

## ESSAYS ON APS CLASSIC PAPERS |

## Discovering the role of the adrenal gland in the control of body function

David C. Randall

*Department of Physiology, College of Medicine, University of Kentucky, Lexington, Kentucky 40536*

This essay looks at the historical significance of three APS classic papers that are freely available online:

**Cannon WB and de la Paz D.** Emotional stimulation of adrenal secretion. *Am J Physiol* 28: 64–70, 1911 (<http://ajplegacy.physiology.org/cgi/reprint/28/1/64>).

**Cannon WB.** The emergency function of the adrenal medulla in pain and the major emotions. *Am J Physiol* 33: 356–372, 1914 (<http://ajplegacy.physiology.org/cgi/reprint/33/2/356>).

**Cannon WB.** Studies on the conditions of activity in endocrine glands. V. The isolated heart as an indicator of adrenal secretion induced by pain, asphyxia and excitement. *Am J Physiol* 50: 399–432, 1919 (<http://ajplegacy.physiology.org/cgi/reprint/50/3/399>).

THE CONTROL OF BODY FUNCTION must have seemed to our scientific forebears much like a “terra incognita” with very few well-defined landmarks. Walter B. Cannon (1871–1945; Fig. 1) contributed significantly to the discovery of a number of “mountains” within this terrain that continue to delineate our understanding of human physiology. Among the grandest of these mountains would certainly be “Mount Homeostasis” (5), and one of the major features flanking this peak might well be known as “Fight-or-Flight Promontory” (2), although Cannon apparently never used this exact terminology. Building on earlier work by Claude Bernard (1), Cannon and his colleagues discovered these features while exploring the role of the adrenal medulla in controlling visceral function. By 1911, physiologists had established “. . . that adrenal secretion is under the control of the thoraco-lumbar autonomic (sympathetic) system” (6), and they understood that the general nature of the cat’s responses when frightened (e.g., dilated pupils, rapid heart beat) were “all signs of nervous discharges along sympathetic paths” (6). This prompted Dr. Cannon and his coauthor D. de la Paz to pose the following question: “Do not the adrenal glands share in this widespread subjugation of the viscera to sympathetic control?” (6).

In 1911 the available technology allowed Cannon and de la Paz to sample blood from cats via a “small flexible catheter. . . coated with Vaseline inside and out” (6) whose tip was situated in the inferior vena cava above the opening of the adrenal vessels; blood was drawn before (“quiet blood”) and a few minutes after (“excited blood”) the animals had been placed near a barking dog. They then tested the effects of the blood upon contraction of muscle in longitudinal sections of intestine. Magnus (9) had shown in 1905 that the rhythmical contractions of this tissue are inhibited by “suprarenin.” Intestinal strips were connected to a lever with a stylus that scratched a path along a smoked paper moving under the stylus on a rotating drum.<sup>1</sup> Throughout his

career Dr. Cannon’s work was characterized by multiple control observations; in this case he showed first that the intestinal strip responded to blood drawn from the adrenal vein and that differences in blood gases did not alter the nature of the response. Cannon and de la Paz (6) found that “[i]n no instance did blood from the quiet normal animal produce relaxation. On the other hand, blood from the animal after emotional disturbance showed more or less promptly the typical relaxation.” No inhibition of contraction was observed in cats whose adrenal glands had been removed, even after the animals had been excited for 4 or 5 h. The authors stated in closing that “. . . the evidence that sympathetic impulses increase the secretion of the adrenal glands, and that during such emotional excitement as was employed in these experiments, signs of sympathetic discharges were observable from the eye of the animal to the tip of its tail, prove[s] that the characteristic effect of adrenal extract on the intestinal strips was due to secretion of the adrenal glands” (6).

Cannon and his colleagues followed the 1911 report with other studies of the physiological effects of adrenal secretions. By 1914, he and others had reported that injection of “the substance produced by the adrenal medulla (adrenin, adrenalin, epinephrine, etc.) is capable of producing many profound



Fig. 1. Walter B. Cannon.

Address for correspondence: D. C. Randall, Dept. of Physiology, Univ. of Kentucky, Lexington, KY 40506-0298 (E-mail:randall@uky.edu).

<sup>1</sup> The present author still has the recording he made as a first-year graduate student of intestinal muscle contractions using the “smoked kymograph.” Moreover, until relatively recently (i.e., when teaching laboratories were largely discontinued), he used this preparation and a polygraph recorder to demonstrate the effects of epinephrine and acetylcholine on smooth muscle motility to undergraduate, medical, and graduate students.

bodily changes. . . : a cessation of the activities of the alimentary canal; a notable shifting of the circulation from the great vessels of the abdomen to the lungs, heart, limbs and central nervous system; an increased cardiac vigor; and an augmentation of the sugar content of the blood" (2). He then championed the view that ". . . the absolutely essential organs—the 'tripod of life'—the heart, lungs and brain (as well as the skeletal muscles)—are, in times of excitement, when the adrenal glands discharge, abundantly supplied with blood taken from organs of less importance in critical moments" (2). But Cannon's views were rigorously challenged by other investigators. In particular, his conclusion that adrenal secretion increased in response to emotional excitement was contested (11), and, at an even more fundamental level, Gley and Quinquaud (8) contended that adrenin was not secreted in sufficient amount to be carried effectively to organs on which it could act. Contemporary physiologists would quickly reject these arguments, but the issues were confused at that time. In fact, then as now, challenges by one scientist of another's observations stimulated additional experiments, and in 1920, Cannon described new experiments in the third (4) of these now classic papers to respond to criticisms of his earlier work and to bolster his previous conclusions.

Cannon's 1920 paper begins with a thorough review of previously published evidence for and against adrenal secretion in response to pain, asphyxia, and emotional excitement. One of the more compelling potential difficulties with earlier work, including the 1911 demonstration, is that the effects of adrenin were tested in blood that had been removed from the body. Cannon's solution was to use the denervated heart, which he noted is "highly sensitive to adrenin" (4), to circumvent the objections leveled at earlier studies. He acknowledged that this solution was triggered by earlier "incidental observations" of other investigators; no scientist, not even a Dr. Cannon, works in a vacuum. He stated that the approach is particularly advantageous because "the method permits a graphic record from which may be judged the latent period and the duration of secretion of the adrenal glands in consequence of stimulation" (4). He explains that the decentralized feline heart ". . . is thus wholly disconnected from the central nervous system and any agency causing an increase in the heart rate must exert its influence through the bloodstream" (4). He then illustrates a tachycardia in the animal when excited compared with the calm state; removing the adrenals in some animals eliminated the response, although some heart rate speeding persisted in other subjects. Although there are certainly limitations to Cannon's experimental approach, his conclusions still stand today. Moreover, the development of heart transplantation renewed interest in the regulation of the denervated heart, and, about 50 years after Cannon's publication, the present author and his colleagues (10) surgically denervated the primate heart and described quantitatively the latency and amplitude of the cardiac chronotropic and inotropic increases during a tone followed by shock; no significant augmentations occurred during a tone followed by food. We cited Cannon's 1920 paper to substantiate the importance of the adrenal contribution to the "fear response" and also noted a later publication where he described the phenomenon of "denervation supersensitivity" (7).

One additional observation regarding the 1920 paper may be worthwhile with respect to the timeless workings of science: in a concluding section of his paper, Cannon examined two theories that were then current "to account for the role played

by the adrenal medulla in the bodily economy" (4). One of these, which he described and then rejected in favor of his "emergency theory," holds that "the function of the secreted adrenin is to maintain the sympathetic endings in a state of responsiveness to nervous stimulation or in a condition of moderate activity or tone" (4). While Cannon's contention that "it is the *sympathetic division of the autonomic system* which is the primary agency in mobilizing the bodily forces in times of great fear or rage" (Ref. 3; Cannon's italics) has stood the test of time, many experiments have also established that other secretions of the adrenal gland, most particularly cortisol, are absolutely essential for maintaining vascular smooth muscle responsiveness to adrenergic stimulation and thereby in the maintenance of on-going vasomotor tone. In this regard, perhaps it is fair to say that no avenue of scientific exploration ever leads to a total dead end.

It often happens that the splendor of a conceptually inspiring peak in our understanding of physiological function transiently obscures our appreciation of other important phenomena. In fact, "Mount Homeostasis," which emphasizes the maintenance of a stable internal environment, appears to have a sister peak, "Mount Variability," which emphasizes the value of an analysis of the dynamic nature of cardiovascular "signals" such as blood pressure (e.g., the precise manner in which blood pressure fluctuates around its "steady state" value). Today large portions of Mount Variability are still enshrouded in mist, much as Mount Homeostasis was in the early 20th century. There is, however, every promise that this new landmark will eventually be as prominent as its magnificent sister.

Walter Cannon's son, Dr. Bradford Cannon, reports ([http://www.harvardsquarelibrary.org/unitarians/cannon\\_walter.html](http://www.harvardsquarelibrary.org/unitarians/cannon_walter.html)) that his father and mother, on their honeymoon, were the first to reach the summit of an unclimbed peak in what is now Glacier National Park at the head of Lake McDonald. The United States Geological Survey subsequently named it Mount Cannon (48.63330 lat., -113.75123 long.). Dr. Cannon's other "mountains" continue to serve as landmarks in our understanding of body function.

## REFERENCES

1. **Bernard C.** *Leçons sur les Phénomènes de la Vie Communs aux Animaux et aux Végétaux*, 2 vols. Paris: Bailliére et Fils, 1878–1879.
2. **Cannon WB.** The emergency function of the adrenal medulla in pain and the major emotions. *Am J Physiol* 33: 356–372, 1914.
3. **Cannon WB.** *Bodily Changes in Pain, Hunger, Fear and Rage: An Account of Recent Researches into the Function of Emotional Excitement*. New York: Appleton, 1915.
4. **Cannon WB.** Studies on the conditions of activity in endocrine glands. V. The isolated heart as an indicator of adrenal secretion induced by pain, asphyxia and excitement. *Am J Physiol* 50: 399–432, 1919.
5. **Cannon WB.** *The Wisdom of the Body*. New York: Norton, 1932.
6. **Cannon WB and de la Paz D.** Emotional stimulation of adrenal secretion. *Am J Physiol* 28: 64–70, 1911.
7. **Cannon WB and Rosenblueth A.** *The Supersensitivity of Denervated Structures*. New York: Macmillan, 1949.
8. **Gley E and Quinquaud A.** La Fonction des Surrénales. I. du Role Physiologique Supposé de l'adrénaline. *J Physiol Path Gen* 17: 807–835, 1918.
9. **Magnus R von.** Versuche am überlebenden Dünndarm von Säugetieren. *Arch Gesamte Physiol* 108: 1–71, 1905.
10. **Randall DC, Kaye MP, Randall WC, Brady JV, and Martin KH.** Response of primate heart to emotional stress before and after cardiac denervation. *Am J Physiol* 230: 988–995, 1976.
11. **Stewart GN and Rogoff JM.** The alleged relation of epinephrine secretion of the adrenals to certain experimental hyperglycemias. *Am J Physiol* 44: 543–580, 1917.