Adolf Fick (1829–1901), Physiologist

A Heritage for Anesthesiology and Critical Care Medicine

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SUBSEQUENT to his enunciation in 1870 of the principle for calculation of cardiac output, Adolf Fick has been cited at infrequent intervals for his many basic contributions to the disciplines of cardiology and medicine.1,2 We seek here to reiterate his genius for the elucidation of certain physiologic functions that now in large measure underlie the practice of anesthesiology and critical care medicine.

Fick was born in Kassel, Germany in 1829 amidst a family of achievers—the father was a municipal architect and his siblings were involved with anatomy, chemistry and the law. After attending the local gymnasium, Fick matriculated at the University of Marburg, where his older brother was a professor of anatomy and another a privatdozent in law. Most providential, however, were his relations with his teacher, Carl F. W. Ludwig, then a privatdozent in anatomy and physiology. Their association eventuated in a lifetime of academic and social friendship. Ludwig (1816–1895) was famous as a teacher of more than 200 eminent scientists, and much of his work was published under the names of his pupils. He described one of the parasympathetic ganglia in the cardiac interatrial plexus, some features of the renal glomerular plexus, and the aortic depressor nerve. He is perhaps best recalled for his invention of the stromuhr, one of the first devices to measure blood flow in a vessel. Fick and Ludwig’s careers spanned an era after the Napoleonic wars wherein Otto von Bismarck unified the German states and established the new country’s relations with its neighbors, Russia, Austria, and France. This union marked the beginning of the golden age of German science, medicine, and aesthetics. During this time, Fick associated with several universities in western Germany and Switzerland, all within a radius of several hundred miles of each other.

In the fall of 1849, Fick transferred temporarily to Berlin where he could attend the lectures of such luminaries as surgeon Bernard Langenbeck, neurologist Mauritz von Romberg, and physician Johann Schönlein. In addition, he could study with Hermann von Helmholtz, Johannes Müller, and Emil Heinrich Du Bois Raymond. To illustrate the caliber of these men, some of their accomplishments are described. Langenbeck is still known for a description of a foot amputation, an incision made in the linea simularis, and also for a “triangle” drawn to locate the hip joint. Romberg is recalled for his test to detect postural sensitivity in the lower limbs. Schönlein is identified with several purpuric states, and Helmholtz is known among other things for his theory of color vision. Müller, a physiologist and pathologist, described the superior ganglion of the glossopharyngeal nerve, the Müllerian ducts, and a special variety of mixed tumor. Du Bois Raymond, physiologist, is known for the law that defines the electrical excitability threshold of a muscle or nerve.

On return to Marburg, Fick was awarded the M.D. degree in 1851 on the basis of a dissertation on the optic tract. Within a short time, he followed Ludwig to Zurich, first as a prosector, but he ultimately succeeded him as Chair of Anatomy and Physiology (1852–1868) after Joseph Moleschott when Ludwig had proceeded to Vienna (fig. 1). The travels were not yet over, however, for Fick succeeded Albert von Bezold at Würzburg in a similar chair position and remained there for 31 yr until his retirement.

Much of Fick’s work during these years paralleled that of Ludwig’s in the devising of instruments for physio-
Fig. 1. Adolf Fick in the early Zürich years. (Reproduced with permission from the Photographic Collection of the Boston Medical Library in the Francis A. Countway Library of Medicine, Boston, MA.)

logic measurement — an aneroid manometer for measurement of blood pressure, a myotonograph and a cosine level (a galvonometer) — but more importantly, his work promulgated physiologic concepts. Fick was Dean of Medicine at Würzburg for several terms and for a time was its Rector. After retirement, Fick continued to be active in public affairs, but he died soon after his 70th birthday in August 1901 (fig. 2).

The Law and a Theory

The Law of Diffusion

While at Zürich, Fick recognized early on that diffusion was one of the most essential events within the living organism. In 1842, Carl Ludwig had tried to confirm some concepts about kidney function in a series of experiments on "imbibition and endosmosis" (these terms relate to transport by osmosis across membranes), which Fick redefined in 1854. The most important communication, however, "Über Diffusion," appeared in 1855. Although Fick believed that his theory would put an end to any dispute, the theory failed because of the inability to perform precise quantitative experiments (experimental proof, as in the work on cardiac output, would appear ≈25 yr later).

In 1850 and 1851, Thomas Graham, an English chemist (1808–1869), published extensively on the subject of diffusion, recognizing that the speed of diffusion increased with rising temperatures and that there was a correlation with the densities of the substances in solu-
tion. Essentially, he stated that the relative rapidity of diffusion of two gases varies inversely as the square root of the densities; however, he was unable to establish the elementary basis of the process. Poisson had suggested that "capillarity" was the reason for diffusion through a membrane even as Becquerel had attributed diffusion to a kind of electrical phenomenon. Both theories were soon abandoned, and Brücke and Ludwig developed a molecular approach.5

With his proclivity toward mathematics and ultimately on the basis of an awakening knowledge of molecular physics, Fick concluded that "the distribution of a compound dissolved in a solvent takes place in the same way as warmth is distributed within a conductive material (Fourier's Law)." Thus, Fick finally formulated the law that is nowadays known as the Graham–Fick law of diffusion.

"The intensity of the flow of diffusion at any point and at any time is proportional to the differential quotient of the density of solution with regard to the path of flow valid at this point and this time."4 Other facets of the "law" are shown in (fig. 3). "The volume of gas flow per unit time moving across a tissue sheet is directly proportional to the area of the sheet and the difference in partial pressures between the two sides but inversely proportional to tissue thickness."4

\[ V_{\text{gas}} = \frac{AD(P_1 - P_2)}{T} \]

where \( V_{\text{gas}} \) is the amount of gas transferred, \( A \) is area, \( D \) is a diffusion constant, \( P_1 - P_2 \) is the difference in partial pressures, and \( T \) is thickness. \( D \) is directly proportional to the gas solubility but inversely proportional to the square root of its molecular weight.

A moment's reflection recalls how essential diffusion is in understanding uptake and distribution of anesthetic agents, why pathologic alterations in the pulmonary capillary membrane lead to hypoxemia, and how essential diffusion is in placental and in cerebral transfer.

**A Theory for Measurement of Cardiac Output**

Fick's contribution on this subject appeared several centuries after Harvey had written the master work, *De Motu Cordis*, a volume of merely 70 pages, including a preface, introduction, and 17 chapters. Lcakc,5 remarked that Harvey had established a central principle of modern physiology and medicine, but it also demonstrated the most effective method of procedure in the natural sciences:

"Apart from measuring blood volume by drainage in sheep and probably some other mammals, Harvey made no actual measurements in regard to the circulation yet he used quantitative reasoning in a most effective way to prove his point. First he considered the amount of blood put out by the heart in a single beat (an amount probably derived from ventricular volumes in various animal species), and then showed that the amount which would be forced out by the heart in a relatively short while, say an hour, would be much more than could be in the body at any one time, as he knew from having measured blood volume. His figure here, of about one-tenth body weight, is fair."

After Harvey, knowledge of the circulation arose from animal and human dissection (Leonardo and Vesalius), injection techniques, microscopical observations, and use of flowmeters. Although Fick offered no experimental data, he had been studying the cardiac output for some time. For example, there was a publication on the ventricular stroke volume as determined by plethysmography in the forearm. In 1870, therefore, Fick stated (according to one source, apparently quoted by an intermediary):

"It is astonishing that no one has arrived at the following obvious method by which [the amount of blood ejected by the ventricle of the heart with
each systole] may be determined directly, at least in animals. One measures how much oxygen an animal absorbs from the air in a given time, and how much carbon dioxide it gives off. During the experiment one obtains a sample of arterial and venous blood; in both the oxygen and carbon dioxide content are measured. The difference in oxygen content tells how much oxygen each cubic centimeter of blood takes up in its passage through the lungs. As one knows the total quantity of oxygen absorbed in a given time one can calculate how many cubic centimeters of blood passed through the lungs in this time. Or if one divides by the number of heart beats during this time one can calculate how many cubic centimeters of blood are ejected with each beat of heart. The corresponding calculation with the quantities of carbon dioxide gives a determination of the same value, which controls the first.\^{16}

Simply stated, the cardiac output can be calculated from the oxygen consumption of breathing divided by the difference in oxygen content between the left and right heart chambers, i.e., Cardiac output (l/min) = Oxygen consumption (ml/min)/Arteriovenous oxygen difference in mixed blood (ml/l).

This equation is known as the indirect Fick principle, because at the time there were no means for measurement of the components. In the indirect method, it was necessary to equilibrate expired air with alveolar gas to determine the oxygen content of mixed venous blood; in addition, the oxygen consumed on uptake can only be assayed indirectly (e.g., measurement of inspired and expired volumes and their oxygen contents). Arterial puncture eventually was applied for determination of oxygen content of arterial blood (analysis as in the Van Slyke method in the 1930s). The Fick principle also can be applied when other gases are substituted in the equation, CO₂ for example, although that is a more evanescent gas. A steady physiologic state must pertain during measurement.

W. F. Hamilton\^{1} stated:

"This much quoted paragraph of Fick's has been little read, because it carries a very simple message that is self-evident, once it is grasped, and needs no careful re-reading. It is much quoted, because it is a turning point in the development of the quantitative measurement of blood flow, and from its central idea or principle have come many and various techniques that have given us the soundest measurements of the output of the heart and the flow of blood through organs."

After the advent of cardiac catheterization in the 20th century, the Fick principle was ultimately verified around 1930, as shown in figure 4. For this technique, Werner T. O. Forssman (1904), German surgeon, and Andre F. Courand and Dickinson W. Richards were awarded the Nobel Prize in 1956.

Finally, implicit in the Fick equation is the principle of all dilution methods for determining blood flow, for if one knows the amount of a substance that enters or leaves a stream and the concentration difference resulting from such entrance or removal, the size of the stream can readily be calculated. Fick's equation also
underlies all of the dilution methods for measuring blood flow (use of various indicators, the thermal dilution principle) and the stratum on which all methods of blood flow are based: cerebral, hepatic, renal, pulmonary, and uterine blood flow.

In addition to his many scientific papers and his classic textbook *Medical Physics* (1856) Fick wrote on other subjects: *A Compendium of Physiology* (written in 1860-1890), *Handbook of Anatomy and Physiology of the Sense Organs*; and *Circulation of Blood* (1872). At various times, he was honored by several of the major European Universities. In 1929, two of his sons born in the Zürich era founded the Adolf Fick Fund, which bestows a prize every 5 yr for an outstanding contribution to physiology.

References