

Arthur E. Guedel Memorial Anesthesia Center

"Sympathetic-ologists"

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A recent review article on the sympathetic nervous system (Neukirchen M et al. *Anesthesiology* 109:1113-1131, 2008) emphasizes that this division of the autonomic nervous system has become especially important to the practicing anesthesiologist. The following report examines just how we became "sympathetic-ologists", and whether we deserve to take on that role.

Anesthesiologists of the Guedel era certainly were not preoccupied with the sympathetic nervous system. The word "sympathetic" does not even appear in either of Guedel's two books, and it is rarely mentioned in Gwathmey's, Lundy's, or Cullen's textbooks, and then mostly in relation to hypotension after spinal anesthesia. The sympathetic nervous system had been thoroughly described by physiologists by 1900, but it still had not generated much interest from practicing clinicians by 1945—a curious situation indeed, given that the agents that they used (ether and nitrous oxide) were well known to activate the sympathetic nerves.

However, this lack of interest in the sympathetic system becomes understandable when one considers the attitude of the medical community toward cardiac and autonomic function just 64 years ago. The demise of Franklin Delano Roosevelt in April 1945 is a prime example, because he died of a cerebral hemorrhage, the etiology of which was untreated malignant hypertension. The leading physicians of that era, such as Paul Dudley White (of WPW syndrome fame), were not impressed by the health risks of hypertension. For example, White wrote in his 1937 textbook *Heart Disease*: "High blood pressure may be a natural compensatory phenomenon and should be left alone even if there was effective treatment." Roosevelt's personal physician, Admiral Ross McIntire, was an ENT specialist, and had treated him for recurrent bronchitis and sinusitis, but his symptoms of shortness of breath, orthopnea, and high blood pressure, clearly suggesting malignant hypertension and congestive heart failure (Figure 1), were left to play themselves out without medical intervention.

In the 1960s, cardiologists took notice of several studies, including the Framingham Heart Study, that revealed a correlation between hypertension and mortality. Thiazide diuretics were discovered to decrease blood pressure, and a host of new drugs of various new classes have followed, which now

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include beta blockers, sympatholytics (both central and peripheral), calcium channel antagonists, and of course potent ACE inhibitors and angiotensin blockers. In 1988 the Nobel Prize in Medicine was awarded to Sir James Black, in part for his contribution to the discovery of the first beta-blocker, propranolol, introduced in 1964. Black stated in his autobiography that his goal was to discover a therapy that would decrease myocardial metabolic demands and that decreasing the heart rate by beta-adrenergic blockade seemed to be an effective approach.



Figure 1: Churchill, Roosevelt, and Stalin meet at Yalta (now part of Ukraine) in February 1945. Roosevelt's blood pressure was reported to be 260/150 just prior to the conference and was not treated. Churchill's physician Lord Moran noted that Roosevelt was "looking straight ahead with his mouth open as if he were not taking things in." Moran gave him less than a few months to live. Roosevelt died of a massive cerebral hemorrhage less than three months after this photograph was taken. *Courtesy of the FDR Presidential Library and Museum, Hyde Park, New York.*

Anesthesiologists were quick to pick up on this approach. Perioperative beta adrenergic blockade, thoracic epidurals, MAC-BAR (Minimum Alveolar Concentration for Blockade of Adrenergic Responses), high-dose opioid anesthesia, hypotensive anesthesia, and sympatholysis were promoted as methods to reduce myocardial ischemia in the perioperative period. Drugs like esmolol, metoprolol, and now even dexmedetomidine were added to our anesthesia drug carts.

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The word “sympathetic” is now commonly used in our conversations and widely used in our literature. The term “sympathetic” is used 58 percent more times in the leading textbook of anesthesiology compared to the use of the word in the leading textbook of medicine, and 48 percent more times than in the leading textbook on emergency medicine. We have essentially become the “sympathetic-ologists” of clinical medicine.

Now, however, our long-held theories and practices concerning the benefits of perioperative beta blockage are being held up to the light of new science. Our therapies are sometimes inconsistent and, moreover, are poorly understood by our surgical and medicine colleagues, who continue to advise us merely to “keep the blood pressure up.” Perioperative beta-adrenergic blockade for the non-cardiac patient is being questioned in prominent medical journals (Bangalore S, *Lancet* 372:1962-1976, 2008). We appreciate sympatholysis during the case, but we do need the sympathetic nervous system to be working properly when we want the patient to get out of bed. Increasingly, patients are coming to surgery taking highly potent antihypertensives, and when the anesthetic and beta adrenergic blockade are added, blood pressures can **decrease too low** and sometimes are **to a large degree** unresponsive to our traditional sympathomimetic therapies (phenylephrine and ephedrine). The recent emphasis on fluid restriction may further compound this problem.

If we are to continue to be true “sympathetic-ologists,” we need to step back, reevaluate, and perhaps redefine our ideas. With all the controversy regarding the “sympathetic nervous system,” it is worth noting that physicians have grappled with similar questions on the unconscious control of bodily functions for nearly 2000 years.

For one thing, the word “sympathetic” is a misnomer. It was coined in ancient Greece to signify those occasions when disease in one part of the body had effects on noncontiguous body parts: “sym” (together) and “pathy” (feeling). The word had the same meaning 1500 years later when Robert Whytt (1751) wrote his classical essay on sympathy between the body parts. To Whytt, all sympathy was reflex action occurring through the nerves. The consensual light reflex occurred because the “sentient principle” in the brain expressed “sympathy” between the right and left pupil.

The attachment of the word “sympathetic” to the chain of ganglia outside the spinal cord between T1 and L2 started with Jacob B. Winslow in 1732. Winslow noted that these ganglia were all connected together and thought that they might provide for unconscious “sympathy” between diverse body parts. The nerves that emerged from the ganglia were therefore called “sympathetic nerves.”

The idea that the sympathetic chain was a separate and autonomous nervous system was promoted by Xavier Bichat (1799), who thought there were two separate nervous systems, the animal system represented by the brain and spinal cord, and the vegetable system represented by the “little brains” that lie along the vertebral column (Figure 2). Bichat died at the early age of 33, but his ideas of two nervous systems lasted for nearly 100 years.



Figure 2: Xavier Bichat (1771-1802) promoted the idea of two separate and independent nervous systems. His idea was that the sympathetic ganglia were “little brains” that did their work without any conscious control. Pourfour du Petit had previously demonstrated (1727) that the cervical sympathetic nerves did not arise from the brain as Galen, Vesalius, and Willis had all erroneously concluded. Consequently, Bichat’s theory was widely accepted at the time.

Claude Bernard’s classic work in 1852 demonstrated that the function of the sympathetic nerves was to innervate the smooth muscles (primarily vascular) of the body and thereby adjust the delivery of vital nutrients to tissues according to their metabolic needs. The connection between the conscious brain and the unconscious brains was suspected but not fully demonstrated until William H. Gaskell (1885) convincingly demonstrated that the intermediolateral nucleus (IML) of the spinal cord sent fibers directly into the sympathetic ganglion *via* the white rami communicantes from T1 to L2. The IML received abundant innervation from the brain stem (vasomotor center) and hypothalamus, and this anatomical substrate was the connection that buttressed the association between the central nervous system and blood pressure, through the sympathetic nerves.

John N. Langley mapped out the pathways of the sympathetic nerves by painting the ganglia with nicotine, an agent that first stimulates and then blocks ganglionic transmission. Langley’s summary of the sympathetic system, appearing in the year 1900, was the definitive work throughout the 20th century.

Two recent books^{1,2} and the review article in *Anesthesiology* have highlighted the advancements made in our understanding of the sympathetic nervous system over the past 20 years. These documents indicate that the sympathetic

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nervous system is not simply the neural substrate for the “flight or fight” response to stress. Rather it is finely tuned to control each organ system and has influences on immunity, nociception, lipolysis, glandular secretions, gastrointestinal motility, and renal function (renin secretion). Clearly, it has much wider effects than those on just heart rate or blood pressure, although baroreceptors and the cardio-accelerator nerves are vital components.

This wider view of the sympathetic nervous system elucidates that it is composed of three peripheral neurotransmitters, 10 peripheral receptor subtypes, nearly 20 central neurotransmitters, 18 peripheral co-transmitters, approximately 100 sympathetic ganglion (little brains of Bichat), multiple CNS nuclei (Whytt’s sentient principle) in the spinal cord, brain stem, and hypothalamus, millions of single neurons, and smooth muscle neuromuscular junctions throughout the body from toes to the top of the head. It is a massive orchestra with thousands of instruments and it plays 24 hours a day.

When faced with the astounding complexity of the sympathetic nervous system, it might be appropriate for us to abrogate our historical role as “sympathetic-ologists” and perhaps even discontinue our use of the word “sympathetic.” Most of our rudimentary clinical discussions on the topic could be carried out without much loss of meaning, and perhaps more accuracy, if we substituted the words “heart rate” or “blood pressure” or “cardiovascular stimulation or inhibition” for “sympathetic.”

However, now that we have opened the discussion on the term “sympathetic,” there is no easy retreat. Once anesthesia and surgery begin, the “little brains of Bichat” and the “sentient principle of Whytt” are thrown into some degree of disarray. Our job is to guide the “little brains” through this difficult surgical period and work with them to protect cardiac, renal, gastrointestinal, and immune functions. When the procedure is over we need to help them regain their equilibrium, even in the presence of adequate pain control. Now we have new tools to assess the sympathetics, including heart rate variability, plethysmography, TEE, and cardiac output monitors. Another 70 years should be adequate to meet this challenge, but if the motivation is not there, then perhaps we should follow Guedel’s example and not use the word at all.

References

- 1: Goldstein, David S. *Adrenaline and the Inner World*. Johns Hopkins University Press, 2006
2. Janig, Wilfred. *The Integrative action of the Autonomic Nervous System*. Cambridge University Press, 2006.