. These corrections included the temperature coefficient of expansion of glass. In one case the measured volume of the glass viscometer bulb changed from 13.341 ml at 10°C to 13.472 ml at 45°C, thus necessitating a 1% correction in calculating rate of flow. At the same time the diameter of the flow tube (also calculated from the coefficient of expansion of glass) changed from 0.1411 mm at 10°C to 0.1412 mm at 45°C, and a 0.3% correction was used in accordance with the fourth-power law. Other second-order temperature corrections were made to take into account changes in temperature (and hence density) of the water and/or mercury columns in the manometers.

Pressure

Second-order corrections to the pressures indicated by the U-tube manometers included *1*) the height of the column of liquid in the measuring bulb, which diminished from the top to the bottom meniscus during the course of the experiment; *2*) the pressure of water at the outflow orifice relative to that in the manometer; *3*) the capillarity (surface tension) in the

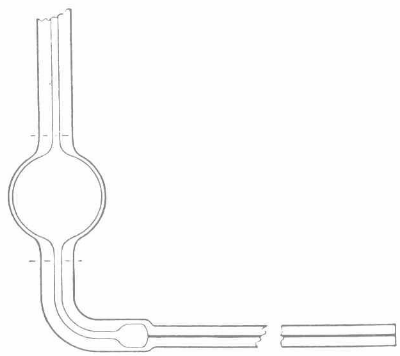


FIG. 5. Poiseuille viscometer. Poiseuille found that he could not obtain consistent flow measurements through small tubes if the efflux emerged to air. Consequently he submerged the entire bulb and flow tube in a water bath (CDEF, Fig. 4) and measured flow rate from the time taken to empty the bulb in the manner shown. Volume of each bulb was determined by weight of mercury, and corrections were made for varying counterpressures due to surface tension at bulb walls and for temperature effects on bulb volume and diameter of capillary tubing. [From Barr (1).]

capillaries of the measuring bulb and at the walls of the bulb itself (the latter correction was complex because of the changing diameter of the liquid surface within the bulb during the course of each experiment); and *4*) the differences in weight of air (atmospheric pressure) at the surface of each limb of the U-tube manometers, taking into account the change in density of air in the high-pressure limb of the manometer. It may seem surprising that the variation of barometric pressure with altitude is sufficient to have a significant effect on the determination of pressure in a simple vertical U-tube manometer, yet such is the case. The correction at an indicated pressure difference (column height) of 2019.6 mmH_2O was −2.9 mmH_2O in one example described by Poiseuille. At higher pressures, when mercury is used instead of water, this interesting correction is negligible.

The numerical examples here provide some insight into the meticulous, quantitative thinking underlying the experimental work leading to the discovery of Poiseuille's law. The law was stated explicitly by Poiseuille in the following equation

$$Q = K \frac{\Delta P \times D^4}{L} \quad (1)$$

where ΔP is the pressure difference (mmHg at 10°C), D is the mean equivalent diameter of the tube (mm), L is the length (mm), and Q is the volume flow rate (mm^3/500 s).

The K in Equation 1 is proportional to what is now defined as fluidity, or the reciprocal of viscosity. However, the units that Poiseuille used to calculate K are not readily converted to cgs units. I have therefore carried out the conversion shown in Table 1, utilizing the original data for pressure, flow, and tube dimensions for each of the seven tubes described in chapter III, p. 513–520 of the 1846 treatise (35). More complete tables based on Poiseuille's data from 40 different tubes (or segments of the tubes listed in Table 1) are available in appendix D of Bingham's monograph (2). The standard error for viscosity of water calculated from the data on each of the seven tubes was only 0.053% of the mean, despite the fact that the ratio of the fourth power of the tube radii varied by almost 5,000,000 and hydrodynamic resistance varied by almost 250,000-fold. Indeed one must pay tribute to Poiseuille's experimental skill and the refinement of his correction factors.

TABLE 1. *Viscosity of Water Calculated From Poiseuille's Original Data*

Tube	Radius, cm × 10^3	Length, cm	Flow Resistance*, $dyn \cdot s \cdot cm^{-5}$	Viscosity†, $dyn \cdot s \cdot cm^{-2}$ (P)
F	32.608	38.383	1.132	0.01309
A	7.080	5.110	67.872	0.01311
B	5.670	2.357	76.015	0.01309
C	4.275	2.440	2.435×10^2	0.01309
D	2.187	2.517	3.671×10^3	0.01309
E	1.469	2.310	16.352×10^3	0.01309
M	0.697	1.850	26.056×10^4	0.01305
Mean				0.013087
SD				0.000018
SE				0.000007

Original data converted to cgs units assuming that 1 mmHg at 10°C in Paris = 1,331 dyn/cm^{-2}. * Flow resistance = $\Delta P/Q \times 10^6$. † Viscosity calculated from $\eta = \pi r^4 \Delta P / 8QL$. Units $dyn \cdot s \cdot cm^{-2}$ are poises (P). [From Poiseuille's 1844 treatise (35).]

Poiseuille determined the variation of fluidity as a function of temperature with equal refinement, obtaining the relationship

$$K = 1836.7\ (1 + 0.033681T + 0.00221T^2) \quad (2)$$

The absolute value of viscosity of water at 10°C (calculated as in Table 1 from the mean of seven tubes) was 0.013087 ± 0.000007 $dyn \cdot s \cdot cm^{-2}$. This value is within 0.1% of the value based on the work of Bingham (2) and given in the *Handbook of Chemistry and Physics* (15).

The calculations of viscosity summarized in Table 1 do not include corrections for the pressure required to accelerate fluid down the tubes (kinetic energy corrections); indeed Poiseuille did not take accelerative forces into account. Nevertheless he did note the related fact that in any given tube there was a critical length below which there were increasing deviations from his law, and he found that this critical length was related in some unspecified way to increasing tube diameter. For this reason he only used tubes that were longer than the critical length, and the data of Table 1 show no indication of systematic errors that could be accounted for by kinetic energy corrections.

Poiseuille formulated Equation 1 to fit his copious and accurate experimental data, but he was an experimental scientist rather than a theoretician and failed to understand the fundamental physics of his system. It was not until 1860 that E. Hagenbach (13) derived Poiseuille's law from first principles by using Newton's definition of viscosity and elementary calculus. Hagenbach derived the flow equation in the form it is seen today, and he generously suggested that the equation be named after Poiseuille "wir werden die obigen Formel die Poiseuille'schen Formel nennen." It is evident from Hagenbach's paper that he had studied Poiseuille's work in detail and indeed he utilized the latter's data to calculate the coefficient of fluidity or reciprocal viscosity (*Zähigkeit*) from his theoretically derived equation. Since Poiseuille was still alive and active at the time of Hagenbach's publication, it seems strange that no correspondence or records exist to indicate that Poiseuille acknowledged Hagenbach's important theoretical contribution with its generous and laudatory treatment of Poiseuille's own work.

In 1875 Ostwald (25) questioned the propriety of naming the flow law after Poiseuille on the grounds that a German physicist, G. Hagen, published a similar law prior to Poiseuille. It is true that Hagen published an empirical law of flow through tubes in 1839 (12). The metal tubes used by Hagen were shorter and had larger diameters than the glass capillaries used by Poiseuille. Consequently the kinetic energy term, proportional to the square of flow velocity, was important and Hagen clearly recognized this factor in stating that

$$P = k_1Q + k_2Q^2 \tag{3}$$

where P is pressure and Q is volume flow rate.

Hagen showed that k_2 (the kinetic energy component) depends on density but not directly on temperature, whereas k_1 (proportional to what is now defined as viscosity) is very sensitive to temperature. The measurements made by Hagen on three tubes were not comparable to those of Poiseuille in terms of precision or range of pressures, flows, and tube dimensions. Moreover Ostwald (25) was in error when he stated that Poiseuille first published his law of flow in 1843. Ostwald had cited the 1843 report (5) of the committee assigned to evaluate Poiseuille's published communications to the Academy of 1840–1841, but in fact Poiseuille first reported his results to the Société Philomatique in 1838 (31) as has already been noted. There seems very little justification, therefore, for the insistence of Ostwald (25) and later by Prandtl and Tietjens (40) that the law of flow should be renamed for Hagen. It is strange, nevertheless, that neither Poiseuille nor the select committee of the Academy ever referred to Hagen's paper (12), which was published in the principal German journal of physics and chemistry.

In addition to extensive measurements of the fluidity of pure water, Poiseuille carried out some interesting and important experiments on solutions, including electrolytes (24) and alcohol (33, 35). The latter measurements are of particular interest to physical chemists because they clearly distinguished density and surface tension from viscosity, and they foreshadowed fundamental discoveries of the relationship between viscosity and intermolecular forces in solution. Poiseuille found that pure alcohol, despite its low density and surface tension, was actually more viscous than pure water. Yet addition of water to alcohol increased the viscosity still further until it reached a maximum at an alcohol concentration of about 45% (w/w). This value was more than 3 times greater than that of pure water. To anyone who has watched sherry drain slowly down the side of a glass, this observation may not be surprising; a priori one might suppose, however, that viscosity would be related to density or surface tension. Certainly the discovery of a maximum viscosity in a binary mixture more than threefold that of either of the pure components was a remarkable and unexpected one.

Poiseuille was led to his precise measurements of the flow of liquids through capillary tubes because of his interest in factors controlling the flow of blood in the living microcirculation; yet the extreme accuracy of his measurements in vitro was quite unnecessary. The non-Newtonian behavior of whole blood and the geometrical complexity of branching vessels in the microcirculation introduce factors that render Poiseuille's law inapplicable except as a first approximation and a valuable teaching aid. Nonetheless the quantitative features of Poiseuille's research eventually found important application to microcirculatory physiology, namely to the measurement of capillary permeability.

CHARACTERIZATION OF MEMBRANE PERMEABILITY BY HYDRODYNAMIC FLOW (POISEUILLE'S LAW) AND DIFFUSION (FICK'S LAW)

Proportionality between flow rate, pressure drop, and fluidity (reciprocal viscosity) is characteristic of flow through porous media, including artificial or biological membranes containing aqueous channels of ultramicroscopic dimensions. As early as 1872 Guérot (11) proposed that the flow permeability of membranes might be characterized in terms of an "equivalent" membrane containing homogeneous cylindrical pores of diameter and number giving a hydrodynamic resistance corresponding to that defined by Poiseuille's law. Thus any membrane having a measurable hydrostatic or osmotic flow per unit pressure drop could be defined in terms of an equivalent membrane having N cylindrical pores of radius r and length Δx (thickness of membrane)

$$\frac{Q}{\Delta P} = \frac{N\pi r^4}{8\eta\Delta x} = \frac{A_p r^2}{8\eta\Delta x} \tag{4}$$

where A_p is the total cross-sectional area of the pores and η is the viscosity.

In artificial membranes of known thickness Δx the value of A_p can be estimated experimentally by the ratio of wet to dry weight or by electrical conductivity (17). It is then a simple matter to solve for the number and radii of cylindrical pores, which would offer the same resistance to flow as the unknown membranes. This technique, with variations, has been widely used for the calibration of artificial membranes of graded pore size (for reviews see refs. 8, 41).

In living membranes neither the pore area A_p nor the membrane thickness Δx can be determined as in artificial membranes. However, their ratio $A_p/\Delta x$ can be deduced from Fick's law of diffusion (7)

$$\frac{A_p}{\Delta x} = \frac{\dot{n}}{D\Delta c} \tag{5}$$

where $\dot{n}$ is the measured rate of diffusion of an appropriate tracer through the membrane, D is its coefficient of free diffusion, and Δc is the concentration difference across the membrane. Combination of Equation 4 with Equation 5 yields the equivalent pore radius

$$r = \sqrt{\frac{8\eta D\,\Delta c}{\dot{n}} \times \frac{Q}{\Delta P}} \tag{6}$$

Equation 6 was first derived by Pappenheimer et al. (26) in 1950 and was used to characterize the permeability of capillary walls in mammalian muscle (27) and in artificial membranes (41). The results and discussions of the many correction factors that must be considered for this application of Poiseuille's law to living capillaries are taken up in the chapters by Curry, Michel, and Crone and Levitt in this *Handbook*.

The treatise on flow of liquids in glass tubes (1846) was Poiseuille's last important work, although he continued to publish in *Comptes Rendus* on such diverse topics as the ventilation of ships (34), a theory of breathing (36), and the concentrations of glucose (37) and urea (38) in the blood of vertebrates. His last publication, dated one year before his death in 1869, was an inconsequential note on arterial blood pressure (39).

In 1858 Poiseuille applied for a position in the Paris public school system and in 1860 obtained a relatively menial position as Inspector of School Sanitation in the district of the Seine. The dossier on Poiseuille in the city files reveals that he was not well suited for this position, which indeed seems most inappropriate for a distinguished contributor to the Academy of Sciences and member of the Paris Academy of Medicine. The reasons that led Poiseuille at the age of 61 to apply for this position—his first "professional" job—are uncertain. It is known that in his application of 1858 Poiseuille stated that he was born in 1799, placing his age at 59 and thus making him eligible for the position and eventually a retirement income. In fact, Poiseuille was born in 1797, as attested by his birth certificate and certificate of matriculation at the École Polytechnique in 1815. Perhaps some personal disaster occurred in 1858 making it necessary for Poiseuille to seek employment for the first time at such a late age. It is a curious fact that in 1860 and again in 1868 Poiseuille withdrew his name as candidate for election to the prestigious Academy of Sciences to which he had aspired throughout his career. In his letter of withdrawal addressed to the President of the Academy he writes, "je pense, néanmoins, dans les circonstances présentes, devoir retirer ma candidature." One wonders what circumstances led to this unusual request for withdrawal from such a desirable candidacy.

In the seventeenth century, Isaac Newton defined viscosity in fundamental terms, and it is a fair guess that the inventor of calculus could easily have derived Poiseuille's law had there been any special reason for him to be interested in the flow of fluids through cylindrical tubes. It remained instead for Poiseuille, 170 years later, to discover the law by experiment. Poiseuille was a superb experimentalist with an intense and lifelong interest in the physiology of the circulation. We have seen how his interest led to invention of the mercurial manometer, systematic explorations of pressures in the arteries and veins, pioneering studies on axial flow in the living microcirculation, and finally to classic experiments on flow of liquids in glass capillary tubes. Surely, we can think of Poiseuille as one of the first great pioneers in the field of microvascular research, to which the present volume is dedicated.

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