Recognition of American Physiological Society members whose research publications had a significant impact on the discipline of physiology

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Submitted 6 November 2012; accepted in final form 11 December 2012

Tipton CM. Recognition of American Physiological Society members whose research publications had a significant impact on the discipline of physiology. Adv Physiol Educ 37: 15–27, 2013; doi:10.1152/advan.00145.2012.—Society members whose research publication during the past 125 yr had an important impact on the discipline of physiology were featured at the American Physiological Society (APS)’s 125th Anniversary Symposium. The daunting and challenging task of identifying and selecting significant publications was assumed by the Steering Committee of the History of Physiology Interest Group, who requested recommendations and rationales from all Sections, select Interest Groups, and active senior APS members. The request resulted in recommendations and rationales from nine Sections, one Interest Group, and 28 senior members, identifying 38 publications and 43 members for recognition purposes. The publication recommendations included 5 individuals (Cournand, Erlanger, Gasser, Hubel, and Wiesel) whose research significantly contributed to their selection for the Nobel Prize in Medicine or Physiology, 4 individuals who received multiple recommendations [i.e., Cannon (3), Curran (2), Fenn (3), and Hamilton (2)], and 11 members who had been APS Presidents. Of the recommended articles, 33% were from the American Journal of Physiology, with the earliest being published in 1898 (Cannon) and the latest in 2007 (Sigmund). For the brief oral presentations, the History of Physiology Steering Committee selected the first choices of the Sections or Interest Group, whereas rationales and representation of the membership were used for the presentations by senior members.

During the past 125 yr, the history of the American Physiological Society (APS) has been recorded by numerous authors (2–4, 24, 30, 36, 46). Surprisingly, there is a paucity of details concerning the published research accomplishments of APS members. Of the information available, the overwhelming majority pertains to research achievements of previous presidents, with limited details regarding the accomplishments of regular members. Therefore, the History of Physiology Group Steering Committee (HPGSC), which planned the symposium for the 125th anniversary of APS, included the recognition of APS members whose research publications had significantly advanced the discipline of physiology.

Securing and Evaluating Recommendations From the Membership

With the goal of involving the membership within the symposium process, Chairs of Sections and select Interest Groups were requested to involve their Steering Committees in providing recommendations and rationales to HPGSC for inclusion and presentation purposes. When it became apparent that not all Sections or invited Interest Groups were participating, requests for recommendations were extended to each individual classified as a senior member (>70 yr of age or older). Collectively, 38 recommendations were received from 9 sections, 1 interest group, and 25 senior members, which involved 43 different physiologists, 18 separate journals, and 3 books (Table 1).

Each recommendation submitted included the names and photographs of the member(s) to be recognized, a copy of the relevant publication, and a rationale for its submission. Sections and Interest Groups who submitted more than one recommendation were requested to list them in rank order. Once received, the Web of Science Citation value for the article was added, and the article was submitted to HPGSC members for deliberations. To minimize bias, the name of the nominator was removed for HPGSC consideration. The author served as chair. Thus, recommendations from the Sections, a single Interest Group, and the senior members were evaluated by the HPGSC for presentation purposes at the anniversary symposium. To achieve majority consensus, program consideration prevailed: specifically, to recognize as many members and areas as possible, to select the first choice of the Section or Interest Group, and to recognize an individual only once.

The recommendations received included 5 regular members whose research contributed to their subsequent Nobel Prize in Physiology or Medicine (Cournand, Erlanger, Gasser, Hubel, and Wiesel), 4 individuals who received more than one nomination [Cannon (3), Curran (2), Fenn (3), and Hamilton (2)], and 11 physiologists who had previously served as APS Presidents (Table 2). Of the journals, the American Journal of Physiology contained 33% of the recommended studies, with Physiological Reviews and the Journal of Physiology each publishing 8.3% of the results (Table 1).

Recommendations From the Nine Sections and a Single Interest Group

The Cardiovascular Physiology Section. The Cardiovascular Physiology Section selected a chapter (Table 1) from the 1923 text (75) of Carl J. Wiggers (Fig. 1) that discussed the dynamics of the cardiac cycle that included the heart beat, mechanics of valve action (pressure changes during systole and diastole), the volume curve of the ventricles, the nature of the ventricular ejection system, and the temporal relationships of pressure and volume that existed during the continuous phases that were included within Fig. 28 (75), which has become known as the Wiggers diagram. The nine continuous phases began with the isometric contraction phase and ended with auricular systole, with the chapter listing pressure and volumes results plus phase time periods values from numerous investigators, including Chauveau, Marey, Frank, Tigerstedt,
### Historical Perspectives

**THE 125TH ANNIVERSARY SYMPOSIUM**

Table 1. *APS members whose publication was recommended for its significant impact of the discipline of physiology*

<table>
<thead>
<tr>
<th>Section, Interest Group, or Individual Submitting the Recommendation</th>
<th>Member(s) to Be Recognized</th>
<th>Title of Article, Chapter, or Book That Was Recommended</th>
<th>Reference</th>
<th>Web of Science Citation Record</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Section</td>
<td>Carl J. Wiggers*</td>
<td>The temporal relation of volume and pressure curves and phases of the cardiac A cycle and the sequence of dynamic events (the Wiggers diagram).</td>
<td>75</td>
<td>Not available</td>
</tr>
<tr>
<td>Cardiovascular Section</td>
<td>Arthur C. Guyton</td>
<td>Circulation: overall regulation.</td>
<td>38</td>
<td>410</td>
</tr>
<tr>
<td>Central Nervous System Section</td>
<td>Joseph Erlanger and Herbert S. Gasser*</td>
<td>The compound nature of the action current of nerve as disclosed by the cathode ray oscillograph.</td>
<td>22</td>
<td>120</td>
</tr>
<tr>
<td>Central Nervous System Section</td>
<td>David H. Hubel and Torsten N. Wiesel</td>
<td>Receptive fields of single neurons in the cat’s striate cortex.</td>
<td>47</td>
<td>1,392</td>
</tr>
<tr>
<td>Cellular and Molecular Physiology Section</td>
<td>Walter F. Boron and Paul DeWeer*</td>
<td>Intracellular pH transients in squid giant axons by CO₂, NH₃, and metabolic inhibitors.</td>
<td>5</td>
<td>581</td>
</tr>
<tr>
<td>Endocrinology and Metabolism Section</td>
<td>Walter B. Cannon*</td>
<td>Organization for physiological homeostasis.</td>
<td>13</td>
<td>433</td>
</tr>
<tr>
<td>Environmental and Exercise Physiology Section</td>
<td>John O. Holloszy*</td>
<td>Biochemical adaptations in muscle: effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle.</td>
<td>45</td>
<td>801</td>
</tr>
<tr>
<td>Environmental and Exercise Physiology Section</td>
<td>Jere H. Mitchell</td>
<td>The physiological meaning of the maximal oxygen uptake test.</td>
<td>53</td>
<td>471</td>
</tr>
<tr>
<td>Gastrointestinal and Liver Physiology Section</td>
<td>Robert K. Crandall</td>
<td>Intestinal absorption of sugars.</td>
<td>15</td>
<td>433</td>
</tr>
<tr>
<td>Neural Control and Autonomic Regulation Section</td>
<td>Michael J. Brody*</td>
<td>Prevention of the development of renal hypertension by anteroverentral third ventricle tissue lesions.</td>
<td>8</td>
<td>115</td>
</tr>
<tr>
<td>Neural Control and Autonomic Regulation Section</td>
<td>Walter B. Cannon</td>
<td>The receptive relaxation of the stomach.</td>
<td>11</td>
<td>182</td>
</tr>
<tr>
<td>Renal Section</td>
<td>Maurice Burg*</td>
<td>Preparation and study of fragments of rabbit single nephrons.</td>
<td>9</td>
<td>1,092</td>
</tr>
<tr>
<td>Respiration Section</td>
<td>Wallace O. Fenn, Herrmann O. Kahn, and Arthur B. Ochs*</td>
<td>A theoretical study of the composition of alveolar air at altitude.</td>
<td>25</td>
<td>179</td>
</tr>
<tr>
<td>Respiration Section</td>
<td>John R. Pappenheimer</td>
<td>Role of cerebral fluids in control of respiration as studied in unanesthetized goats.</td>
<td>56</td>
<td>318</td>
</tr>
<tr>
<td>Physiological Genomics Interest Group</td>
<td>Curt D. Sigmund*</td>
<td>Local production of angiotensin II in the subfornical organ causes elevated drinking.</td>
<td>61</td>
<td>47</td>
</tr>
<tr>
<td>Jamison, Rex</td>
<td>Alfred N. Richards*</td>
<td>Observations on the composition of glomerular urine, with particular reference to the problem of resorption in the renal tubule.</td>
<td>71</td>
<td>Not available</td>
</tr>
<tr>
<td>Weibel, Ewald</td>
<td>Andre Courmand*</td>
<td>Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle.</td>
<td>14</td>
<td>350</td>
</tr>
<tr>
<td>Strata, Piergiorgio</td>
<td>Horace W. Magoun*</td>
<td>Brain stem reticular formation and activation of EEG.</td>
<td>54</td>
<td>2,495</td>
</tr>
<tr>
<td>Post, Robert L.</td>
<td>Robert L. Post*</td>
<td>Membrane adenosine triphosphatase as a participation in the active transport of sodium and potassium in the human erythrocyte.</td>
<td>58</td>
<td>865</td>
</tr>
<tr>
<td>Yates, F. Eugene</td>
<td>Ernst Knobil*</td>
<td>Cirhoral oscillations in plasma LH levels in the ovariectomized Rhesus monkey.</td>
<td>20</td>
<td>320</td>
</tr>
<tr>
<td>Bradley, Robert M.</td>
<td>Lloyd M. Beidler</td>
<td>Properties of chemoreceptors of tongue of rat.</td>
<td>5</td>
<td>277</td>
</tr>
<tr>
<td>Koizumi, Kiyomi</td>
<td>Walter B. Cannon</td>
<td>Movements of the stomach studied by means of Roentgen rays.</td>
<td>10</td>
<td>Not available</td>
</tr>
<tr>
<td>Hedley-Whyte, John</td>
<td>Walter B. Cannon</td>
<td>The treatment of shock.</td>
<td>12</td>
<td>Not available</td>
</tr>
<tr>
<td>Binder, Henry J.</td>
<td>Peter F. Curran</td>
<td>A model system for biological water transport.</td>
<td>17</td>
<td>354</td>
</tr>
<tr>
<td>Folk Jr., G. Edgar</td>
<td>G. Edgar Folk, Jr.</td>
<td>Physiology of hibernating bears.</td>
<td>27</td>
<td>Not available</td>
</tr>
<tr>
<td>Stuart, Douglas G.</td>
<td>Alexander Forbes</td>
<td>Amplification of action currents with the electron tube in recording with the string galvanometer.</td>
<td>28</td>
<td>55</td>
</tr>
<tr>
<td>Burg, Maurice B.</td>
<td>Carl W. Gottschalk</td>
<td>Micropuncture study of the mammalian urinary concentrating mechanism: evidence for the concentrating hypothesis.</td>
<td>35</td>
<td>616</td>
</tr>
<tr>
<td>Halberg, Franz</td>
<td>Franz Halberg</td>
<td>Chronobiology.</td>
<td>39</td>
<td>660</td>
</tr>
<tr>
<td>O’Rourke, Michael</td>
<td>William H. Hamilton</td>
<td>An experimental study of the standing waves in the pulse propagated through the aorta.</td>
<td>40</td>
<td>2,058</td>
</tr>
<tr>
<td>Baker, Careleton H.</td>
<td>William H. Hamilton</td>
<td>Studies on circulation, IV. Further analysis of the injection method, and of the changes in hemodynamics under physiological and pathological conditions.</td>
<td>48</td>
<td>163</td>
</tr>
<tr>
<td>Blatteis, Clark M.</td>
<td>Harold T. Hammel</td>
<td>Thermoregulatory responses to hypothalamic cooling in unanesthetized dogs.</td>
<td>41</td>
<td>190</td>
</tr>
</tbody>
</table>

Continued
and Wiggers (75). In subsequent years, the Wiggers diagram contained absolute time values for the phases, listings for the pressures (in mmHg), and results for volume changes (in ml) plus tracings for myograms, heart sounds, and the electrocardiograph (74).

Since 1923, nearly all major and contemporary texts devoted to cardiovascular physiology used by instructors of undergraduate, graduate, allied health, and medical students as well as postgraduate medical professionals have used the Wiggers diagram to facilitate teaching of the dynamics of the cardiac cycle, the significance and interrelationships of aortic, atrial, and ventricular pressure-volume curves, the origin and basis of heart sounds, and the electrical events of the heart beat. Furthermore, the Wiggers diagram is used to explain the physiological and pathological changes occurring during the cardiac cycle in health and disease states.

The Cell and Molecular Physiology Section. The Cell and Molecular Physiology Section recommended a “hallmark” publication (6) for cell physiologists that was conducted by Boron and De Weer (Fig. 2, A and B), as shown in Table 1. Because of the variability and uncertainty associated with the measurement of intracellular pH measurements of squid axons and the difficulty in assessing intracellular proton activity, these two APS members developed the necessary methodology to secure meaningful data while introducing the concept of the “NH₄ prepulse.” Essentially, ion-selective pH microelectrodes were inserted into squid giant axons within a weak acid solution (10 mm NH₄Cl) that was in equilibrium with a gas (NH₃). This resulted in a rapid increase in intracellular pH (alkalinization) because the reaction facilitated the reversible, equilibrium chemistry of NH₃ + H⁺ ↔ NH₄⁺ (pKa = 9.2). The end result was a rapid membrane transit of NH₄⁺ followed by the immediate binding of cellular H⁺ to form NH₄⁺. Within minutes, once NH₄Cl has been removed from the bathing solution, NH₃ rapidly exits, and the reverse reaction occurs (6). Because the exposure period results in an accumulation of intracellular NH₄⁺, the reversal reaction is associated with a marked increase in cellular acid loading. By exploiting this physical chemistry process, Boron and De Weer were able to examine membrane transport mechanisms that removed cellular acids or added cellular bases to restore cellular pH homeostasis. In the decades that have followed the 1976 publication, countless cellular physiologists have used their technique to investigate transport mechanisms.

Table 2. List of former APS Presidents who were recommended because of research publications

<table>
<thead>
<tr>
<th>Individual</th>
<th>Years</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walter B. Cannon</td>
<td>1914–1916</td>
<td>10–13</td>
</tr>
<tr>
<td>Joseph Erlanger</td>
<td>1926–1929</td>
<td>22</td>
</tr>
<tr>
<td>Wallace O. Fenn</td>
<td>1945–1948</td>
<td>23–25</td>
</tr>
<tr>
<td>Carl J. Wiggers</td>
<td>1949–1950</td>
<td>74 and 75</td>
</tr>
<tr>
<td>William P. Hamilton</td>
<td>1955–1956</td>
<td>40 and 48</td>
</tr>
<tr>
<td>Hermann Rahn</td>
<td>1963–1964</td>
<td>25</td>
</tr>
<tr>
<td>John R. Pappenheimer</td>
<td>1964–1965</td>
<td>56</td>
</tr>
<tr>
<td>Arthur C. Guyton</td>
<td>1974–1975</td>
<td>38</td>
</tr>
<tr>
<td>Ernst Knobil</td>
<td>1979–1980</td>
<td>49</td>
</tr>
<tr>
<td>Stanley G. Schultz</td>
<td>1992–1993</td>
<td>64</td>
</tr>
<tr>
<td>Walter F. Boron</td>
<td>1999–2000</td>
<td>6</td>
</tr>
</tbody>
</table>

Fig. 1. Carl J. Wiggers (1883–1962). [Photograph courtesy of the American Physiological Society (APS).]
The Cell and Molecular Physiology Section not only regarded this publication to be a hallmark study but also considered the text to be a mathematical and intellectual achievement that should be required reading for graduate students and postdoctoral fellows with an interest in assessing active proton movement.

**The Central Nervous System Section.** The Central Nervous System Section’s first choice was the 1924 publication (22) of Erlanger and Gasser (Fig 3, A and B), as shown in Table 1. Contrary to frequent summaries pertaining to their article, Gasser was not a student but an investigator and colleague of Erlanger at Washington University in St. Louis, MO. Collectively, they pioneered the use of the cathode ray oscilloscope for recording the electrical activity of single nerve fibers within a nerve bundle (22). With their “elegant new technique” (35a), they showed that thick nerve fibers conduct impulses faster than thin nerve fibers and observed that as the action current moved along the nerve, it dissociated into three and sometimes four waves. Subsequently, they demonstrated that nerve fibers, according to their conduction velocities, could be divided into three main groups (groups A–C) and that nerve fiber changes in excitability could enhance or decrease succeeding impulses. Finally, this publication was chosen by the Central Nervous System Section because it significantly contributed to Erlanger and Gasser’s selection for the 1944 Nobel Prize in Physiology or Medicine, which was awarded for their “discoveries concerning the highly differentiated properties of single nerve fibers” (35a).

**The Endocrinology and Metabolism Section.** The Endocrinology and Metabolism Section recommended the 1929 article...
(13) by Walter Cannon (Fig. 4) that was published in Physiological Reviews (Table 1). The focus of the article was on how physiological homeostasis was organized, and in the Introduction, Cannon (13) reminded readers of Claude Bernard and his concept of the "milieu interieur" and the wisdom that "all the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment." In his definition of homeostasis, Cannon (13) stated "The coordinated physiological reactions which maintain most of the steady states in the body are so complex, and are so peculiar to the living organism, that it has been suggested (Cannon 1926) that a specific designation for these states be employed–homeostasis." He discussed the organization for physiological homeostasis using glucose metabolism as the model system. In addition, he mentioned homeostatic relationships for protein, fat, and calcium while discussing aspects pertaining to homeostatic functions of hunger and thirst, homeostasis by regulating processes, the maintenance of uniform temperature, the role of the autonomic nervous system, and some postulates regarding homeostatic mechanisms (13).

Cannon’s article was recommended because the Endocrinology and Metabolism Section wanted to recognize his extraordinary influence on the discipline of physiology, emphasize that his classic article should be required reading for all graduate students in physiology, remind the membership that the essence of endocrinology is regulatory homeostasis, and to reiterate that the concepts and principles expressed in this publication are the foundation for much of the metabolic research currently being conducted. Finally, the Section wanted to impress on the membership that homeostasis was not system specific but is instead relevant to nearly everyone’s research.

The Environmental and Exercise Physiology Section. The 1967 publication (45) of John Holloszy’s (Fig. 5) investigations on mitochondrial biogenesis in rodents (Table 1) with progressive treadmill exercise was the first study to effectively demonstrate this specific biochemical adaptation in skeletal muscles. He reported that succinate dehydrogenase, reduced diphosphopyridine nucleotide dehydrogenase, DPNH cytochrome c reductase, succinate oxidase, and cytochrome oxidase activities, expressed per gram of muscle, significantly increased (~2-fold) in response to 12 wk of chronic exercise (training). The cytochrome c concentration was also significantly elevated, indicating that altered respiratory enzyme activity was associated with an increase in enzyme protein (45). When mitochondrial O2 consumption was assessed, trained animals exhibited a significant two-fold increase compared with their nontrained counterparts. He also found that the muscles of trained animals exhibited a high level of respiratory control and tightly coupled oxidative phosphorylation and concluded that an increase in electron transport capacity was associated with an increase in the capacity to produce ATP, thereby explaining the elevation in aerobic work capacity of trained animals and humans.

This publication was selected because it introduced an era of exercise biochemistry within the exercise science community while attracting and stimulating individuals to investigate organ and subcellular biological systems in animals and humans that were impacted by exercise. Furthermore, the study was the beginning of investigations pertaining to 1) molecular and transcription factors that govern mitochondrial biogenesis and 2) how various cells can alter gene expression and their phenotypes.

Fig. 4. Walter B. Cannon (1871–1945). [Photograph courtesy of APS.]

Fig. 5. John O. Holloszy (1933–). [Photograph from the collection of Charles M. Tipton.]
The Gastrointestinal and Liver Physiology Section. Before the 1960 publication of Robert K. Crane’s (Fig. 6) article in *Physiological Reviews* (15) (Table 1), selective permeability of the intestines meant different things to different investigators, especially as it pertained to the absorption of glucose. To some, all sugars were absorbed by a phosphorylation-dephosphorylation process. However, Crane (15) believed that neither phosphorylation-dephosphorylation reactions were involved nor any covalent reactions were responsible for intestinal glucose transport. In the article, he proposed the concept that a \( \text{Na}^+/\text{H}^+ \)-glucose cotransporter was the mechanism responsible for intestinal glucose transport. This was the first time that flux coupling was proposed for a biological reaction. In addition, Crane elucidated why \( \text{Na}^+/\text{H}^+ \)-dependent glucose transport was superior to other possible explanations.

Subsequently, research by Stanley Schultz (64) as well as by Crane (16) supported the concept articulated within the review article. However, the importance of this publication was the research that it stimulated, notably, the findings that led to the cloning of \( \text{Na}^+/\text{H}^+ \)-glucose linked transporter 1 protein by the laboratory of Ernst Wright, which dramatically demonstrated that a single mammalian protein could mediate ion-coupled transport (42).

The Neural Control and Autonomic Control Section. According to Buggy et al. (8), by 1977, substantial evidence had been published indicating that the central nervous system was associated with the presence of renal hypertension because of the dipsogenic and arterial pressure results that occurred after the intracranial administration of angiotensin. Moreover, previous findings from different laboratories at the University of Iowa had suggested that the responsive neural site was the anteroventral third ventricle (AV3V) (8). Therefore, the laboratory of Michael J. Brody (Fig. 7) undertook an experimental study (8) to determine the effect of electrolytic lesions in the AV3V region of rats assigned to various groups that included sham, lesioned, unilateral nephrectomy, and renal wrapped as well as combinations thereof (Table 1).

Water intake and pressure responses were assessed after thirst challenges and intravenous infusion of angiotensin and norepinephrine. They reported that only the shamlesioned renal-wrapped animals exhibited significant elevations in water intake and pressure responses, which convincingly demonstrated that 1) the AV3V region was necessary for the development of renal hypertension and 2) the central nervous system was important for its occurrence (8).

Michael J. Brody was recommended because of his seminal research contributions and productivity pertaining to the neural control of autonomic regulation (between 1960 and 1990, he was associated with 202 peer-reviewed publications). In addition, the Neural Control and Autonomic Control Section honors his memory each year by awarding The Michael J. Brody Award to a promising young investigator who has made a significant research contribution to the understanding of neural control and autonomic regulation.

The Renal Physiology Section. Before the 1966 study (9) conducted by Maurice Burg (Fig. 8) and colleagues at the National Institute of Health (Table 1), there was no accurate or reliable method to study the mechanisms of transcellular transport across renal tubule epithelia because it was impossible to control the driving forces for solute or water transport while simultaneously measuring the fluxes involved. Burg and coworkers perfected a method for the dissection and in vitro study of fragments of single intact rabbit nephrons from “all” regions of the kidney.
that would enable them to perfuse the tubules to gain insights on the mechanisms of epithelial transport.

This method, which subsequently became a gold standard for functional measurements in renal physiology, was directly or indirectly responsible for virtually all the subsequent progress made in the areas of renal tubule transport and transport regulation (9).

The importance of this publication, besides establishing a gold standard for renal methodology, is that it led to a rapid explosion of knowledge concerning transporter mechanisms and was extremely instrumental in select studies that eventually cloned the transporter proteins critical to renal function (31).

The Respiration Section. Beginning in 1941 and continuing beyond 1945, the Office of Scientific Research and Development of the United States Government had a contract with the University of Rochester that included conducting research on high-altitude physiology. Emerging from the contract was the publication of a theoretical study (25) pertaining to the composition of alveolar air at high altitude by Fenn, Rahn, and Otis (Fig. 9), as shown in Table 1, which was the first choice of the Respiration Section. The essential purpose of the publication was to provide a graphic solution to various mathematical equations that considered alveolar gas composition as a function of barometric pressure, inspired gas composition, and the respiratory exchange ratio. Select equations were presented graphically in 10 figures in which $PCO_2$ was plotted on the ordinate against $PO_2$ on the abscissa. The selected article had a discussion with sections devoted to breathing air, breathing pure $O_2$, the alveolar air equation, the ventilation equation, ventilation when inspired air contains $CO_2$, equivalent altitudes, advantages of inspired $CO_2$ at altitude, $O_2$ isoventilation lines, $CO_2$ isoventilation lines, and survival limits on the $CO_2$-$O_2$ diagram. One goal of the publication was to use a mathematical approach to demonstrate various "relationships in a clear and quantitative way which would be helpful in both teaching and research" (25).

The results in the publication provided the foundation for a new era of theoretical and applied respiratory physiology that enhanced the understanding of respiratory control and other topics that included ventilation-perfusion relationships and pulmonary gas exchanges in normal, hyperbaric, and microgravity conditions as well as in patients with lung diseases.

The Physiological Genomics Interest Group. Established at the beginning of the 21st century, the Physiological Genomics Interest Group recommended a 2007 publication (61) from Curt Sigmund (Fig. 10), as shown in Table 1. Previous research had demonstrated that the renin-angiotensin system, through its actions with the kidney and the central nervous system, had an important influence on body fluid regulation. Moreover, results had indicated the subfornical organ (SFO) in the brain was an important cardiovascular control region regulating fluid homeostasis in response to infusions of angiotensin II (61). However, it was uncertain whether the influence of the SFO was related to the local synthesis of renin and angiotensinogen (AGT). Using "state of the art" genomic methodology, Sigmund and colleagues produced double transgenic (SRA) mice that expressed human renin

Fig. 8. Maurice B. Burg (1931-). [Photograph courtesy of Hedewen Lisa Brooks.]


Fig. 10. Curt D. Sigmund (1960-). [Photograph courtesy of Mingyu Liang and Curt D. Sigmund.]
and human (h)AGT. These mice exhibited increased water and salt intake plus elevated urinary volumes, which were significantly reduced after chronic intracerebroventricular infusion of the angiotensin II inhibitor losartan. Subsequently, they used a transgenic mouse model that expressed a floxed version of hAGT so that SFO-specific ablations of hAGT\textsuperscript{lox} would occur with microinjections of an adenovirus encoding Cre recombinase. The results indicated that SRA\textsuperscript{lox} mice demonstrated decreased water intake when the SFO demonstrated 1) a diminished loss of hAGT and 2) reduced angiotensin peptide immunostaining. The authors concluded that the genetic evidence strongly implicated de novo synthesis of angiotensin II in the SFO and that the SFO was “an integral player in fluid homeostasis” (61).

Although the Web of Science Citation number has yet to reach classic status (>100), it accomplished the goal of the Physiological Genomics Interest Group, which was to demonstrate the importance of genomic approaches in obtaining insights on physiological mechanisms.

**Senior Member Recommendations**

A 1908 publication (44). Before the publication of the article (44) by Lawrence J. Henderson (Fig. 11) on the relationship between the strength of acids and their capacity to preserve neutrality of solutions (Table 1), textbooks of human physiology had little information pertaining to the acid-base balance of fluids, especially concerning blood. In fact, Austin Flint wrote only one sentence on the subject in 1896 (26). Henderson, a physical chemist at Harvard University, was the first to understand and mathematically explain the ability of blood to neutralize large volumes of acids. In 1908, he rewrote the law of mass action for the dissociation of a weak acid so that it also applied to a mixture of a weak acid and the salt that was formed (when a strong base was used) and produced the following equation: $H^+ = K \times HA/MA$, where $K$ is a constant (the dissociation constant of the acid divided by the degree of ionization of the salt) and HA and MA represent the amount of acid and salt present in the solution, respectively. This equation became known as the “Henderson equation” and was used when acid-base calculations were performed. Also in 1908, Henderson conducted laborious experiments and calculations to determine the $K$ values and ionization constants for a variety of acids, some of which were present in blood, and found that the values for carbonic acid and the dihydrogen phosphate ion had the highest efficiency for preserving neutrality in a simple solution and therefore had the best capacity to act as a acid-base stabilizer (44). A year later, Soren P. Sorensen (67) in Copenhagen, Denmark, defined pH as the negative log of the hydrogen ion concentration and introduced the term “buffer” for substances capable of preserving the neutrality of solutions.

Before 1917, the Henderson equation had gained greater prominence and acceptance. However, during this year (1917), Karl Hasselbalch in Copenhagen, Denmark, used the concepts and terminology of Sorensen and applied the Henderson equation to carbonic acid. The result was the Henderson-Hasselbalch equation, $pH = pK + \log\left(\frac{\text{HCO}_3^-}{\text{H}_2\text{CO}_3}\right)$, which, according to Severinghaus (personal communication) (Table 1), has been used by students, investigators, and clinicians throughout the world to solve acid-base problems while becoming the basis of all acid-base and blood gas understanding. Moreover, when used to solve $\text{PCO}_2$ values, this equation became the method of choice for decades to determine blood $\text{PCO}_2$ levels. Although the invention and utilization of blood gas analyzers ended the use of the equation for clinical purposes (J. W. Severinghaus, personal communication), its educational value lives on in textbooks for students and health professionals.

A 1924 publication (71). Before the article (71) was published (Table 1) that highlighted the contribution of Alfred N. Richards (Fig. 12) and his Fellow, J. T. Wearn,\textsuperscript{1} urine formation was poorly understood and the subject of considerable controversy (19). Ludwig (52), in 1842, argued that glomerular filtration was a passive process, whereas 30 yr later, Heidenhain (43) proclaimed the 1842 glomerular secretion theory of Bowman (7) was responsible for urine formation along with tubule secretion. Although in 1901 Cushney (18) suggested that tubule reabsorption was involved, most investigators felt that the evidence was indirect and inconclusive.

After Richard’s laboratory developed techniques to measure microliter volumes of fluids and quantify the concentrations of proteins, chloride, and glucose, they perfected a fine quartz pipette to obtain glomerular fluid by inserting the pipette through the capsule of Bowman into the glomerulus of the kidney of a living animal (frog). As a result, they became the first investigators to collect and analyze glomerular fluid and urine simultaneously (71). Glomerular fluid was shown to be a protein-free filtrate with chloride and glucose being present in blood but absent in urine. However, when glucose was infused in sufficient quantities to markedly elevate plasma and glomerular concentrations, glucose appeared in the urine. After indigo-carmine dye was injected into a vein, they observed that the dye was filtered and secreted by the

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\textsuperscript{1} Not an APS member at the time of manuscript submission.
tubules and not by the glomerulus. These collective results not only resolved an 80-yr-old controversy [i.e., glomerular fluid was a protein-free filtrate of blood that underwent tubular reabsorption of solutes to form the final urine (19)], it revealed a threshold for glucose reabsorption and indicated that glomerular filtration was a passive process.

It is of interest that in 1969, this landmark experiment was considered by Carl W. Gottschalk (a renowned renal physiologist) “...to be the most significant single original experiment in renal physiology” (34). According to Carl F. Schmidt, a Fellow mentored by Richards, the article by Wearn and Richards was the beginning of a long series of chemical studies on glomerular, tubular, and bladder fluids that became “the crowning achievement” of Richard’s laboratory (63). Finally, its findings contributed to the investigations of Wirtz et al. (76) and Gottschalk and Mylle (35), who were attempting to resolve the controversy associated with the formation of hypertonic urine by mammals.

A 1945 publication (14). Andre F. Cournand (Fig. 13) was recommended for a publication (14) concerning the role of catheterization and the measurement of cardiac output in normal and diseased individuals (Table 1). Inherent with the recommendation were the 1929 self-insertion of a catheter into his heart by Werner Forssmann (21), the 1936 report of Cournand and Richards (72) that rejected the use of the indirect Fick method with mixed venous blood to assess pulmonary blood flow, and the 1941 mixed venous blood and cardiac output results using the Fick principle by Cournand and Ranges (72), which Weibel described as the first significant measurement of cardiopulmonary function in healthy and diseased subjects. Before the publication of the *Journal of Clinical Investigations* article (14), the authors reported that 260 catheterizations from the right auricle or right ventricle of normal and hospitalized subjects had been performed before the methodology was used for their 1945 investigation. The results emphasized the relationships between age and the cardiac index (using the Fick principle) and arteriovenous O2 differences in normal and diseased subjects. In both populations, they included findings that included CO2 content, PCO2, pH, and O2 saturation in arterial blood and mixed venous blood. The importance of their publication is related to the fact it significantly contributed to the 1956 Nobel Prize in Physiology or Medicine that was awarded to A. F. Cournand, W. Forssmann, and D. W. Richards2 “for their discoveries concerning heart catherization and pathological changes in the circulatory system” (51a).

It is the opinion of Dr. Roberta Goldring, Director of the Andre Cournand Pulmonary Physiology Research Laboratory at the Bellevue Hospital (New York, NY), that the publication “marked the beginning and was the major influence on the development of the fields of cardiology, cardiac surgery, pulmonary medicine, and critical care medicine as we know them today” (33). This perspective was embellished by medical writers for Columbia University University Bellevue Hospital Cardiopulmonary Laboratory, who stated that “just about everything modern medicine knows about the heart and lungs was made possible by the work of Frederick Cournand and Dickinson Richards, whose groundbreaking research revolutionized cardiology and pulmonology” (21).

A 1949 publication (54). Horace W. Magoun (Fig. 14), founder of the Brain Institute of the University of California (Los Angeles, CA), was recommended because of the scientific

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2 Not an APS member at the time of manuscript submission.
Before 1949, it was known that transitions from sleep to wakefulness or from states of relaxation and drowsiness to alertness and attention were characterized by a disruption of the synchronization of discharge of elements from the cerebral cortex, which caused an alternation of electroencephalographic (EEG) recordings (replacement of high-voltage slow-activity waves with low-voltage fast-activity waves) (54). However, it was uncertain whether activation could be produced either by a variety of afferent stimulation that aroused the subject to alertness or by a centrally generated process. Subsequently, in a chloralose-anesthetized cat, Moruzzi and Magoun (54) identified and stimulated the brain stem reticular formation and observed 1) evoked generalized desynchronization of the EEG and 2) the replacement of high-voltage slow-activity waves with low-voltage fast-activity waves that was similar to the response elicited with sensory stimulation. In addition, they demonstrated “with an unaesthetized encephale isole preparation,” that the well-established phenomenon of behavioral and EEG cortical arousal could be activated with reticular stimulation. These results established the concept of an ascending reticular system that had an important functional role in the regulation of the sleep-wakefulness cycle (54). According to a 1981 Current Contents article (17a), their identification of the neural structures responsible for the control of the general level of cerebral activities led to new approaches and views in neurophysiology (mechanisms of EEG arousal), neuropharmacology (barbitral narcosis), and clinical neurology.

The importance of this publication to the scientific community was reflected, in part, by the number of citations listed in the Web of Science Citation Report (Table 1), as their 2,495 citations was...
by far the highest citation number of any publication submitted to the HPGSC and was a contributing factor for Magoun and colleague’s article being selected for presentation purposes.

A 1960 publication (58). The origin of Ref. 58 (Table 1) began in 1954, when Robert L. Post (Fig. 15) was a faculty member at Vanderbilt University investigating the kinetics of active Na\(^+\) and K\(^+\) transport in human erythrocytes (50). His interest in membrane ATP increased 3 yr later, when he became aware of the 1957 findings of Jens C. Skou (1997 Nobel Prize in Chemistry) from the nerves of crabs that indicated that ATPase activity required both Na\(^+\) and K\(^+\) simultaneously, which suggested that ATPase may be required for the active extrusion of Na\(^+\) from the nerve fiber (66).

With students as co-investigators, Post perfected a broken human erythrocyte membrane preparation and was the first to identify an insoluble ATP-cleaving enzyme system involved in the active transport of Na\(^+\) outward and K\(^+\) inward. In fact, this group observed that transport was stoichiometrically coupled to the hydrolysis of ATP, with 3 Na\(^+\) transported outwardly and 2 K\(^+\) transported inwardly (58). Therefore, they not only perfected a method for identifying a transport system in a preparation of broken membranes but also demonstrated that ions could be substrates for translocation. The publication was significant in that the information influenced numerous studies on the distribution of Na\(^+\)- and K\(^+\)-dependent ATPases in animal tissues and encouraged Post and his laboratory to conduct further research that led to the formulation of the Post-Albers cycle, a cycle that effectively describes the sequence of reactions of the Na\(^+\)-K\(^+\)-ATPase by which the charge translocations occur (1, 50, 57). In addition, Post and the publication were honored when the article was reprinted as a classic article during the centennial of the Journal of Biological Chemistry (50).

A 1970 publication (20). Ernst Knobil (Fig. 16) was recommended because a publication (20) from his laboratory impacted the discipline of endocrinology and the area of clinical endocrinology (F. E. Yates, personal communication) (Table 1). Before 1960, the detection and interpretation of endocrine signals in the plasma were difficult because of the lack of precision of the existing methodology. Although this situation changed after the introduction of the radioimmunoassay (RIA) technique, which markedly improved the assessment of hormonal specificity and sensitivity in low volumes of plasma, uncertainty continued as to how to explain and interpret results pertaining to hormonal secretions, pulsatility, and pulse trains (F. E. Yates, personal communication; and Ref. 20). Using RIA methodology, Dierschke et al. (20) secured blood samples from female normal and wardly and 2 K\(^+\) transported inwardly (58). Therefore, they not only perfected a method for identifying a transport system in a preparation of broken membranes but also demonstrated that ions could be substrates for translocation. The publication was significant in that the information influenced numerous studies on the distribution of Na\(^+\)- and K\(^+\)-dependent ATPases in animal tissues and encouraged Post and his laboratory to conduct further research that led to the formulation of the Post-Albers cycle, a cycle that effectively describes the sequence of reactions of the Na\(^+\)-K\(^+\)-ATPase by which the charge translocations occur (1, 50, 57). In addition, Post and the publication were honored when the article was reprinted as a classic article during the centennial of the Journal of Biological Chemistry (50).

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The article provided new insights on endocrine secretions and was responsible for the concept of a hypothalamic pulse generator rhythmically driving causal GnRH release and led to further studies on the rhythmic and pulsatility characteristics of reproductive hormones (37, 49, 55). In addition, the publication was influential in the development of leuprolide (Lupron), a GnRh agonist resulting in long-term inhibition of the release of LH and follicle-stimulating hormone (62) that has significantly impacted clinical endocrinology by being used in infertile female patients with hypothalamic amenorrhea, in female patients undergoing treatment of endometriosis, and in male patients with metastatic prostate cancer (F. E. Yates, personal communication; and Refs. 29 and 62). Moreover, it is an excellent example of the translation of basic physiological research into clinical practice (F. E. Yates, personal communication).

Closing Comments

As APS celebrates its 125th anniversary, it can take great pride in the myriad of achievements that have occurred during this time interval. However, none are more important than its scientific contributions to the discipline of physiology. The distinctive feature of this anniversary year is that APS membership, for the first time, has identified the publications that they believe have enhanced the discipline and advanced the profession. Although the identification and selection process can be improved, it should be continued, and the hope is that it will not take 125 yr for implementation.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: C.M.T. conception and design of research; C.M.T. performed experiments; C.M.T. analyzed data; C.M.T. interpreted results of experiments; C.M.T. prepared figures; C.M.T. drafted manuscript; C.M.T. edited and revised manuscript; C.M.T. approved final version of manuscript.

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