

ESSAYS ON APS CLASSIC PAPERS |

The pioneering use of systems analysis to study cardiac output regulation

John E. Hall*Department of Physiology and Biophysics, School of Medicine, University of Mississippi Medical Center, Jackson, Mississippi 39216*

This essay examines the historical significance of an APS classic paper that is freely available online:

Guyton AC, Lindsey AW, and Kaufmann BN. Effect of mean circulatory filling pressure and other peripheral circulatory factors on cardiac output. *Am J Physiol* 180: 463–468, 1955 (<http://ajplegacy.physiology.org/cgi/reprint/180/3/463>).

IT IS A TRIBUTE to Arthur Guyton's genius that his concepts of cardiovascular regulation often seemed heretical when they were first presented but stimulated investigators throughout the world to test them experimentally and are now widely accepted. In fact, many of his concepts of cardiovascular regulation are now integral components of what is taught in most medical physiology courses.

One of Dr. Guyton's most important legacies was his application of principles of engineering and systems analysis to cardiovascular regulation. He used mathematical and graphical methods to quantify various aspects of circulatory function before computers were widely available. He built analog computers and pioneered the application of large-scale systems analysis to modeling the cardiovascular system before the advent of digital computers. As digital computers became available, his cardiovascular models expanded dramatically to include virtually all aspects of cardiac and circulatory functions. This unique approach to physiological research preceded the emergence of biomedical engineering, a field that he helped to establish and to promote in physiology, leading the discipline into a much more quantitative science.

The APS classic paper published by Guyton (Fig. 1), Lindsey, and Kaufmann in 1955, "Effect of mean circulatory filling pressure and other peripheral circulatory factors on cardiac output" (5), is an excellent example of the analytical approach that Dr. Guyton applied to all areas of research, including cardiac output regulation. The importance of this paper was its emphasis on venous return as a determinant of cardiac output and the systematic analysis of the various factors that influence venous return.

Guyton, Lindsey, and Kaufmann demonstrated, mathematically and experimentally in dogs, that venous return is proportional to the mean circulatory filling pressure minus the right atrial pressure, or the "pressure gradient for venous return." They also noted, however, that venous return increased to a greater extent than predicted to occur as a result of increased mean circulatory filling pressure because of the effect of

elevated venous pressure to reduce the impedance to venous return. This led them also to investigate the various factors that influence resistance to venous return, including the effects of arterial and venous resistance and blood viscosity.

This classic paper extended Dr. Guyton's previous work, also published in the *American Journal of Physiology* (6), which defined the concept of "mean circulatory filling pressure" as "...the pressure which would be measured if the heart should suddenly stop pumping blood and all the pressures in the circulation should be brought to equilibrium instantaneously."

These concepts were presented at a symposium entitled "Regulation of the Performance of the Heart" on April 13, 1954, in Atlantic City, NJ, under the auspices of the American Physiological Society. As noted by Lewis Katz, chair of the symposium and a leading figure in cardiac physiology, "The sharp differences of opinion about the manner by which this regulation is achieved point out fundamental differences in the methods and techniques employed in attacking this problem and the various approaches to the interpretation of the available data" (8).

Guyton's analysis (2) was very different from the others, including some of the "heavy hitters" in cardiac physiology,

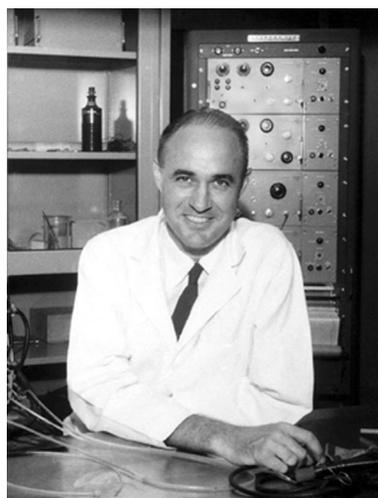


Fig. 1. Arthur C. Guyton.

*Address for correspondence: J. E. Hall, Guyton Professor and Chair, Dept. of Physiology & Biophysics, Univ. of Mississippi Medical Center, Jackson, MS 39216 (E-mail: jehall@physiology.umsmed.edu).

such as Stanley Sarnoff, Donald Gregg, Lewis Katz, Dickinson Richards, and Robert Rushmer. Most investigators had focused on the pumping ability of the heart itself. In contrast, Guyton emphasized the importance of venous return and the fact that the heart normally acts as a “sump pump,” pumping all of the blood that returns to the heart from the peripheral circulation.

Combining the tools of mathematics, physics, engineering, and physiology, he proved with experimental studies and systems analyses the importance of venous return and local metabolic control of the regional vasculature in controlling the cardiac output. In fact, he demonstrated that except in unusual circumstances, such as heart failure, the peripheral circulation and venous return are more important in determining cardiac output than the heart itself. Although these concepts led to intense debate and opposition from many of the leading investigators in this field, 50 years later they are widely accepted and discussed in almost every major physiology textbook.

Dr. Guyton continued to develop his systems analysis of cardiac output regulation that culminated in his classic textbook *Circulatory Physiology: Cardiac Output and Its Regulation* (4). Guyton’s mathematical analysis of cardiac and peripheral circulatory regulation preceded his more complex computer models that are still the most comprehensive models

of cardiac output regulation yet developed. His systems analysis approach to physiology also extended to other areas, including renal physiology, body fluid regulation, and hypertension, leading to the first large-scale computer model of the entire cardiovascular system (Fig. 2) (3). He would be amused and delighted to learn that his quantitative systems approach to research has recently become touted as the wave of the future for biomedical research under the “new” name of “systems biology.”

Dr. Guyton gave us an imaginative and an innovative approach to research and an unprecedented depth of understanding of the cardiovascular system. His early mathematical analysis of cardiac output was simple but elegant and became an important tool for research as well as for teaching. He had a gift for taking complex concepts and simplifying them so that they were understandable by medical students as well as by physiologists and biomedical engineers.

All who knew Dr. Guyton were duly impressed with his clarity of thought, his logic and problem-solving abilities, his depth of understanding of complex physiological systems, and his passion for physiology. His accomplishments, however, extended far beyond science, medicine, and education, and are summarized in accounts of his fascinating life (1, 7). Those of us who had the privilege of working with him witnessed

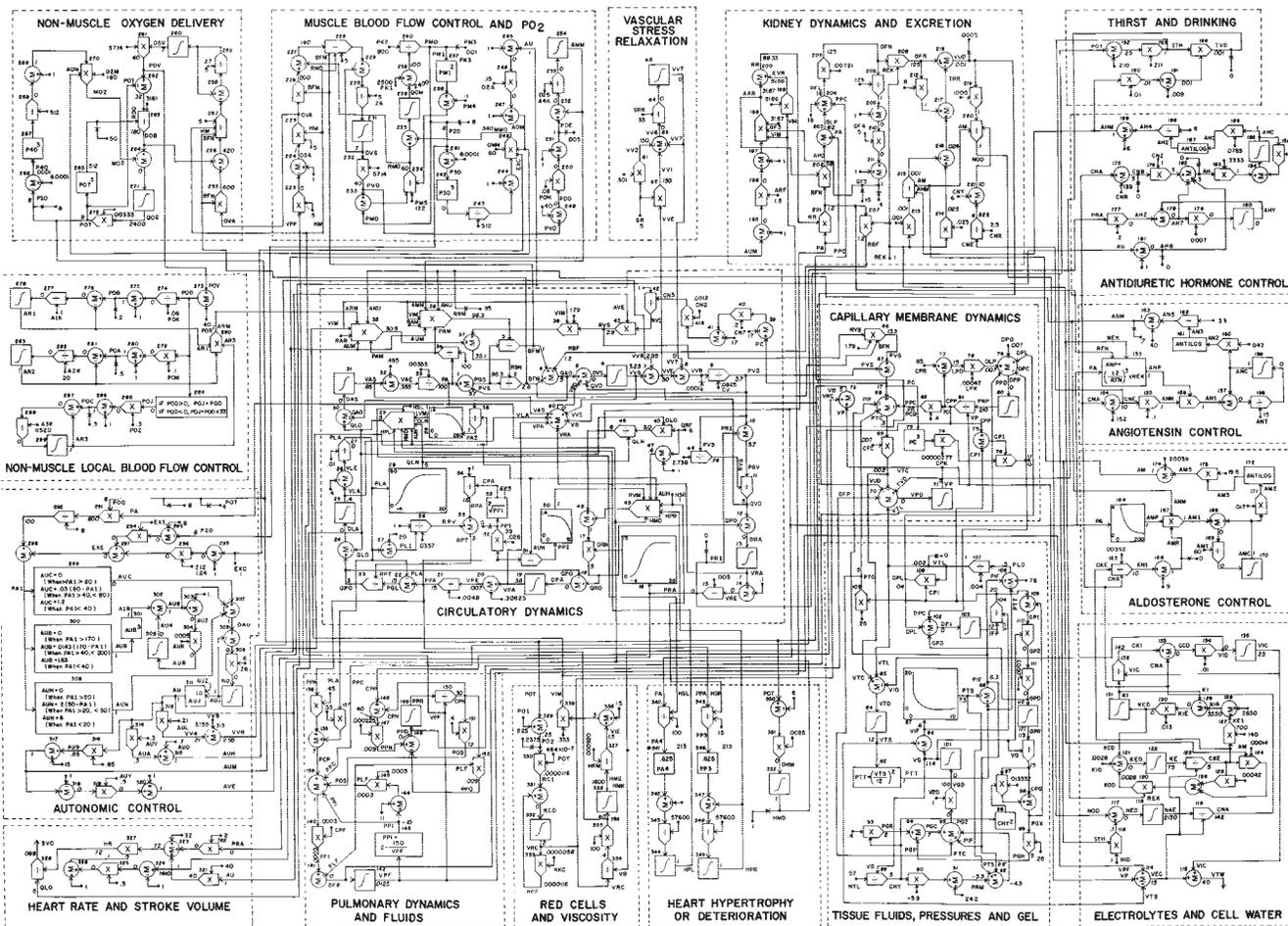


Fig. 2. Arthur Guyton’s computer model of the cardiovascular system. This was the first large-scale computer model that integrated the many factors influencing the peripheral circulation, the heart, the endocrine systems, the autonomic nervous system, the kidneys, and body fluids. (Reprinted, with permission, from the *Annual Review of Physiology*, Volume 34 copyright 1972 by Annual Reviews www.annualreviews.org.)

firsthand his gentle but indomitable spirit and are grateful for his gifts to us and to the world.

Arthur Guyton was an inspiring role model for life as well as for science, and we owe him a tremendous debt.

REFERENCES

1. **Brinson C and Quinn J.** *Arthur C. Guyton—His Life, His Family, His Achievements*. Jackson, MS: Hederman Brothers, 1989.
2. **Guyton AC.** Determination of cardiac output by equating venous return curves with cardiac output responses. *Physiol Rev* 35: 123–129, 1955.
3. **Guyton AC, Coleman TG, and Granger HJ.** Circulation: overall regulation. *Annu Rev Physiol* 34: 13–46, 1972.
4. **Guyton AC, Jones CE, and Coleman TG.** *Circulatory Physiology: Cardiac Output and Its Regulation*. Philadelphia, PA: Saunders, 1963.
5. **Guyton AC, Lindsey AW, and Kaufmann BN.** Effect of mean circulatory filling pressure and other peripheral circulatory factors on cardiac output. *Am J Physiol* 180: 463–468, 1955.
6. **Guyton AC, Polizo D, and Armstrong GG.** Mean circulatory filling pressure measured immediately after cessation of heart pumping. *Am J Physiol* 179: 261–267, 1954.
7. **Hall JE, Cowley AW Jr, Bishop VS, Granger DN, Navar LG, and Taylor AE.** In memoriam and tribute—Arthur C. Guyton, MD. *Physiologist* 46: 126–128, 2003.
8. **Katz LN.** Symposium on the regulation of the performance of the heart. *Physiol Rev* 35: 90, 1955.