Concept Paper

The Traditional Autonomic Narrative Misleads Yet Persists — A Critical Review and Proposed Alternative to Replace It

David Adelson *

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The Traditional Autonomic Narrative Misleads yet Persists—A Critical Review and Proposed Alternative to Replace It

A Revised Theory of Autonomic Function

David W. Adelson

David Geffen UCLA School of Medicine, Division of Digestive Diseases, Los Angeles, California, USA; dwadelson@gmail.com

Abstract

The dominant narrative of autonomic nervous function remains essentially that proposed by Walter B. Cannon over a hundred years ago. It emphasizes sympathetic mediation of "fight-or-flight" responses and catabolism and associates the parasympathetic system with "rest-and-digest" functions and anabolism. Dual innervation of tissues and an antagonistic relationship between the divisions is presented as the rule, with minor exceptions. Extensive evidence accumulated over the past century renders these generalizations untenable, as autonomic neuroscientists have been pointing out for decades. Yet such critiques have not changed how the system is taught or understood. To remedy this situation, it is proposed that an alternative framework is needed that aptly summarizes sympathetic and parasympathetic functions, respectively. Here, following a systematic critique of the traditional approach, such an alternative is proposed based on a consideration, first, of functions in tissues innervated by only one branch, such as the kidneys, and then, of specific functions in tissues receiving dual innervation where distinct regulatory responsibilities of one or the other branch is clear, e.g. respiratory sinus arrhythmia and the pupillary light reflex. The proposed schema describes the sympathetic division as the body's "quartermaster," responsible for regulating physico-chemical conditions and distributing metabolic resources to meet, and where necessary adjust, current and anticipated demand, under all circumstances. In contrast, the parasympathetic division is described as the body's "coordinator," regulating secretory and smooth muscle activity involved in interactions and exchanges with the outside world—eating, breathing, speaking, voiding, looking, mating, moving, etc—often closely articulated with associated somatic motor activity. The schema emphasizes that in each tissue, the activity of the respective branches relates to their respective regulatory responsibilities, and not to a generically counterbalancing relationship to the other. The proposed alternative leads to novel hypotheses regarding the function of autonomic innervation in cases where its physiological importance remains obscure, such as the parasympathetic supplies to pulmonary and cerebral vasculature and to airway smooth muscle. It is offered to stimulate debate directed toward the creation of a consensus alternative narrative that can displace the misleading traditional narrative and advance a more realistic view of autonomic function.

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Introduction

The traditional description of the functions of the sympathetic and parasympathetic divisions of the autonomic nervous system (ANS) remains ubiquitous, over a century after its introduction by Walter B. Cannon [1]. One can find it summarized in any number of medical textbooks, in the biomedical literature, and on numerous websites. The following example is typical:

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"The two divisions of the autonomic nervous system are the sympathetic division and the parasympathetic division. The sympathetic system is associated with the fight-or-flight response, and parasympathetic activity is referred to by the epithet of rest and digest. Homeostasis is the balance between the two systems. At each target effector, dual innervation determines activity. For example, the heart receives connections from both the sympathetic and parasympathetic divisions. One causes heart rate to increase, whereas the other causes heart rate to decrease," [2].

Other treatments explicitly associate the respective branches with catabolic and anabolic activity, as for example, "[t]he autonomic nervous system is the primary neural mediator of physiological responses to internal and external stimuli. It is composed of 2 branches: the sympathetic nervous system, which mediates catabolic responses, and the parasympathetic nervous system, composed of the vagus nerve, which regulates anabolic responses," [3].

Comparable descriptions are provided in most physiology texts intended for students in biomedical fields. Similar versions are found throughout the peer-reviewed biomedical literature. For example, a recent review on neuroimmune effects on stem cells stated:

"As a counterbalance to the sympathetic nervous system, the parasympathetic nervous system innervates many of the same targets as the sympathetic nervous system to decrease arousal after a threat has subsided and to promote rest-and-digest responses under steady state. … The counterbalancing nature of the sympathetic and parasympathetic nervous systems is crucial for creating an equilibrium that maintains organismal physiology," [4].

Typically, such assertions are made without any supporting citation. They reflect accepted wisdom. Neither reviewers nor editors demand support for the claims. Anecdotally, over many years of asking biomedical professionals in the clinic for their understanding of these systems, not one has offered any other description, although experts in these fields in many medical institutions know better.

Despite its prevalence, this story is not demonstrated fact. Rather, it describes an early interpretation based on extrapolations from a relatively small number of observations, assembled and compellingly described by Cannon. Evidence accumulated over the past century indicates that this story is highly misleading, a point that autonomic neuroscientists have been making for many decades.

Consider for example the following statement, published initially in 1999 by Jänig and McLachlan in Mattias and Bannister's authoritative text Autonomic Failure. Summarizing a comparison of the results of excitation of sympathetic and parasympathetic nerve trunks from over a dozen tissues they wrote:

"The table shows that the idea of antagonism between the parasympathetic and sympathetic nervous systems is largely a misconception. Where there are reciprocal effects on the target cells, it can usually be shown either that the systems work synergistically or that they exert their influence under different functional conditions," [5].

Few would be able to claim greater authority in autonomic neuroscience than these authors, widely respected experts in the field who between them have published hundreds of peer-reviewed articles on the subject, along with various chapters and books. And they are hardly alone in pointing out important flaws in the traditional narrative. The error addressed above is just one of many problems with the traditional story of the ANS that they and many others have repeatedly highlighted. For example, in a 2010 systematic review of sympathetic cardiovascular regulation Malpas wrote, "Historically, the sympathetic nervous system (SNS) has been taught to legions of medical and science students as one side of the autonomic nervous system, presented as opposing the parasympathetic nervous system," [6]. His review presents exhaustive evidence to the contrary, and yet, fifteen years later, and more than a quarter century after Jänig and McLachlan's critique, textbooks of anatomy and physiology, videos on biomedical topics, and the professional biomedical literature all continue to propagate and reinforce this fiction. These criticisms and many others seem not to have changed appreciably how the subject is taught nor how it is broadly understood. For the

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situation to change, something beyond individual critiques of particular features of the story must be required.

The premises of the present work are several. The first is that the traditional narrative cannot be corrected by amendment. Rather, it is misleading in essentially all its major assertions, and its distortions promote a misguided picture of autonomic regulation. It cannot be considered an apt simplification or introductory presentation of the subject. This is not because the compelling examples on which it was based were incorrectly described, but rather because of the interpretive and logical leaps by which general principles were extrapolated from these examples. The 'classical' interpretations were reasonable hypotheses at the time they were proposed, given the then-limited evidence available, but their many failings can now be clearly discerned. Second, because the initial story is so familiar, so persuasive, and has become so entrenched in modern thinking, demonstrations that individual elements of it are problematic or frankly in error are unlikely to cause it to be abandoned. To displace this narrative, it is not enough to point out its various flaws individually, as has been done already, for decades. The flawed underlying logic from which its generalizations arose must systematically be laid bare, and the many critiques that have been made of it must be reviewed together, so as to render inescapable the conclusion that the traditional narrative must be repudiated. Yet, even if repudiated by a community of experts, the traditional narrative still is unlikely to be discarded unless an alternative framework for organizing observations and succinctly and accurately describing the respective regulatory roles of the sympathetic and parasympathetic divisions of the ANS is developed, to serve as a consensus substitute template for future teaching of the subject.

The traditional narrative derives its power in part because it distills experimental observations into simple principles with simple rubrics. The sympathetic system is responsible for "fight-or-flight". The parasympathetic system is responsible for "rest-and-digest". The two oppose each other. While these rubrics distort understanding and promote error, their simplicity is key to their persistence. It would appear crucial that we identify alternative, clear descriptions that can appropriately summarize a now much larger body of available evidence.

It should be noted, however, that the value of producing such alternative descriptions has been questioned. For example, in his insightful 1997 paper, "Inadequate frameworks for understanding bodily homeostasis", Blessing assailed the very idea of an 'autonomic nervous system' [7]. He asserted that this concept, along with several other 'big ideas' that remain foundational in the teaching of neurobiology – including those of the limbic system and the reticular activating system – obscure and mislead more than they clarify and inform. He argued that it was improper to consider the autonomic nervous system (ANS) as a separate nervous system at all, asserting that the coinage reinforces the misconception that autonomic function is separable from and independent of the rest of the nervous system (despite Langley's caveats on this point [8]). Blessing emphasized that only the nervous system as a whole can carry out the functions attributed to the ANS. He aptly critiqued many of the misleading concepts implicit in the notion of an ANS, ultimately arguing that the terms autonomic, sympathetic, and parasympathetic should be abandoned, and asserted that we should, "refer instead to visceral neurons, both afferent and efferent. These neurons can then be seen as representing one mechanism whereby the brain communicates with the bodily organs," [7].

In contrast, in his recent comprehensive monograph on the ANS, Jänig argued in favor of the utility of the terms sympathetic and parasympathetic as they were originally defined anatomically, while cautioning against referring to sympathetic or parasympathetic "**functions**" because to do so, "generates misunderstandings and gives a wrong impression of how these systems work," [9].

In recent decades, superior reviews of the ANS published by various experts have retained the basic terms and anatomical designations introduced by Langley, accurately describing an array of autonomic functions while avoiding the misleading generalizations of the traditional schema [9–13]. However, as noted, the existence of these works has yet to alter the teaching and popular understanding of the subject broadly.

The present work argues that it is possible to develop overarching alternative descriptions of sympathetic and parasympathetic regulatory responsibilities, respectively, that can productively

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organize our thinking about them, while dispensing with the errors and biases of the traditional narrative. Furness has suggested referring to sympathetic and parasympathetic pathways as divisions rather than as 'systems,' to reduce undue associations implicit in the latter term (J.B. Furness, personal communication).

Any alternative formulation of autonomic function should not be based on specious generalizations of the sort that Jänig and Blessing warn against. Yet it is important, and possible, to identify generalizations that enlighten rather than mislead. As Langley put it, "The number of facts which have accumulated on these subjects is so vast that it is imperative to try and co-ordinate them. Every day results are published on quite trivial evidence because no general scheme is borne in mind, and because there is no standard of probability. Such results only serve to obscure the subject; if they were subjected to proper scrutiny, they might become valuable evidence for a general law," [14].

The effort to develop an appropriate narrative of autonomic function is not solely a matter of academic interest. The existing story of the ANS is at the heart of much current medical thought and practice, implicitly or explicitly. For example, the view that the sympathetic division is fundamentally a "fight-or-flight" system underpins the widespread use of drugs targeting peripheral adrenergic signaling to manage a variety of medical conditions. In the United States in 2020, over 250 million prescriptions for adrenergic agonists and antagonists were written, comprising over 10% of the total for the 300 most prescribed medications (Table 1).

Table 1. List of medications that target peripheral adrenergic signaling among the top 300 medications prescribed in the US in 2020. Source: https://clincalc.com/DrugStats/Top300Drugs.aspx, which summarizes MEPS prescribed medicines file data. Note that some prescriptions comprise two distinct compounds, only one of which targets peripheral adrenergic signaling.

Rank	Medication	Number of prescriptions (2020)	Number of patients (2020)	Class
6	Metoprolol	66,413,692	15,007,908	beta adrenergic antagonist
7	Albuterol	61,948,347	17,902,020	beta2 adrenergic agonist
21	Trazodone	26,210,731	5,294,364	5-HT-2A receptor, H1 receptor, and alpha-1-adrenergic receptor antagonist
24	Tamsulosin	24,692,402	5,856,108	selective alpha1A-adrenergic receptor antagonist
26	Carvedilol	23,159,628	4,948,170	beta1, beta2, alpha1 adrenergic blocker
53	Atenolol	12,860,512	3,143,500	beta1 selective beta blocker
75	Clonidine	9,867,546	1,956,023	alpha2 adrenergic agonist
84	Tizanidine	8,705,644	2,269,444	alpha2 adrenergic agonist
115	Fluticasone; Vilanterol	5,678,546	1,087,587	glucocorticoid agonist; long lasting beta2 agonist
143	Timolol	4,295,412	949,166	beta2 adrenergic antagonist
150	Albuterol; Ipratropium	3,967,936	902,034	beta2 adrenergic agonist; acetylcholine antagonist

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160	Mirabegron	3,570,676	838,764	beta3 adrenergic agonist
175	Brimonidine	3,271,308	860,260	alpha2 adrenergic agonist
181	Phentermine	3,071,041	824,329	indirect sympathomimetic
190	Prazosin	2,675,264	460,446	alpha1 adrenergic inverse agonist
195	Dorzolamide; Timolol	2,482,440	604,169	carboanhydrase II inhibitor; beta adrenergic antagonist
209	Doxazosin	2,303,044	559,689	alpha1 adrenergic antagonist
210	Labetalol	2,301,338	586,272	alpha and beta adrenergic antagonist
211	Terazosin	2,285,079	612,834	alpha1 adrenergic antagonist
224	Fluticasone; Umeclidinium; Vilanterol	2,125,887	463,445	glucocorticoid agonist; muscarinic antagonist; beta1 agonist
239	Nebivolol	1,889,275	492,665	b1 selective adrenergic antagonist
251	Epinephrine	1,730,366	1,221,585	adrenergic agonist
254	Umeclidinium; Vilanterol	1,668,008	380,037	muscarinic antagonist; adrenergic agonist
256	Brimonidine; Timolol	1,661,947	344,927	alpha2 adrenergic antagonist; beta2 adrenergic antagonist
267	Bisoprolol	1,467,218	351,588	beta1 adrenergic antagonist
288	Formoterol; Mometasone	1,218,644	277,290	beta2 adrenergic agonist
290	Bisoprolol; Hydrochlorothiazide	1,205,616	299,975	beta1 adrenergic antagonist; thiazide diuretic
300	Guanfacine	1,082,830	271,573	alpha2a adrenergic agonist

Additionally, the ongoing picture of sympathetic and parasympathetic activities as fundamentally oppositional and counterbalanced has led to the notion that the ratio of their respective activities, i.e. “sympathovagal balance”, provides an index of general physiological “balance.” This in turn has been used to support claims that therapies that measure and adjust this ratio to achieve an appropriate “sympathovagal balance” will improve health. While this concept has been effectively critiqued in the technical literature [15], it still enjoys broad public resonance and continues to drive active commercial development efforts.

Most importantly, our ability to explore the integrative action of these pathways is severely limited if we think solely in terms of whether an increase in discharge along one or the other pathway increases or decreases some endpoint. A more physiologically grounded theory of the respective responsibilities of the two autonomic branches, one that can provide a more useful context for hypothesis-driven research, is needed urgently.

The present work offers an alternative summary of the functions of the sympathetic and parasympathetic divisions of the ANS. In the interest of limiting scope, and as with the original

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definition of the ANS, consideration of the important and involved topic of the relationship of this motor output to visceral afferent input is deferred.

The alternative schema offered here is proposed in the hope of stimulating discussion and constructive debate among experts in many fields, with the goal of developing a consensus alternative to the durable, seductive, and yet profoundly misleading caricature that continues to dominate teaching of this subject. To repeat, we should not accept unjustified summaries of sympathetic or parasympathetic function. However, it is justifiable, desirable, and even urgent that we work to find better ones than those that presently dominate. We should strive to identify functional descriptions – abstractions - that are testable, that reflect the existing state of knowledge, that distill a large and diverse body of experimental work into a tractable schema, and that provide a framework for evaluating novel findings. Such a schema should make explicit its simplifications, pointing out where these run into difficulties, and should neither discount nor ignore facts that do not fit the story. Rather, the story should be revised to accommodate the facts.

History and Critique of the Existing Autonomic Schema

Origins

Many properties of the neurons that Langley labeled "autonomic" were well known long before his coinage of the term e.g., [16]. In his 1921 monograph, The Autonomic Nervous System, Vol 1, Langley reviewed various terms previously used to describe what these neurons did, and pointed out how earlier rubrics distorted understanding of their function [8]. He addressed, for example, why the terms 'involuntary' and 'vegetative' were misleading and explained why finding an alternative mattered enough that it made sense to coin a new term, one unburdened by the biases of the existing designations. As Jänig among others has put it, the taxonomy Langley developed has stood the test of time [9].

Since at least the 1700s, the motor pathways innervating smooth muscle and glands were understood as a coherent system, one distinct from somatic motor innervation, responsible for regulating visceral activity throughout the body [17]. Originally, this entire system of motor innervation of secretory tissue and smooth muscle, including vascular smooth muscle, was referred to as sympathetic [8,17]. Langley, however, pointed out the existence of regions along the rostrocaudal neuraxis where preganglionic nerve cell bodies of this system were absent [8,14]. He proposed restricting the term sympathetic to those pathways originating in the thoracolumbar intermediolateral column (IML), and proposed excluding from that designation those whose preganglionic neurons were located in areas either rostral (tectal, bulbar) or caudal (sacral) to it [14]. Since cranial and sacral pathways had a good deal in common with each other but differed from the thoracolumbar pathways in important respects, he argued that these should be seen as distinct subdivisions of what he termed the autonomic nervous system (ANS). By 1905 he had proposed the term parasympathetic to refer to the craniosacral division of the ANS [8]. It should be emphasized that this term indicated an anatomical relationship between the preganglionic cells of this division and those of the thoracolumbar division, though one that implied a host of functional distinctions. The enteric nervous system (ENS), with which both sympathetic postganglionic and parasympathetic preganglionic fibers communicate, was designated as an additional component of the ANS. Other intrinsic networks, such as that of the heart [16], were not included.

Amongst the features by which sympathetic and parasympathetic divisions were distinguished from each other was the predominant neurotransmitter released from the postganglionic nerve terminals of each, the main sympathetic postganglionic transmitter later shown to be noradrenaline [18,19] and the main parasympathetic transmitter being acetylcholine. Application of these transmitters or their receptor agonists to target tissues broadly mimicked effects of electrically stimulating whole visceral nerve trunks identifiable as either sympathetic or parasympathetic, respectively [8].

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Whilst Langley originated the terms autonomic and parasympathetic and conducted pioneering studies on the anatomy and physiology of the ANS, it was primarily Walter Cannon who created and advanced the narrative of the respective functions of the sympathetic and parasympathetic branches of the ANS that has been taught ever since.

Cannon first put forth this narrative in his 1915 monograph Bodily Changes in Pain, Fear, Hunger and Rage, and modified it only slightly, adding some key caveats, in his 1932 book The Wisdom of the Body [1,20]. Modern versions of the narrative follow closely the arguments, evidence, logic and conclusions of the original presentation.

The story is so familiar, and has been so influential, that it can be difficult to view these systems in any other way. It is therefore important to take a step back to examine how, when, and on what basis the original arguments were constructed, and to consider the key logic, facts, and assumptions embedded in the account. Doing so lets us see how coming at the subject from a very different angle of approach – a distinct pedagogy - can, and does, yield a very different picture, one fundamentally at odds with the 'canonical' version of the story.

In the years preceding 1915, one line of research in Cannon's laboratory focused on the physiological effects of adrenaline, and on the emotional states in which circulating adrenaline levels rose markedly [21,22]. In these reports, Cannon first began emphasizing the association that William McDougall had made in his book Introduction to Social Psychology [23], between the "flight instinct" and "fear emotion," and "pugnacity instinct" and "anger emotion." This was later distilled into the seminal rubric "fight-or-flight". One of Cannon's group's studies demonstrated that the increase in blood glucose and the appearance of glucose in the urine in response to emotional excitement (emotional glycosuria) resulted from adrenaline secretion [24,25]. Another concerned the ability of adrenaline to increase the force of skeletal muscle contraction and reduce muscle fatigue [26]. Yet other work showed that adrenaline injections, emotional excitement, or splanchnic nerve stimulation accelerated the coagulation of the blood, and that the effects of the latter two manipulations depended on the splanchnic innervation of the adrenals [27–29]. Cannon recapitulated this body of work from his laboratory and that of others in 1914 in a paper entitled, "The emergency function of the adrenal medulla in pain and the major emotions," which, as the title indicates, focused on the role of adrenaline in intense emotional contexts [22].

In his 1915 monograph, he then combined these ideas with observations on various aspects of digestive function e.g. [30,31] and autonomic control to create the now familiar template [1]. The work opened with a discussion of the impact of various emotions on digestive activity. Cannon divided emotions broadly into two classes, those "favorable" and those "unfavorable" to digestive activity (salivary secretion, secretion of gastric juice, movements of the stomach and intestines, etc). He highlighted the studies of Pavlov and co-workers, which had demonstrated cephalic phase stimulation of gastric activity via the vagus nerve [32]. Later he addressed the suppression of cephalic phase responses to the sight and smell of food by emotional excitement - anger, fear and pain - summarizing these findings as follows: "The conditions favorable to proper digestion are wholly abolished when unpleasant feelings such as vexation and worry and anxiety, or great emotions such as anger and fear, are allowed to prevail," [1]. In more modern terms, we might describe this antagonism in terms of the relationship between ingestive and aggressive/defensive behavioral states. Later in his monograph, Cannon also referred to an antagonism between aggressive/defensive behavior and sexual function.

Having laid this foundational distinction, he then proceeded to a chapter on, "the general organization of the visceral nerves concerned in emotions." This chapter reprised and cited many of the features of the autonomic nervous system identified by Langley. The sympathetic innervation of the cardiovascular system was described, and it was pointed out that the sympathetic innervation carries, "impulses to arteries and arterioles of the skin, the abdominal viscera, and other parts, keeping the smooth muscle of the vessel walls in a state of slight contraction or tone, and thus serving to maintain an arterial pressure sufficiently high to meet sudden demand in any special region; or, in times of special discharge of impulses, to increase the tone and thus also the arterial pressure." It is

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worth noting Cannon's recognition in this passage of a role for ongoing sympathetic drive to the vasculature and the adjustment of such tone in the distribution of blood depending on need, a point which is often absent in modern introductions of the subject, though it has been confirmed in many ways [6].

Returning to the role of the vagus nerve in stimulating digestive activity, Cannon asserted an essential overarching role of parasympathetic pathways in conservative and restorative functions, referencing also the slowing of the heart and narrowing of the pupil as follows:

"A glance at these various functions of the cranial division reveals at once that they serve for bodily conservation. By narrowing the pupil of the eye they shield the retina from excessive light. By slowing the heart rate, they give the cardiac muscle longer periods for rest and invigoration. And by providing for the flow of saliva and gastric juice and by supplying the muscular tone necessary for contraction of the alimentary canal, they prove fundamentally essential to the processes of proper digestion and absorption by which energy-yielding material is taken into the body and stored. To the cranial division of the visceral nerves, therefore, belongs the quiet service of building up reserves and fortifying the body against times of need or stress," [1].

He then proceeded to describe the sacral innervation and its role in control of colorectal and bladder emptying, and of sexual function, concluding that, "[l]ike the cranial division, the sacral is engaged in internal service to the body, in the performance of acts leading immediately to greater comfort," [1].

Cannon next pointed out that sympathetic outflow antagonized the effects of craniosacral outflow: "Thus the cranial supply to the eye contracts the pupil, the sympathetic dilates it; the cranial slows the heart, the sympathetic accelerates it; the sacral contracts the lower part of the large intestine, the sympathetic relaxes it; the sacral relaxes the exit from the bladder, the sympathetic contracts it," [1].

He makes similar arguments regarding the relationship between the sympathetic and sacral outflows. Here he notes that the, "nervi erigentes are the part of the sacral autonomic in which the peculiar excitements of sex are expressed," that the sympathetic is the "division which is operated characteristically in the major emotions," and that, "the suppression of the sexual instinct by conflict is one of the most notorious experiences of this kind in everyday life." However, he does note that, "When the acme of excitement is approaching it is probable that the sympathetic division is also called into activity," and further, that, "the completion of the process…may be due to the overwhelming of sacral by sympathetic nervous discharges. As soon as this stage is reached the original feeling likewise has been dissipated," [1]. He concludes the chapter on the visceral nerves by observing activation of sympathetic nerves had effects broadly similar to those elicited by circulating or superfused adrenaline.

The next nine chapters recapitulate many of the observations and ideas described in the 1914 work on the emergency functions of the adrenal medulla, extending the associations to include the sympathetic system more broadly, and pointing out the physiological utility of the changes wrought by powerful sympathetic activation in the context of what he terms the "major" emotions, primarily those related to aggressive/defensive behavioral states.

After a chapter covering the subject of hunger, Cannon next turned to the critical question of the "interrelations of emotions." The chapter on this topic begins with the comment that, "[e]motions gain expression through discharges along the neurons of the autonomic nervous system." Though rarely recognized, the problematic view that distinct emotional states are expressed along distinct peripheral neural paths, is deeply embedded in the traditional narrative.

After reminding the reader that where dual innervation is present, the outflows of the two branches of the ANS tend to produce antagonistic effects, he proceeds to the, "antagonism between emotions expressed in the sympathetic and cranial divisions of the autonomic system" [1]. Here he argues that, "The cranial autonomic, as already shown, is concerned with the quiet service of building up reserves and fortifying the body against times of stress," and that, "all the bodily changes which occur in the intense emotional states - such as fear and fury - occur as results of activity in [the

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sympathetic] division." He concludes this section by claiming that, "the natural antagonism between these two processes in the body-between saving and expenditure, between preparation and use, between anabolism and catabolism - and the correlated antagonism of central innervations, that underlie the antipathy between the emotional states which normally accompany the processes." This notion, of a fundamental autonomic balance resulting from the opposition of sympathetic and parasympathetic drives, and of a fundamental association of sympathetic function with aggressive emotional states and of parasympathetic function with conservative states has been exceptionally and lastingly influential. Interestingly, Cannon later repudiated the concept of what is now typically referred to as sympathovagal balance in a 1929 study on the effects of total sympathectomy [33], as will be discussed below. The concept has nonetheless remained central to the autonomic pedagogy.

Cannon's original conceptual framework and his approach to describing it became the lens through which all future work was viewed and integrated. It remains the basis of the modern story of autonomic function in popular thinking, and that of a great many biomedical professionals, in diverse areas of biomedical research.

Critique of the Traditional Narrative of Autonomic Function

As has been noted above, the traditional schema is fraught with numerous errors and distortions that render it inappropriate as a basis for teaching or understanding autonomic function. Let us now consider the variety of problems of logic and interpretation embedded in this traditional autonomic narrative.

Inappropriate Extrapolation from Early Examples

It is worth noting that at the time of Cannon's 1915 monograph, the first descriptions of the effects of adrenal medullary extracts [34,35], the discovery of the first hormone [36], the coinage of the term hormone itself [37], and the coinage of the terms autonomic and parasympathetic [14] were all within one to two decades old. Thus, the story describing these systems formed early. Many of the issues with the narrative of the ANS arise from inappropriate extrapolations from the early vivid examples used by Cannon to elaborate to general rules. This type of error can be seen more easily by considering an analogy.

Imagine that every textbook of anatomy, kinesiology or exercise physiology, in describing the functions of the limbs began with the example of their respective motions during typical walking or running. Imagine further a persistent emphasis on the reciprocal, rhythmic pattern in the movements of the limbs in these cases, highlighting that this reciprocal pattern of motion was important to maintaining balance. That the limbs move reciprocally during typical walking or running, and that this pattern plays a role in maintaining balance is obviously true. But consider if this example were then extrapolated to the assertion of a general principle that the arms and the legs have a fundamentally oppositional relationship and that their counterposed activity is essential to maintaining balance. This would not only be incorrect, it would also actively undermine understanding of the functions of the limbs, respectively, and their relationships to each other. It would not in any way account for the relative patterns of motion (or lack thereof) while cycling, or while playing the violin. If these latter examples were treated as minor exceptions to the general rule established by the commonplace example of motion during walking and running, and if counterexamples to the commonly observed pattern during walking and running were ignored or discounted, other than within a community of experts, the result would be widespread misunderstanding. Arms and legs do not fundamentally counterbalance each other. They do different things and sometimes they move reciprocally to maintain balance. Any accurate description of their respective functions would emphasize not the reciprocity seen in canonical examples, but rather, the distinct natures of their respective roles in a variety of tasks.

Of course, there is no danger of such a misunderstanding where our limbs are concerned since we are all intimately familiar with what arms and legs do. In fact, we would consider it ridiculous to assert that reciprocal motion between them was a general rule, and was a pattern required to maintain

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balance. However, in the case of internal functions, whose purposes are unfamiliar, difficult to measure and, until recently, impossible to monitor continuously and at high resolution, we fail to notice the logical error. The initial, compelling story about them, extrapolated from vivid but limited examples, continues to bias our views, even in the face of a mass of evidence contradicting the early assertions.

The Effects of Mass Excitation Do Not Define the Regulatory Functions of a Nerve Supply

Several of the logical leaps and errors of the traditional picture of ANS function relate to important points about nerve function that are obvious when we think about somatic motor function, but which are often underappreciated when considering autonomic function. Usually, we do not speak of the overall "level" of somatic motor nerve activity. It is obvious that for skeletal muscle function what matters is the spatial and temporal pattern of activation that produces the intended motion. Somatic motor nerve activity generates a vast repertoire of highly articulated movements and forces, each appropriate to meeting specific demands or goals. Further, somatic motor control is not less concerned with coordinating fine movements requiring minimal force than with mediating powerful contractions of large muscles. The total amount of somatic impulse activity itself does not indicate the degree or nature of the coordination accomplished by such activity. Similar levels of mass activity in a somatic nerve can occur during very different types of movements, depending on the patterning.

Yet even though there are clearly organized patterns of discharge apparent in recordings from autonomic nerves [38–51], autonomic activity is frequently described in terms of its level - e.g. high, or low, increased or decreased - in the same way that we typically describe hormonal signaling, as though spatial and temporal patterning were not the essential feature and purpose of neural regulation.

There are various reasons for the differences in how we think about spatiotemporal patterning in somatic vs. autonomic motor nerves, but several stand out. Among these, our ability to explore the nature and impacts of physiological coordination in visceral tissues is often quite limited. In many systems, it is hard to recognize and quantify relevant physiological changes driven by coordinated neural activity. Effects on target tissues are often measured in terms of simple endpoints, such as changes in heart rate, or in the total amount of motion (integrated motility) of a segment of the gut, rather than in terms of its fine structure. Stimulation of whole nerve trunks, blocking activity in these trunks, and superfusion of neurotransmitter agonists and antagonists are the typical methods used to study autonomic function. This is much like studying musical composition or performance by striking or damping all the keys of a piano at once. We do not describe musicians as playing "more" or "less" based on the number of notes they play per unit time, nor the average volume of the notes played. However, it is common to find autonomic activity described this way, other than in studies focused on the information content of such activity [e.g. 40, 51, 52].

When discussing somatic motor function, we do not make interpretive errors conflating the significance of level vs. pattern. Electrical stimulation of a whole somatic nerve produces unpatterned contraction – spasm. It does not produce the complex, fluid motion characteristic of ordinary activity because the stimulus lacks the necessary temporal and spatial sequencing in the firing of individual nerve fibers. But since we are quite familiar with the complexity of normal physical movements, it takes little imagination to see how patterned nerve activity would give rise to patterned motion.

Unlike with somatic nerves, shocking an autonomic nerve often produces a 'physiological' pattern of response, and autonomic function is frequently explored using electrical stimulation (i.e. mass simultaneous activation) of autonomic nerve trunks. Changes in the frequency of applied shocks can alter the amplitude of complex responses, and at times can also cause shifts in the pattern or nature of response (see for example [46], Fig. 2). But it is difficult if not impossible to explore how changes in the relative timing of the firing of different nerve fibers in an autonomic nerve might elicit different patterns of output in target tissues. Efforts to investigate such relationships must overcome challenges resulting from the complexity of the connectivity, the difficulty in appreciating,

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measuring, or manipulating subtle differences in function, and a general ignorance of the variety of meaningful physiological responses in the target tissue, not to mention the parallel difficulty of attracting funding to such a speculative and difficult project. Thus, much experimental work has used as a relevant endpoint the increase or decrease in simple measures of activity, e.g. integrated intraluminal pressure in the gut. Yet if we stop to think, for example, about the more than one hundred distinct biologically active substances produced in enterocytes (a great number of which are capable of contracting smooth muscle strips in vitro), the 16 distinct types of identified enteric neurons organized into complex networks [11], the vast complexity of the gut microbiome, and the fact that on the order of 3/4 of the immune system is localized to the gut, then perhaps we do an injustice to think of the extrinsic neural drive to the GI tract, as just one example, simply in terms of increases or decreases of mass activity.

In the case of the intrinsic GI innervation, the enteric nervous system (ENS), the accessibility of the tissue and the many sensitive anatomical and physiological recording techniques applicable to it has made it possible to learn a great deal about the specificity of the neural circuits and the variety of patterns of impulse activity and resulting patterns of motions they are able to generate [11,13,52,53]. Methods presently available for studying the extrinsic autonomic innervation generally provide inferior resolution and are more technically demanding than are those used to study the ENS. But there is no *a priori* reason to assume that it is only the level of extrinsic autonomic activity and not its spatiotemporal patterning that matters in terms of regulatory function. And indeed, there exists a body of research into the information content to be found in the discharge pattern of individual neurons in autonomic pathways e.g. [54]. However, in many quarters autonomic activity is still discussed primarily in terms of level alone. It is to be hoped that projects such as the NIH SPARC initiative may lead to a broader appreciation of the information content present in the impulse activity of autonomic nerve fibers [55].

To appreciate how the pattern of autonomic activity, as distinct from its level, impacts function, consider the sympathetic regulation of the distribution of blood flow in the systemic circulation. Via adjustments in sympathetic signaling, the central nervous system continuously regulates the pattern of arteriolar resistances and venular and venous capacitances throughout the systemic vasculature [6,56]. The CNS, via the sympathetic nerves, controls the relative distribution of cardiac output between and within the various parallel systemic circuits, at pressures appropriate for the proper functioning of the tissues which each of these perfuses. This occurs not just during times of elevated skeletal muscular activity, e.g. during fight or flight or play or mating, but continuously, across all behavioral states, be they aggressive/defensive or otherwise [6,50,57–60]. Importantly, the distribution of the blood flow along downstream parallel vascular paths can vary without requiring a change in the total impulse activity in upstream nerve trunks, if adjustments in vasoconstrictor activity in fibers supplying one set of vessels are offset by reciprocal changes in those supplying others. That is, even when mass sympathetic discharge recorded in a nerve remains constant, this constant level of mass activity may still be driving variations in the pattern of differential blood flow in parallel vascular beds, due to variations in the detailed pattern of firing. Similarly, a given increase or a decrease in mass activity upstream can produce many different patterns of distribution of blood flow downstream; some vessels may receive an increased share of cardiac output even as the bed as a whole receives less, depending on the relative resistances of the various subcircuits. The function of the sympathetic cardiovascular innervation is not to increase or decrease blood supply per se any more than the function of the somatic motor supply is to increase or decrease muscle activity per se. Rather, it is to coordinate distribution of blood flow within the systemic circuit to meet the metabolic needs of all tissues, just as the function of the somatic motor supply is to coordinate the pattern of motions and forces needed to accomplish a wide variety of tasks.

It is also critical to keep in mind that the function of a nerve supply is not defined by only the effects of increased firing, i.e. excitation. We understand the function of photoreceptors to be the detection of light (or, more broadly, the mediation of vision) and are not troubled that photoreceptors signal exposure to light via a reduction, not an increase, in neurotransmitter release. We do not claim

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that photoreceptors exist to detect darkness because they are depolarized in the absence of light and hyperpolarized in its presence.

Tonically active motor neurons can raise or lower the level of the activity they regulate by adjusting ongoing discharge rate either up or down. Whether the regulated variable is directly or inversely proportional to the firing rate, i.e. the polarity of the response, is a separate question, and one not fundamentally tied to the physiological factors driving variations in activity. To repeat, it is a mistake to conflate the function of a nerve supply with the effects of excitation per se.

Note, however, that this is precisely how the traditional autonomic narrative describes the roles of the sympathetic and parasympathetic nerve supplies. It is common, for example, to read that the sympathetic system increases heart rate, while the parasympathetic system decreases it. Indeed, the earlier cited quote from Cannon provides an excellent example of this flawed logic, one commonly repeated in modern treatments: "Thus the cranial supply to the eye contracts the pupil, the sympathetic dilates it; the cranial slows the heart, the sympathetic accelerates it; the sacral contracts the lower part of the large intestine, the sympathetic relaxes it; the sacral relaxes the exit from the bladder, the sympathetic contracts it," [1].

Recall too that, as quoted above, Langley (1903) wrote that: "In the cases in which this double nerve supply exists, the nerves coming from one system do not necessarily produce a different effect from that produced by the other; but, if the effect is different, then all the central nerve-strands of one system have one effect, and all the central nerve-strands of the other system have one and a different effect."

Such usage suggests that it is the ** nerve strands ** that produce the effect, rather than that it is specifically an increase in impulse activity in the majority of fibers in these nerve strands that produces the effect. The distinction may seem subtle, but it is critical. It is at the heart of the misunderstanding about the respective physiological functions of these pathways. In their review of the ANS, Jänig and McLachlan produced a table listing the effects of stimulating the sympathetic or parasympathetic supply to a variety of tissues, the title of which made explicit that the effects listed were effects of excitation [5,12], but most treatments are not this careful and instead imply that one or the other nerve supply per se is responsible for changes of a given polarity. This is misleading.

The great majority of autonomic fibers are tonically active [12], and changes in the activity along a given tonically active pathway can alter the degree of activity in the target tissue in either direction, depending on the polarity of the change. Consider for example the variation in heart rate due to respiratory sinus arrhythmia (RSA). During each respiratory cycle, variations in parasympathetic drive alternately accelerate and decelerate the heart during inspiration and expiration, respectively [61–65].

Or consider pupillary control. Pupillary diameter is determined by a balance of the tone of the iris sphincter muscle, referred to as the constrictor muscle since increases in its tone narrow the pupil, and that of the radial muscle, referred to as the dilator or dilatator since increases in its tone widens the pupil. In broad terms, though with caveats, parasympathetic drive to the sphincter exerts the predominant influence on the sphincter muscle tone, while sympathetic drive exerts the predominant influence on the radial muscle tone [66]. Lowenstein and Loewenfeld demonstrated that either parasympathetic inhibition or sympathetic excitation alone can dilate the pupil [67]. Interestingly, in the anesthetized animals they studied, "differences in velocity, extent and duration between the two types of pupillary dilatation give each of the reactions a characteristic shape in the pupillogram. It is thus easy to differentiate between them without having to go, in each experiment, through the complicated maneuvers of selective denervation generally needed to determine the nature of the response," [67]. That is, the pattern, but not the direction of the response, per se, provides important information regarding which branch is responsible. Mathôt, however, noted that, "In behavioral experiments, it is not possible to distinguish 'undilation' from constriction, or 'unconstriction' from dilation" [68,69]. Leaving aside the complexities of specific phenomena, the relevant point is that changes in discharge along either the so-called constrictor or so-called dilator pathways can produce either narrowing or widening of the pupil, the difference being one of the polarity of the change in

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impulse activity needed to effect widening or narrowing. The important question concerns what factors cause one or the other branch to produce narrowing or widening, under what circumstances. Further, it need not be the case that the factors to which each responds always drive oppositional responses, as we shall see.

The impacts of conflating the effects of excitation of a nerve with the purpose of that nerve supply are insidious and undermine a proper understanding of the physiological functions that these pathways regulate. When trying to construct an appropriate framework for describing the functions of the sympathetic and parasympathetic innervation of a given tissue, respectively, we should give careful thought to the regulatory purposes of each, rather than default to the notion that the two systems exert generically opposing influences to achieve some "balance" simply because mass activation of the respective nerves produces opposing effects on a measured endpoint.

Consider again the example the autonomic control of pupillary diameter. The classical story suggests that the sympathetic system is responsible for pupillary dilation and that this dilation is associated with alerting situations ("fight or flight"), that the parasympathetic system is responsible for pupillary constriction and thus with "resting" or "conservative" situations, and that pupillary diameter is controlled by the balance of sympathetic and parasympathetic influences. Again, this confuses the effects of increased nerve activity per se with the purpose of the innervation. It ignores the fact that adjustments in tonic activity of either autonomic branch can change pupillary diameter in either direction, as just noted. Most importantly, it overlooks the question of the functional difference between, for example, an increase in pupillary diameter due to excitation of sympathetic fibers supplying the iris dilator (radial) muscle, vs. an increase in pupillary diameter resulting from a decrease in tone of the parasympathetic drive to the iris sphincter muscle.

A more informative narrative, grounded in experimental work, would concern itself with the physiological circumstances in which the activity of one or the other extrinsic pathway is engaged. In the case of pupillary control, a large body of work reviewed in a later section demonstrates marked asymmetry in the regulatory responsibilities of the two branches. Dynamic pupillary control related to luminance and gaze, i.e. to the visual task, is clearly regulated via parasympathetic fibers in the third cranial nerve. In contrast, sympathetic pathways appear responsible for setting the tonic level of pupillary tone, and for varying pupil size with state of arousal, as will be discussed.

The above arguments emphasize the importance of how we define function or endpoint when attempting to understand the regulatory responsibilities of the respective pathways in tissues with dual innervation. The way we frame the distinct regulatory responsibilities of the two divisions can be thought of as hypotheses, and such hypotheses have the virtue that they can be explored experimentally in ways that blanket statements about oppositional effects cannot.

Sympathetic and Parasympathetic Activities Are Not Generically Counterbalanced

With respect to the question of the pattern of innervation of the two extrinsic branches of the autonomic system, Langley's view differed in subtle but important ways from most modern treatments and is worth quoting again.

"**Thus the tissues receiving efferent fibres from bulbar and sacral autonomic systems have a double nerve-supply, whilst the other tissues have but one**. In the cases in which this double nerve supply exists, the nerves coming from one system do not necessarily produce a different effect from that produced by the other; but, if the effect is different, then all the central nerve-strands of one system have one effect, and all the central nerve-strands of the other system have one and a different effect." (Langley 1903).

Despite Langley's care in making the point that the effect of excitation did not always produce opposing effects, the idea that the two systems functioned fundamentally as counterposed opposites gained traction over the following years. Cannon championed this view initially, as noted in the quotation from his 1915 work above.

In summarizing the relationships between the divisions of the ANS, he further wrote:

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"Sherrington has demonstrated that the setting of skeletal muscles in opposed groups about a joint or system of joints—as in flexors and extensors— is associated with an internal organization of the central nervous system that provides for relaxation of one group of the opposed muscles when the other group is made to contract. This "reciprocal innervation of antagonistic muscles," as Sherrington has called it,** is thus a device for orderly action in the body. As the above description has shown, there are peripheral oppositions in the viscera corresponding to the oppositions between flexor and extensor muscles. In all probability these opposed innervations of the viscera have counterparts in the organization of neurones in the central nervous system," [1].

By the time of his 1929 work on the effects of total sympathectomy in cats, however, Cannon's thinking on the subject had changed, and he argued at length and in depth against the idea of a fundamentally oppositional and balanced relationship between the systems [33]. The detailed arguments he used to contradict his earlier suggestion merit reproducing here, in full. In 1929, he wrote:

"Recent medical literature has many references to hypothetical "vagotonic" and "sympathicotonic" states, and to "autonomic imbalance." The concept underlying the invention of these terms is that the sympathetic and the cranial divisions of the autonomic system are acting constantly in opposition to each other and that the resultant of the conflict is an equilibrium between the two. There is evidence of opposition in some organs, but not everywhere. For example, there is no evidence that sympathetic impulses are acting tonically to inhibit the muscular functions of the stomach and intestines-splanchnic section does not accelerate the passage of material through the canal (see Cannon, 1906). There is no evidence that these impulses act tonically to check the operations of the digestive glands, or to maintain a continuous slight contraction of the muscles of the hairs. It could hardly be expected that exclusion of sympathetic influences could bring about a condition of "autonomic imbalance" in these regions. The chances are more favorable where there is some indication of sympathetic tone.

"For a time after sympathectomy the pupils are constricted, the nictitating membrane extends outward from its corner of the eye, the heart rate is slower, and probably the arterial blood pressure is somewhat reduced. These conditions might be seized upon as evidence of the "vagotonia" which must result when sympathetic tone is banished. But the heart rate is slow after exclusion of the accelerators if the vagi also are cut. Moreover the changes which follow excision of the sympathetic ganglia are not permanent as they might reasonably be expected to be if antagonistic impulses were thus left unopposed. The nictitating membrane is gradually retracted, the pupil becomes less constricted and the denervated blood vessels probably regain to some degree a local tonic state (Langley, 1900).

"In short, pathological symptoms are remarkable for their absence. Thus when conditions are actually produced in the body that would most effectively induce "vagotonia" and "autonomic imbalance," the phenomena attributed to that state are local, slight and temporary," [33].

Modern autonomic scientists might take issue with some of the points Cannon makes here, including the suggestion of a minimal degree of tonic sympathetic drive to the gut, but this does not diminish the relevance of the arguments countering his earlier proposal. Despite his repudiation of it, however, the notion of a functional opposition and counterbalanced relationship between sympathetic and parasympathetic divisions of the ANS persists. Indeed, this view of a fundamental antagonism between the activities of the two – and the related notion of a fundamental importance of a global "autonomic tone" and an imagined sympathovagal balance - has been among the most durable, and is among the most misleading, parts of the autonomic story [15].

Gibbins criticized this oft-repeated canard in his review of the functional organization of the ANS: "…the insightful work of Walter Cannon has been parodied relentlessly, so that autonomic pathways end up divided into two divisions, the sympathetic and parasympathetic, that struggle against each other to maintain homeostatic balance in the face of potentially fatal stress on one hand (sympathetic "flight or fight") or idle inactivity on the other (parasympathetic "rest and digest").

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Despite the wide-spread prevalence of some version of this view in the popular and scientific literature alike, it is both over-simplistic and misleading," [10].

Jänig and McLachlan have also addressed this point, as already noted, by summarizing the effects of stimulation of sympathetic and parasympathetic nerve trunks on a variety of nerve tissues, demonstrating that the notion of a fundamental reciprocity between the branches is untenable [12].

This is not to say that changes in sympathetic drive and parasympathetic drive do not at times act in opposing directions in target tissues. They obviously do. However, to select those cases where this is the case and to then generalize them to an overarching principle of counterbalanced regulation is unjustified and misleading. That excitation in each branch may producing opposing effects on a given endpoint in a particular circumstance is not equivalent to defining the two systems as fundamentally and functionally counterposed. Again, this is like taking the reciprocal motions of the arms and legs during the everyday examples of walking or running as indicative of the essential functional relationship between the limbs. Clearly, coordination of activity between pathways with convergent targets occurs continuously, as for example happens both for the dynamic variations in heart rate and pupil diameter. But this is a different matter than saying that the two systems fundamentally act reciprocally.

Extensive experimental work in many tissues supports the view that the respective branches of the ANS each regulate the activity of target tissues in distinct ways, based on distinct factors. Sympathetic and parasympathetic pathways mediate qualitatively different aspects of physiological regulation, just as, for example, fiscal and monetary policy impact qualitatively different aspects of economic activity. Jänig and McLachlan's (1999) point that, "the systems work synergistically or […] exert their influence under different functional conditions," must be kept front of mind. It is this point that any pedagogy on the subject should emphasize. Just as importantly, we should seek to explore and understand the nature of these qualitative differences.

Not "Fight or Flight" – Not "Rest and Digest"

The Sympathetic Is Not Fundamentally a Fight-or-Flight System

Ask most people – including most biomedical practitioners - what the sympathetic system does, and they will respond that it is involved in "fight-or-flight" responses. They do this for a reason. The example of how sympathetic activation leads to diverse physiological responses as part of the coping response to exigency is used to introduce the essential role of the system in nearly every overview of the ANS, at every level from the most elementary to advanced texts. If people "know" only one thing about the autonomic nervous system, it tends to be this.

As already noted, these concepts can be directly traced to Cannon's early narratives, based on a fundamental juxtaposition of the emotions favorable vs those unfavorable to gastric secretomotor activity. Let us now turn to the logical and interpretive flaws embedded in this description.

First among these is treating the pattern of physiological responses evoked by emotions "unfavorable" to gastric secretions as stereotypic. Citing Biedl (1913), Cannon (1914) summarized the responses to "fight-or-flight" situations:

"Fear and anger - as well as worry and distress - are attended, as already stated, by cessation of the contractions of the stomach and intestines. These mental states also reduce or temporarily abolish the secretion of gastric juice. Adrenin injected into the body has the same effect. Besides checking the functions of the alimentary canal, adrenin drives out the blood which, during digestive activity, floods the abdominal viscera. This blood flows all the more rapidly and abundantly through the heart, the lungs, the central nervous system, and the limbs."

Before proceeding to a critique of the extrapolated view of the essential nature of sympathetic function, a brief detour is in order.

In a pair of remarkable books, Human Gastric Function (Wolf and Wolff, 1943) and The Stomach (Wolf, 1965), the impact of various emotional states on gastric function, observed in conscious human subjects with gastric fistulae, were described extensively by the authors. Such open-ended

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investigations likely could not be performed today due to their exploratory, descriptive, and uncontrolled nature. These studies revealed that feelings of hostility can lead to great engorgement and reddening of the gastric mucosa and an increase in gastric contractions and acid secretion, as opposed to the reduction in gastric blood flow and motility that the narrative of the fight-or-flight effects on the gut would suggest. Further, marked differences were observed between the gastric effects of resentment, anger, worry, and fear, respectively. Some feelings that we would lump together under the rubric of "fight-or-flight" emotions elicit increased gut motility, acid secretion and engorgement, others to blanching of the gastric mucosa and a cessation of contraction and acid secretion. The temporal profiles of the responses also vary depending on the specifics of the situation. In describing their findings, the authors devoted substantial time and effort to describing in detail the temperaments and personal histories of their experimental subjects. They recognized and emphasized that such context affected the changes in gastric activity that were associated with distinct emotional states in individual subjects.

Such observations demonstrate the need for caution when forming catchall categories from disparate states having only some features in common. We may shout to warn others of danger, when coaching young athletes playing sports on a large field, or to overcome excessive background noise at a party. What each of these states has in common is the need to use greater than normal volume to communicate. But to try to create an essential category from such disparate states based on the common need for volume would be a mistake and, if used to describe essential characteristics of vocal communication, would create great misunderstanding.

This brings us to one core problem – though not the only one - with associating the functions of the sympathetic system fundamentally with responses to what Cannon referred to collectively as "emergency" conditions [22].

The notion that adrenaline is a "stress" hormone, and that its primary function is to promote the body's response to emergency situations was extrapolated from such reasoning and persists to this day. But note the inversion. That there is profound secretion of catecholamines from the adrenal medulla and increased sympathetic activity throughout the body, and in particular to the cardiovascular system, during times of emergency or excitement is not evidence that response to emergency is its fundamental signaling purpose, any more than the fact that we shout during emergencies or that our legs are maximally active during urgent flight merits describing either the voice or the limbs as fundamentally associated with responses to urgency or threat. Nor does demonstrating that impairing the functions of the limbs or the voice has the greatest impact on responses to exigency. Yet in the case of adrenaline and the sympathetic system, such logic has underpinned the view of their essential purpose since Cannon's time. The existence of careful work demonstrating the continuous regulation of adrenaline secretion as part of ongoing homeostatic regulation [70,71] has not affected its reputation as fundamentally a "stress hormone."

By insistently focusing on examples that emphasize the effects of sympathetic signaling during times of excitement or threat, we encourage and reinforce a foundational logical leap and error. The legs are maximally active during vigorous activity – fight, flight, and any number of forms of physical exertion that are not related to either fight or flight (play, sex, etc). Paralyzing or amputating the legs impairs most the most extreme forms of physical exertion most dramatically. An amputee is still able to move about a room and to maintain balance, but she is unable to run (without prostheses). However, these observations do not constitute proof that the fundamental role of the legs is to engage in fight-or-flight responses, nor does it argue against their essential role as part of a general system for locomotion and balance. And were these observations used as such proof, again, the result would be a fundamental misunderstanding.

To repeat, that a system is maximally active under a given set of circumstances does not demonstrate that responding to such circumstances is the fundamental purpose of that system. Nor does evidence that impairing a given system interferes with an organism's response to extreme challenge constitute supporting evidence for such an interpretation, though it is used in this way. In the case of the autonomic system such logical errors persist because, unlike with the legs or the voice,

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we are not conscious of the pattern, for example, of sympathetic firing during our daily activities. We are not consciously aware, for example, that sympathetic activity is involved in regulating blood sugar at all times, or in regulating gastric vasomotor function at all times including during digestion [71–76]. Unfortunately, the incessant use of the marked physiological responses to duress as the characteristic example of sympathetic function skews our thinking about its purposes, leading to profound misunderstanding.

In this regard, it is noteworthy that, in introducing his seminal 1915 work, Cannon pointed out that we are familiar with the "surface manifestations of excitement," among which he listed, "contraction of blood vessels with resulting pallor,' the pouring out of "cold sweat," the stopping of saliva-flow so that the "tongue cleaves to the roof of the mouth," the dilation of the pupils, the rising of the hairs, the rapid beating of the heart, the hurried respiration, the trembling and twitching of the muscles, especially those about the lips." He went on to point out that there are, "other organs, hidden deep in the body, which do not reveal so obviously as the structures near or in the skin, the disturbances of action which attend states of intense feeling," and that special methods are required to, "determine whether these deep-lying organs also are included in the complex of an emotional agitation," [1].

Note that among these surface manifestations listed, not one would lead us to think that that the essential function of any of the structures so engaged – blood vessels, sweat glands, salivary glands, pupils, hair, the heart, the respiratory system, the skeletal muscles and especially those about the lips – was fundamentally associated with the response to exigency. We do not associate any of these "surface" systems primarily with responding to fight-or-flight situations. Yet the deeper structures and systems – the sympathetic system and the adrenal medulla – about which relatively little was known when these ideas were first introduced - have been associated in this way ever since, to our detriment.

This view of the sympathetic system as a whole as primarily concerned with stress responses was further advanced by Cannon et al.'s interpretations of the effects of total sympathectomy in his 1929 work, "Some aspects of the physiology of animals surviving complete exclusion of sympathetic nerve impulses," [33]. The observation that sympathectomized animals could survive indefinitely under ordinary laboratory conditions was taken as evidence that the function of the system was primarily to respond to emergency conditions. The summary from this paper is worth quoting directly:

"The slight effect resulting from sympathectomy raises the question as to the function of the sympathetic. This question is considered with regard to the natural conditions which excite the sympathico-adrenal system, and the conclusion is drawn that this system, dispensable in the protected conditions of the laboratory, finds its great service at times of critical emergencies when it adjusts the internal organs of the body for use of the mechanisms responding to external exigencies."

Yet the same paper contains many observations that could support a view different from the one associating sympathetic function primarily with stress situations, were it not for the bias toward that conclusion. For example, it was noted that, "[s]ympathectomized animals are very sensitive to cold; having lost the means of conserving heat they seek warm places, and when placed in a frigid environment they lose heat more rapidly than normal animals," and that, "The basal metabolism usually falls somewhat after sympathectomy, especially after the cervical portion is excised, but as a rule removal of the sympathetic chains does not reduce the basal metabolic rate more than 10 per cent," [33].

In addition to these observations, it was also noted that emotional excitement evoked by physical restraint did not evoke any change in blood sugar in sympathectomized animals, while the blood sugar of control cats rose by a third. Similarly, in sympathectomized animals but not controls, such excitement failed to increase blood pressure and red and mononuclear blood cell counts, though the number of subjects tested did not allow for statistical analysis.

The results above clearly indicate a role for the sympathetic in key physiological changes in response to duress. However, the leap to the conclusion that the sympathetic is inherently an

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"emergency response system" is unwarranted, for all the reasons given above. The problem is that any narrative accounting for a set of facts can be used to reach an inappropriate conclusion if it omits contrary facts. Critically, one's initial perception may cause one to downplay or ignore facts that contradict that initial view. Bias is a powerful force.

In this case, the view that the sympathetic division is primarily concerned with and exists to respond to "fight-or-flight," or more generally "stressful," situations is untenable. Sympathetic regulation certainly plays a role in the many physiological events associated with such situations. But extensive evidence accumulated over the decades demonstrates that sympathetic activity continuously regulates the state of the internal milieu, across all behavioral states. For example, it, "plays a key role in the moment-to-moment regulation of cardiovascular function at all levels from quiet resting to extreme stimuli" [6]. This includes control of arterial pressure, cardiac output and total peripheral resistance over both short and long time spans, as well as the articulated pattern of arteriolar resistances that determine the distribution of cardiac output among the tissues, and of venular and venous capacitances that influence venous return [6,60,77,78]. Sympathetic nerves regulate the output of adrenal medullary epinephrine and norepinephrine in response to even slight variations in blood glucose and blood pressure, respectively [71]. The sympathetic division provides the sole innervation of the kidney [79,80], and is responsible regulating renal function including continuous influences on renin secretion, urine production and salt balance, renal blood flow and glomerular filtration [46,58,59,81]. The sympathetic division regulates various aspects of normal digestive processes including but not limited to the control of intestinal fluid fluxes, as well as regulating changes in cardiovascular function associated with digestive function [11,13,73,82]. It provides the sole innervation of adipose tissue [83–87] and is involved in regulating diverse aspects of adipose tissue function including mobilization and deposition of lipid reserves [84,88,89]. It provides the sole innervation of piloerector muscles, eccrine sweat glands, and the cutaneous vasculature and regulates thermal control continuously [90]. Sympathetic activity regulates the sleep wake cycle via pathways connecting the hypothalamus, via the superior cervical ganglion, to the pineal gland [91,92], whose synthesis of melatonin is regulated by norepinephrine [93]. The forgoing list is not exhaustive.

Again, it must be emphasized that we do violence to our understanding of the purpose of a given nerve supply when we think solely in terms of the effects of great increases in mass discharge. To repeat, the purpose of a nerve supply is to allow a spatially and temporally articulated pattern of signaling. As with speech, it is pattern, and not only volume or rate, that determines specific meaning. We shout in exigent circumstances, but not only then. And our voice is not more an alerting system and less a communication system because it is more forcefully engaged during shouting than when speaking at normal volume, nor is its role in communication when we whisper less fundamental than when we shout. It is not an appropriate first approximation to the truth to say that our voice is fundamentally a fight-or-flight communication system, nor the arms and legs fight-or-flight limbs nor the heart a fight-or-flight pump because each is engaged at maximum intensity during such situations. To emphasize the role of any of these systems in responding to intense demand and thereby to suggest that this is their essential function is a distortion, one that would undermine understanding of their true physiological roles.

The Parasympathetic System Should Not Be Described as a Rest-and-Digest System

The association of the sympathetic system with "fight-or-flight" responses is frequently counterposed to a supposed "rest-and-digest" parasympathetic sphere of responsibility. Such claims are almost always made without any supporting citation. As with the "fight-or-flight" caricature of sympathetic function, this view of parasympathetically-mediated functions obscures observations that do not fit under this rubric and actively promotes misunderstanding of the system. Examined critically, the examples that Cannon offered to support this view of parasympathetic function are not robust proofs. Extensive evidence accumulated since his early proposals indicates that this rubric also should be abandoned.

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Of course, it is certainly true that during times of duress and exertion sympathetic activity suppresses many aspects of digestive activity and may shunt blood from the abdominal viscera to the skeletal muscles to support exertional activity. But while the patterns in the distribution of metabolic resources and tissue function differ between aggressive/defensive vs. ingestive states, it does not follow that changes in parasympathetic activity are responsible for the redistribution of metabolic resources during the latter.

It is worth asking, for example, what experimental work shows that parasympathetic activity is responsible for the redistribution of blood flow from skeletal muscle to the splanchnic beds following arousal? I am unfamiliar with such work, and the absence of a parasympathetic innervation of either the skeletal muscle vasculature or most of the splanchnic vasculature (exceptions include areas within the portal circulation [94]) and specific secretory tissues suggests that autonomic control of the redistribution of cardiac output following arousal is sympathetically-mediated, just as the redistribution in the other direction at the start of arousal is sympathetically-mediated. This is not to ignore autoregulatory effects on the distribution of blood flow as visceral tissues become activated due to parasympathetic excitation, but it is important to note that there is abundant evidence of the sympathetic regulation of systemic and gastrointestinal blood flow during normal digestive processes [73–76,95].

The notion that parasympathetic activation of the GI tract is only associated with digestive and restful states is also contradicted by the observation that hostile emotions powerfully stimulate gastric motor and secretary activity via vagal pathways, as has already been discussed [96–98]. Excitation of vagal pathways is also responsible for the marked increase in gastrointestinal motility under conditions of cold restraint stress, among others [99]. Thus, it is inappropriate to consider vagal activity as solely concerned with stimulation of gastric activity under “conservative” or restful conditions.

With respect to its involvement in resting or conservative states, while there exists extensive evidence of an important role of the sympathetic regulation of the sleep-wake cycle via adrenergic control of pineal melatonin production [93,100], evidence for parasympathetic control of melatonin secretion is largely lacking, although evidence does exist for a relatively sparse parasympathetic innervation of the pineal gland [101]. And a fundamental parasympathetic association with anabolism generally is belied by the absence of a parasympathetic innervation of either adipose tissue [84,86,87] or skeletal muscle, two key loci of anabolic activity.

“Evidence” for the supposed rest-and-digest sphere of responsibility of the parasympathetic system typically includes some or all of the following: that increased vagal drive to the gut stimulates gastrointestinal contractility and secretory activity, that parasympathetic stimulation is associated with voiding of the bladder or rectum, that increased vagal drive to the cardiac pacemaker slows the heart, and, in something of a reach, that increased parasympathetic drive to the pupillary sphincter reduces the amount of light input by narrowing the pupil. To this is sometimes added the observation that parasympathetic drive promotes insulin release. Let us consider each of these phenomena in turn.

The parasympathetic innervation of the sphincter pupillae, via the third cranial nerve and the ciliary ganglion, is responsible for the pupillary light reflex and for mediating lens accommodation [66,102]. Each persists in the face of sympathetic but not parasympathetic denervation (though the tonic level of pupillary diameter is reduced by sympathetic denervation) [66,103]. Changes in lens shape depend on the visual task being performed and are not a function of the state of arousal but rather the position of the object of focus. It is difficult to see how parasympathetic control of accommodation or of the pupillary response to light can be shoehorned into a general principle of rest-related functions (and certainly not into a category of digestive functions). Additionally, as noted previously, it is a logical error to associate of the function of a tonically active nerve pathway solely with the effects of increases in tonic activity. Thus, the notion that the constriction of the pupil due to increased parasympathetic drive is generically associated with a reduction in arousal and retreat into a resting state can only be defended if one is committed to such a view *a priori*. It is not an apt

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description of the true purpose of the system, even as a simplification or introductory view. It is frankly misleading to describe the purpose of this innervation as part of a "rest-and-digest" complement of functions.

Similar logic can be applied to the slowing of the heart by the parasympathetic activation in nerves suppling the cardiac pacemaker, at least in some contexts. For example, respiratory sinus arrythmia (RSA) occurs due to the waxing and waning of heart rate with the inspiratory and expiratory phases of the respiratory cycle, respectively [61,62]. Unless one wants to argue that every respiratory cycle consists of an entry into a relatively restful state and an emergence from it into a state of relative arousal, it seems inappropriate to associate parasympathetic regulatory function fundamentally with rest. There exists at all times a level of parasympathetic drive to the cardiac pacemaker, and this level is subject to continuous modulation either up or down – that is, it is responsible for both the slowing and the acceleration of heart rate in anticipation of and in response to intrathoracic pressure changes [104]. RSA is reduced at high levels of sympathetic activation, but it seems far more likely that this component of parasympathetic cardiac control is involved in aspects of cardiorespiratory coordination than in mediating what Cannon called "restorative" functions per se, as will be discussed further in a later section.

With respect to the observation that parasympathetic drive stimulates insulin release, it should be noted that increased parasympathetic firing also stimulates glucagon release [105–107], though presumably via a different population of fibers acting at different times than those responsible for regulating insulin release. This fact, along with the point made earlier that a tonically active fiber supply can either increase or decrease the targeted variable based on the polarity of activity change, makes clear that it is more appropriate to say that the parasympathetic innervation of the pancreas participates in the regulation of the islet hormones that regulate blood sugar levels, not that it is responsible for decreasing blood sugar *per se*. The important question is, under what conditions and for what reasons does the parasympathetic system vary the secretion of insulin and/or glucagon? To answer questions of this sort, an alternative framework for thinking about the regulatory roles of each system is needed, and this question will be addressed after introducing such an alternative.

Of course, cholinergic parasympathetic drive to the gut does stimulate digestive activity. But to emphasize this aspect parasympathetic regulatory activity while downplaying or ignoring the many other aspects of parasympathetic anatomy and physiology undermines understanding of the system. Observations that are either not accounted for, or are accounted for poorly at best, include the roles of parasympathetic nerves in regulating aspects of reproductive function, vision, respiration, and so on, as well as regulating vascular function in specific vascular beds (cerebral, pulmonary, genital, etc) but not in the general systemic circuit.

Thus, we ought to reject rest-and-digest as a summary description of parasympathetic function, and we should not take, a priori, the presence of parasympathetic innervation of any given tissue as suggesting "conservative" regulatory function. To do so is rather like choosing to teach that the function of the hands is primarily related to musicianship based on examples of their role in playing the piano, committing a musical score to paper, and tuning a guitar.

Proposed Alternate Framework

If the traditional autonomic pedagogy is misleading and should be discarded, and if its persistence is due primarily to the absence of a competing narrative as has been argued here, then what story should take its place?

In 1915, of course, the number of facts known about the autonomic system were relatively few, certainly compared to today. Cannon's schema organized, in a compelling and accessible way, many of the known phenomena. Yet today we have access to a much larger body of knowledge, one that demands a reconsideration of the early narrative.

Of course, this larger body of knowledge is a dual-edged sword: we have more information from which to develop a sounder narrative, but any story we tell must account for a much greater volume and diversity of observations. This can complicate the task of distilling overarching principles

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consistent with all that is known. Any alternative schema should provide descriptions that aid in understanding these systems to the degree this is possible, but not beyond.

Distinct Spheres of Regulatory Responsibility of the Sympathetic and Parasympathetic Divisions of the ANS

As has been argued above, we can confidently reject the hypothesis that the sympathetic and parasympathetic activities are generically counterposed and reciprocal. Instead, we should emphasize that the two branches are responsible for qualitatively different aspects of physiological regulation. The challenge is to come up with apt descriptions of the distinct spheres of regulatory responsibility of each that do not distort understanding, as does the traditional narrative. Such descriptions should enlighten rather than mislead and should clarify rather than obscure patterns of integrative action. Ideally, they should provide the basis for exploring the functional interactions between the two branches in those situations where their respective regulatory roles are intimately interrelated, as for example in the case of cardiorespiratory regulation.

To construct an alternative narrative, let us approach the subject from a very different starting point than that of the traditional pedagogy. Rather than beginning with an account of the effects of mass activation or blockade of one or the other type of innervation in those tissues with convergent innervation from both, let us consider first those situations in which one or the other system is wholly or largely absent, and then proceed to situations where a predominant or exclusive role of one or the other branch in specific regulatory activities is well-established. This will help clarify the responsibilities of each branch and thus guide formation of hypotheses concerning the relative roles of each in tissues where they converge.

Functions Regulated via the Sympathetic Division

As already noted, the sympathetic division provides the sole autonomic innervation of the kidneys, as well as of the eccrine sweat glands, piloerector muscles, adipose tissue, and the bulk of the systemic vasculature (with specific exceptions, to be discussed later). What might this pattern of innervation suggest regarding broad sympathetic regulatory responsibilities?

Let us start with the renal innervation. The kidney obviously plays a critical role in controlling the internal milieu. It receives a rich, tonically active, sympathetic supply [39,41,42,108,109]. Interestingly, very little attention has been given to the absence of a renal parasympathetic supply [79,80]. It seems that the implications of this fact for the interpretation of the respective responsibilities of the two branches of the ANS has not received much attention either. I have yet to find an introductory text that lists the kidney among the list of tissues receiving only sympathetic, and no parasympathetic, innervation. Many introductory texts, in fact, continue to prominently feature either Netter's classic illustration of the pattern of whole body autonomic innervation ([110], Section IV Plate 2, p. 70) - or derivatives of it - which clearly shows a parasympathetic innervation of the kidney, subsequently demonstrated (in 1983, see below) not to exist.

Norvell and Anderson, in discussing their 1983 HRP tracing study demonstrating of the absence of labeled cells projecting to the renal nerves in any parasympathetic nucleus (DMV, nucleus ambiguus, nor in sacral segments S1-S3) [79], cited prior studies that noted the presence of acetylcholinesterase positive nerve fibers in the kidney without identifying such fibers as motivation for their work. For example, Barajas et al. had provided evidence that the fibers and terminals expressing acetylcholinesterase were sympathetic [111,112]. It is possible that the bias toward treating dual innervation as the rule causes this demonstration of the absence of renal parasympathetic innervation frequently to be overlooked or dismissed. As of April 2022, PubMed listed only seven citations of Norvell and Anderson's HRP study. Scopus listed twenty-two such citations, several of which have received broader attention. One of the citing works is a recent confirmation of Norvell and Anderson's earlier finding - using fluorogold labeling via microcapsules applied to the renal plexus– of the absence of parasympathetic renal innervation [80]. This lack of parasympathetic renal innervation has important implications for understanding the regulatory responsibilities of the extrinsic branches of the ANS, and this fact should be central to the teaching of the subject.

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The kidney is responsible for controlling long-term blood volume and blood pressure [108,113], hematocrit, whole body fluid and salt balance, and it plays a central role – in cooperation with the lungs – in controlling the pH of bodily fluids. Introductory texts, if they mention sympathetic control of kidney function at all, tend to focus on the sympathetic innervation of the juxtaglomerular apparatus (JGA) and its influences on renin secretion, particularly in the context of hypertension. In fact, all areas of the nephron and its vasculature receive sympathetic innervation, and thus all renal functions –glomerular filtration, regulation of plasma electrolyte and pH balance, osmolarity, urea cycling, etc - are subject to central control via sympathetic pathways [81,108,114]. Differential sympathetic control of distinct aspects of renal function, based on activity pattern, level, and population of fibers activated has been demonstrated [41,43,46,81,108,115].

Central regulation of cardiovascular parameters via the sympathetic supply to the kidney and systemic vasculature is ongoing. Sympathetic pathways control circulating blood volume via renal regulation of salt and water balance, via renal control of hematocrit, and via control of venular capacitance (particularly in the splanchnic beds). By controlling the arteriolar resistances of parallel pathways in the systemic circulation, the sympathetic system controls the proportion of cardiac output that flows through each organ, and along parallel pathways within each of organ. Sympathetic adjustments in venular capacitance are accomplished by a subset of sympathetic ganglion cells distinct from those responsible for controlling arteriolar resistance, demonstrating the articulated nature of such cardiovascular control [116]. By adjusting cutaneous blood flow, piloerection, brown adipose tissue thermogenesis and eccrine sweating, the sympathetic plays key roles in thermoregulation [90]. As the sole motor nerve supply to adipose tissue, sympathetic innervation regulates fat depot mass, cellularity, and lipolysis [84,117].

Thus, it is reasonable to argue that, via sympathetic pathways, the CNS regulates the distribution of metabolic resources and maintains the appropriate physico-chemical environment to support current and anticipated action of the tissues, throughout the body and at all times. As Cannon himself noted in The Wisdom of the Body, “The sacral and cranial divisions of the interofective system, however, operate only indirectly and somewhat remotely to assure a constant state. It is the middle or thoraco-lumbar division which acts promptly and directly to prevent serious changes of the internal environment,” [20, Chapter XVI, p. 262].

Here, it is important to emphasize again that changes in sympathetic activity can adjust the level of regulated physiological variables either up or down, depending on the polarity of the change in activity (i.e. whether it is waxing or waning) [118–122]. Additionally, distinct adrenoceptor subtypes mediate distinct and in many cases opposing effects [123,124]. Sympathetic co-transmitters afford an additional mechanism to differentially modulate sympathetic regulation. A counterbalancing parasympathetic influence is thus not required for complex and varied regulation of innervated targets. Further, sympathetic regulation of physiological variables is not limited to “emergency” situations. Abundant evidence confirms that it occurs continuously, across all physiological states.

This includes digestive states [82]. The digestive hormone, CCK, which is released by intestinal enteroendocrine cells in proportion to the luminal concentrations of protein and fat, mediates increased blood flow in the upper GI tract via inhibition of specific sympathetic vasoconstrictor pathways [72,74,95]. Sympathetic mediation of changes in cardiac output, heart rate, and aortic pressure in response to anticipation of feeding has been demonstrated [75,76,82,125]. Thus, sympathetic modulation of gut blood flow occurs as part of the digestive process and not solely or even primarily under conditions of extreme excitement or physical exertion.

Sympathetic regulation of the physiological variables described above is necessarily integrated across the activity of all the tissues of the body. Sympathetic pathways provide the means by which the central nervous system makes coordinated, continuous, temporally and spatially articulated adjustments to physiological activity everywhere in the body. The brain, acting via sympathetic pathways, is thus able to exert anticipatory control of the global distribution of metabolic resources based on experience and learning about how to optimize solutions to complex, dynamic and multidimensional physiological challenges.

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Despite continuous sympathetic regulation of physiological conditions, Cannon et al. showed clearly that the organism can survive complete sympathectomy [33]. How should this be interpreted? As Blessing has emphasized, it is the nervous system as a whole, and not any subset of pathways comprising it, that ultimately regulates the level of activity and the resulting physiological conditions of the body as a whole [7]. Thus, in the extraordinary situation of the absence of sympathetic pathways the brain and body may compensate using other pathways at their disposal to maintain key physiological variables within the ranges necessary to maintain the integrity of the organism, though presumably without the full range of regulatory flexibility and the resultant physiological "virtuosity." This issue will be addressed in greater detail in a later section.

To summarize then, in contrast to the emphasis on the importance of sympathetic function under conditions of outward exertion - 'fight or flight' responses – a more accurate description would emphasize that the sympathetic system generally is concerned with regulating the internal milieu, continuously, under all physiological states, irrespective of whether anabolism or catabolism dominate globally.

Under exigent conditions, the level of sympathetic activity rises, but so too does the level of skeletal muscular activity, and we do not mistake this as a sign that the skeletal muscles of the limbs and trunk are inherently fight-or-flight muscles. Just as we do not describe the systemic vasculature as a fight-or-flight perfusion system, nor the kidney as a fight-or-flight filtration system, the heart as a fight-or-flight hydraulic pump, sweat glands as emergency thermoregulators, fat depots as fight-or-flight energy reserves, nor the voice as a fight-or-flight communication system, we should not describe the nervous pathways that innervate and regulate these tissues as essentially comprising a fight-or-flight nervous system. To consistently describe it as such is to profoundly undermine and distort the understanding of the purposes of the system.

Functions Regulated via the Parasympathetic System

As already noted, in juxtaposition to the claim that the sympathetic regulation is primarily concerned with physiological changes associated with intense exertion, parasympathetic regulation is typically portrayed as conservative, associated with anabolic states, and "rest-and-digest". As also already noted, this description is as misleading as is the characterization of the fight-or-flight nature of the sympathetic system. If parasympathetic regulation should not be viewed as essentially conservative and inherently counterbalancing to sympathetic regulation, then how might we summarize and generalize parasympathetic spheres of regulatory responsibilities?

Proposed Rubric for Understanding Parasympathetic Functions

Despite his emphasis on the "rest-and-digest" functions of the parasympathetic system, Cannon made another observation about the craniosacral innervation in passing, one that provides a useful jumping off point for thinking about parasympathetic function without the distorting bias of the "rest-and-digest" rubric. Of the craniosacral (i.e. parasympathetic) division he wrote:

"Furthermore, the two divisions – sacral and cranial – are similar in being largely subject to interference by the movement of striated muscle. Just as contraction of the bladder and rectum can be aided or checked by nerve impulses from the cerebral cortex, the reactions of the pupil to light or to distance can be induced by voluntary acts. Indeed, as a rule, the workings of the sacral and cranial divisions involve the cooperation of the cerebro-spinal nervous systems to a much greater degree than do the workings of the sympathetic division, because they are much concerned with external orifices surrounded by striated muscle," [20].

Cannon's choice of words - indicating that striated muscular activity "interferes" with parasympathetic control of structures connected with the orifices of the body - is unfortunate, since what he described was cooperation and coordination between somatic and parasympathetic motor functions associated with the activities of the orifices of the body surrounded by striated muscle. It is also possible to take issue with the characterization of the cooperation between the sympathetic and

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"cerebro-spinal" systems as being lesser, quantitatively, than that between the craniosacral and cerebrospinal systems. A less biased approach might describe the former relationship as being qualitatively different from the latter. With these caveats in mind, however, and with perhaps some widening of focus, Cannon's remarks provide an insightful guide.

Viewing parasympathetic regulation as related to the regulation of smooth muscle and secretory activity associated with potentially highly dynamic interactions with the outside world via the orifices of the body surrounded by striated muscle, and involving intimate coordination with specific patterns of activity of the relevant skeletal muscles, allows for a less biased exploration of the common features of craniosacral innervation and its functions. Such an approach has the great advantage that it encompasses many roles of the parasympathetic innervation that are excluded from the "rest-and-digest" rubric while dispensing with biases that the traditional rhyme perpetuates.

So for example, adjustments in lens curvature associated with changes in fixation point via contraction of the ciliary muscle are clearly under parasympathetic control [66]. Loss of parasympathetic, but not sympathetic, innervation impairs this function. Parasympathetic regulation of lens curvature is coordinated in concert with somatic regulation of the ocular (skeletal) muscles controlling eye movements. Together, these coordinated ocular functions allow for effective tracking of and focus on visual stimuli. Thus, the parasympathetic supply to the ciliary muscle is concerned with a basic visual function that has nothing to do with either rest or digestion or anabolism, and it is not markedly counterbalanced by sympathetic influences [126]. Lens accommodation is critically and intimately coordinated with the activity of the ocular muscles, motions of the head, and with visual function *per se*, and not fundamentally with vision only during resting or conservative states. We will discuss this point further when considering control of pupillary diameter, which is regulated by both parasympathetic and sympathetic activity.

As with control of the curvature of the lens, in both the bladder and the colorectum, voiding is under parasympathetic control. Voiding requires coordination with the activity of the skeletal musculature, including the activity of the external urethral and anal sphincters, respectively, in addition to changes in the activity of the muscles of the trunk [127]. Obviously, as with eating, conscious behaviors are involved in urination or defecation as well. That is, while relaxation of internal sphincters during voiding is parasympathetically controlled, in a healthy individual these changes are contingent on a decision to void, changes in position associated with the act, and specific patterns of activity in the abdominal and trunk musculature. With respect to voiding itself, sympathetic denervation or blockade affects the temporal profile of voiding, but the effect is minor and temporary, while parasympathetic regulation is required to mediate these functions normally [127]. The nature of the counter-regulatory relationships between sympathetic and parasympathetic control of bladder tone will be addressed in a later section focusing on tissues with dual innervation.

In each of the examples above, patterned action of skeletal muscle is coordinated intimately with the activity of skeletal muscle. Similarly, in the upper GI tract, action of the skeletal muscles brings food and drink into the mouth, prepares it by mastication and initiates swallowing. Depending on the species, the esophagus is invested with a greater or lesser degree of striated muscle rostrally. Skeletal muscular activity in the mouth, pharynx, and upper esophagus is coordinated with parasympathetically-regulated secretory activity and smooth muscle activity in the more distal esophagus during swallowing, as well as with relaxation of the lower esophageal sphincter and receptive relaxation of the gastric reservoir [30,128–130]. In the case of the genitals, reflex erection and vaginal lubrication – i.e. that resulting from external stimuli - are mediated by the parasympathetic system, although interestingly, and in contrast, psychogenic erection and vaginal lubrication result from changes in sympathetic activity [131].

Taken together, these observations suggest the value of describing many parasympathetic functions as concerned with coordinating specific patterns of smooth muscle and secretory activity associated with interactions of and exchanges between cranial or pelvic structures – and the internal spaces with which they communicate - with the outside world. Of course, all such exchanges also imply and require changes in the distribution of metabolic resources, most prominently in the

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distribution of cardiac output, and so it would be wrong to claim that the sympathetic system is not involved. But the nature of that involvement is qualitatively different and is not as directly tied to and coordinated with the specific patterns of skeletal muscle activity, as occurs frequently with parasympathetic activity, though of course not exclusively so.

This description of the parasympathetic sphere of responsibility also dovetails nicely with the close relationship of somatic motor nuclei with parasympathetic motor nuclei in the central nervous system. Given the way the topic is presently taught, students can be forgiven their surprise when they first learn that the vagus nerve contains a population of somatic motor fibers arising from within the nucleus ambiguus (which fibers are responsible for control of the laryngeal muscles). Similarly, parasympathetic and somatic fibers comingle in the oculomotor, facial, and glossopharyngeal nerves, and the somatic and parasympathetic nerve nuclei that supply the fibers which course in these nerves lie close to each other. It is also interesting to note that the intermediate gray of the sacral segments essentially merges with the ventral horn, while in thoracolumbar segments the intermediolateral column is well-separated from the ventral horn.

Of course, an intimate relationship to skeletal muscle activity need not be seen as a fundamental feature of all parasympathetic regulation. It is doubtful that such coordination is its sole purpose. That is, the description is not meant to exclude those functions that are not tightly coupled to specific patterns of skeletal muscle contraction, such as changes in hepatic or pancreatic secretory activity that may be related to impending digestion and absorption of nutrients postprandially.

We will return later to the question of how the relationship between thoracolumbar and craniosacral innervation in tissues receiving convergent innervation might be interpreted with respect to this description of parasympathetic functions, with special attention given to the innervation of the bladder, gut, heart and iris - canonical examples used in the traditional narrative to illustrate a supposed fundamental counterbalancing oppositional relationship between the activities and functions of the two branches.

Before this, however, let us consider the autonomic innervation of the airways and the pulmonary vasculature, instructive topics that are rarely if ever addressed in the traditional autonomic pedagogy.

Parasympathetic Innervation of the Airways and Pulmonary Vasculature

Airways

Extensive parasympathetic innervation of the airways is present throughout vertebrate phylogeny [132,133]. Vagal preganglionic fibers supply intrinsic ganglia located around airways, and postganglionic fibers emerging from these innervate airway smooth muscle and mucous glands [134,135].

Airway diameter, and thus resistance, is regulated by at least two distinct types of vagal motor fibers that adjust airway smooth muscle tone. Cholinergic parasympathetic drive to the airways is bronchoconstrictive, while nitrergic parasympathetic drive is bronchodilatory [136–138]. The cholinergic pathway is tonically active and decreases or increases in the level of cholinergic drive increase or decrease airway diameters, respectively [135,139,140]. That is, the parasympathetic innervation of the airways does not constrict the airways per se; rather, it regulates airway diameter, either increasing or decreasing airway conductance in an articulated pattern within the respiratory tree, as needed to meet physiological demands, about which more later. A number of conditions or stimuli – hypercapnia, hypoxemia, hypotension, airway irritation – elicit bronchoconstrictive reflexes by activating vagal efferent fibers, while lung inflation causes bronchodilation via bronchodilatory reflexes that inhibit such efferent fibers [132].

In contrast to the extensive parasympathetic supply to airway smooth muscle, sympathetic innervation of airway smooth muscle is much sparser in most species (excepting the guinea pig, in which it is somewhat more well-developed), while in man it is said to be nearly or completely absent [134–136,141,142]. However, airway smooth muscle in all species examined express high levels of β_2-

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adrenergic receptors. These modulate airway diameter in response to circulating adrenaline [143–145]. Thus, while overall airway resistance - and thus total ventilation as a function of the atmospheric-alveolar pressure gradient – is subject to sympathetic modulation via adrenaline release from the adrenal medulla, the neuroanatomy in many species including man argues against a direct role for the sympathetic system in controlling the detailed temporal and spatial pattern of the airflow within the respiratory tree. The physiological significance of the parasympathetic supply of the airways has long been a subject of conjecture [146,147] but the innervation indicates that it is capable of regulating relative airflow along parallel bronchiolar pathways.

Due to the clinical significance of asthma and other disorders of airway function, the neurochemistry, anatomy, and effects on airway diameter of stimulating or inhibiting discrete subpopulations of parasympathetic fibers supplying the airways has been extensively studied. However, it is striking that the physiological importance of the parasympathetic innervation of the airways and of the ongoing regulation of airway resistance in the absence of any pathology is poorly understood and remains the subject of debate. In 1983 Otis wrote, "Although we now have a considerable understanding of the mechanics of bronchial smooth muscle and of the effects of numerous physiological and pharmacological agents on its behavior, the exact role it plays in normal physiological function is unclear. Numerous plausible suggestions have been made, but none has been convincingly demonstrated." [146]. Over a decade later, Gabella noted that despite considerable progress in understanding neural regulation of airway smooth muscle activity, ignorance of its physiological importance persisted [147]. It appears to persist to this day, despite the steady progress in elucidating mechanistic details of the autonomic control of the airways [cf 137]. Still, that the parasympathetic innervation of the airways must be of significant adaptive value is strongly suggested by its conservation throughout phylogeny, especially given that dysregulation of the system can lead to debilitating and potentially lethal respiratory pathology [148]. The persistent uncertainty regarding the significance of this nerve supply highlights the importance of a theoretical context for investigating its function. In this sense, hypotheses that accurately characterize broad principles of parasympathetic regulatory function may be of value. We will return to this topic shortly.

Pulmonary Vessels

Another important fact almost universally excluded from typical autonomic pedagogy concerns the substantial parasympathetic innervation of the pulmonary vasculature via the vagus nerve [149–152]. This pulmonary vascular innervation contrasts with the absence of parasympathetic innervation from most of the systemic vasculature. The degree of parasympathetic innervation of the pulmonary vasculature varies between species, but it is notably less dense than the sympathetic innervation of the same vessels [150,152–154]. There remains disagreement concerning the degree, but not the presence, of parasympathetic innervation of the human pulmonary vasculature [150,152,155]. The functional significance of this innervation, like that of the parasympathetic innervation of the airways, remains obscure, which is to say it is a subject about which few definitive assertions have been either proposed or rejected. This is quite an interesting situation, worthy of consideration.

Functional Implications of the Parasympathetic Pulmonary Innervation

The lungs mediate gas exchange between the atmosphere and the circulation. Respiration requires ventilation - the inspiration of fresh, oxygen-rich air, and expiration of CO_2-laden air. Gas exchange takes place via diffusion in the capillaries of the lungs and requires adequate perfusion of these capillaries. The degree of ventilation and the degree of perfusion vary dynamically throughout the lungs, based on many factors. Efficient gas exchange requires local matching of ventilation with perfusion throughout the respiratory tree [156]. Local ventilation-perfusion mismatches reduce the efficiency of whole-lung gas exchange even when ventilation and perfusion are matched globally, resulting in "physiologic dead space", i.e. regions of the respiratory tree where gas exchange with the pulmonary capillaries is incomplete due to such local mismatches (termed V/Q mismatches)

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[156,157]. Elaborate autoregulatory mechanisms exist to adjust respiratory epithelial blood flow to match alveolar airflow and vice versa, so as to minimize physiological dead space. A great deal of research into the mechanisms responsible for V/Q matching has focused on adjustments resulting from responses to various imposed manipulations or conditions but typically has not addressed pre-action (i.e. feedforward regulation) based on expectation or learning.

In general, research effort into the regulation of the airways and the pulmonary vasculature tends to focus on pathophysiology associated with allergy, inflammation, irritant chemicals, obstructive disorders (e.g. COPD), etc. Little is known of the dynamic coordinated articulation of ventilation and perfusion throughout the lung across a range of physiological demands. Exceedingly few studies have inquired into a possible role for the parasympathetic innervation of the airways and blood vessels of the lung in matching ventilation and perfusion to achieve optimal blood gas exchange and minimize physiologic dead space. With respect to this possibility, it is of interest that Allen et al. noted, in a study of human material, that nerve fibers considered to be parasympathetic on the basis of expression of vasoactive intestinal polypeptide (VIP) immunoreactivity, "seemed most abundant in the small muscular arteries just proximal to the respiratory unit – arteries that can be considered as the resistance vessels of the lung. Extensive innervation of these vessels suggests that the flow of blood into the respiratory unit and capillary bed is partly under neurogenic control," [154]. Thus, the anatomical sites at which these fibers are reliably found at greatest density are those that regulate the pattern of perfusion of the respiratory epithelium within the lung.

The ability to investigate questions of the neural regulation of ventilation-perfusion matching is limited by the considerable difficulty of measuring spatiotemporal patterns of regional blood flow and airflow in vivo. In a behaving animal it is a daunting technical challenge to attempt to study the fine structure of rapidly and regionally varying pressures and volumes – comprising a combination of cyclic and non-cyclic components - and to discern the impact of these changes on variations in ventilation and perfusion. But the ability to manage complex spatiotemporal dynamics is one of the defining features of a nervous system, and so it merits our attention.

Added to the inherent difficulty of studying the problem at all is uncertainty about those conditions under which such regulation would meaningfully affect performance. To draw the analogy with Cannon's findings concerning the effects of total sympathectomy on the physiology of cats and dogs kept in the laboratory [33], absent a specific hypothesis about the purpose of a particular motor nerve supply, and given the existence of multiple reinforcing mechanisms to ensure that the most vital physiological functions are carried out adequately, it may be difficult to discern the purposes of a nerve supply based on ablation studies and/or global measurements of key variables. For example, Fritts et al (1958) showed that acetylcholine infusions into the pulmonary artery did not seem to have a marked effect on gas-exchange performance. Other authors have since referenced that early work as evidence of a likely minor effect of the parasympathetic innervation of the pulmonary vasculature on hemodynamic regulation [152]. However, infusing a bolus of neurotransmitter into a large vessel does not and cannot mimic the coordinating effect of a nerve supply delivering spatiotemporally patterned impulse activity in a dynamic situation, particularly one demanding optimal performance.

Thus, just as we should not take Cannon's finding - that total exclusion of sympathetic innervation does not prevent animals kept in the laboratory from maintaining various physiological variables within a "normal" range - to imply that the function of that innervation is primarily to respond to "emergency" situations, so also we should not take the difficulty of demonstrating the regulatory functions of the parasympathetic supply to airways and pulmonary vessels under normal circumstances to mean that such innervation is unimportant for normal function. In fact, it would require the assertion of such a role and a belief that it matters to justify the research effort that would be needed to explore it in a meaningful way.

Irrespective of whether the parasympathetic innervation of the airways is important for coordinating ventilation and perfusion in anticipation of and response to rapidly changing intrathoracic pressures and other factors throughout the respiratory tree, what is certain is that these

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two fundamental functions of the lung – regulation of the distribution of airflow and regulation of the distribution of blood flow, respectively - are each subject to parasympathetic control. Further, the sparse to absent sympathetic bronchiolar innervation in most species including man indicates that adrenergic signaling in these species cannot coordinate an articulated pattern of alveolar ventilation. Variations in local or regional effects of hormonal adrenergic signaling would need to result from variations in the distribution of adrenergic receptors on the bronchioles, and such variations would lack the ability to respond to dynamic changes in conditions.

Respiration involves the exchange of materials between the external environment and the body, via the nose and mouth, i.e. orifices of the head. The pattern of pressure changes that mediate this exchange are based on the movements of the head and trunk, controlled by skeletal muscle. Intrathoracic pressures vary continuously with postural and positional changes, and with the respiratory cycle, and these ongoing physical variations impact both airflow and perfusion in complex ways throughout the thoracic cavity. Vagal motor drive to both the airways and the blood vessels is tonically active and is subject to modulation via vagal afferent input from a variety of types of receptors, including J receptors, pulmonary stretch receptors, and others [158]. Regulation of airway resistance is important during exercise. For example, Hesser and Lind concluded, in a study on respiratory drive and airway resistance, that, "neural mechanisms compensating for internal flow-resistive loading play an important role in the control of ventilation during exercise, both at normal and at raised air pressures," [159]. During exercise, the rate at which both movement of the head and trunk as well as respiratory motions are occurring is elevated, and the demand for efficient respiratory function is maximal. These and other observations, taken together, suggest that parasympathetic control of the pulmonary system may quite important under "fight-or-flight" conditions, and it is likely that, as with other functions, such regulation occurs across all behavioral states. Further, while the physiological significance of the parasympathetic regulation of airway resistance and pulmonary perfusion are not yet established, whatever their significance, it is not a matter of mediating anabolism per se and it is highly unlikely to be relevant only during anabolic states. Thus, to describe the parasympathetic division as primarily or fundamentally associated with states of rest and digestion or anabolism is to obscure or ignore the important question of its role in respiration, among many other functions.

Extending the Hypothesis to Interpret Relationships in Tissues with Dual Innervation

General Considerations

As noted earlier, in most descriptions of ANS function, the effect of shocking whole nerve branches, and similarly, the effect of superfusion of the predominant parasympathetic or sympathetic postganglionic neurotransmitter (i.e. acetylcholine and noradrenaline, respectively) typically is conflated with the regulatory purpose of the innervation, leading to formulations such as, "The autonomic nervous system is important for homeostasis because its two divisions compete at the target effector. The balance of homeostasis is attributable to the competing inputs from the sympathetic and parasympathetic divisions (dual innervation)." [160]. This is erroneous. As has already been emphasized above, the function of a nerve supply is not equivalent to the effects of increases in mass activity in that nerve supply.

Based on a consideration of tissues receiving solely a sympathetic innervation, it was proposed above that the thoracolumbar system be described as the set of pathways responsible for the regulation of the physico-chemical environment of the tissues, and for regulating the distribution of metabolic resources appropriate to present and anticipated demand, at all times. A possible terse summary of this function is that the sympathetic division serves as the body's quartermaster, and/or the "regulator" of the physico-chemical state of the body.

Rather than describing parasympathetic function in terms of a specious essential complementarity to sympathetically-regulated functions, it was then proposed that an apt description of craniosacral function, broadly speaking, is that it is concerned with dynamic

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interactions and exchanges with the outside world via the orifices of the body (cranial, and sacral) - often requiring intimate coordination with the activity of skeletal muscle. It clearly also is concerned with coordination of internal functions with specific movements of the head and trunk, such as adjusting systemic blood pressure in response to rapid positional changes, or heart rate with the respiratory cycle, and possibly also with regulating cerebral blood flow, to be discussed later. A possible rubric under which the very great array of parasympathetically-mediated functions might fit, then, is that of "coordinator" of interactions with and exchanges between the internal and external milieux.

While the proposed schema describes the sympathetic division as "the quartermaster" responsible for regulation of the internal environment, and the parasympathetic division as "the coordinator" of target tissue activities associated with interactions with the outside world, it nonetheless should be pointed out that each has responsibilities that could be considered to fall under the rubric of the other. For example, sympathetic regulation is involved in differentially distributing (coordinating) blood flow related to specific patterns of expected muscular activity [119]. Conversely, parasympathetic regulation involved in coordinating transfer of gases into and out of the body obviously has a significant role in regulating the state of the internal milieu, including the pH of the extracellular fluids. The aim of a revised narrative, however, is not to come up with terms capable of exclusively describing the full range of activities of the respective branches of the ANS. Instead, it is to provide terms that can summarize a large body of knowledge in a way that does not undermine the understanding of respective regulatory responsibilities. As long as the sense in which these terms are intended is understood, they may serve this purpose usefully.

By describing sympathetic and parasympathetic pathways as responsible for qualitatively different spheres of regulatory action, and by calling attention to what is known about these differences, the door is opened to more useful interpretations of the relationships between them in tissues innervated by both. This produces more interesting and more physiologically meaningful questions than the simplistic and misleading question of which branch is responsible for increasing and which for inhibiting a given type of activity of a particular tissue. The nature of the interactions between the extrinsic branches of the ANS is not stereotypic across nor within tissues. Rather, the specific nature of these interactions depends on the tasks being accomplished. Phase relationships between the patterns of activity in each branch are in general not uniform nor consistent, but rather, are highly variable, and depend on the distinct demands of any given situation. In the case of autonomic regulation of the heart, this has been directly demonstrated in an extensive series of investigations by Kollai and co-workers, via simultaneous recordings of the cardiac sympathetic and parasympathetic nerves under a variety of conditions [161–170], as will be discussed further below.

With respect to the concept of "autonomic tone", it is certainly the case that in tissues receiving a dual innervation, the activity of the tissue depends on the convergent influences of both branches. Where dual innervation does occur, rather than seeing the functional relationships as analogous to those between flexor and extensor muscles, as originally proposed and later repudiated by Cannon [1,33], perhaps a better analogy is the relationship between the innervation of the spinal motor neuronal pool by the pyramidal (corticospinal) and extrapyramidal (vestibulospinal, rubrospinal, reticulospinal, tectospinal) tracts. Whether the influence from each is inhibitory or excitatory in any given instance is not the central point. What is important is that each is responsible for qualitatively different aspects of motor control - the former being generally described as broadly concerned with directed movements, and the latter with regulation of muscle tone, balance, posture, and locomotion – all of which must be coordinated to produce appropriate patterns of output. Thus, when considering the effects of pyramidal vs. extrapyramidal inputs to a lower motor neuron, the default assumption is not that these distinct sources of input exist to counterbalance each other, and so their respective roles can be investigated without this bias.

In this regard, Saper's comment regarding the ANS premotor areas that "the interconnectivity of its components, located at virtually every level of the neuraxis, is more similar to a network than a strict hierarchy," is relevant [171]. The output systems and the reflexes that modify them are

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unlikely to be organized for the purpose of achieving given levels of simple physiological endpoints via the balancing of impulse activity in the two opposing arms *per se*.

Below, the rubrics of quartermaster and coordinator, respectively, are applied to suggest a possible approach for interpreting the distinct spheres of regulatory responsibility of each branch in the cases that the traditional pedagogy offers as canonical examples of intrinsically oppositional control: the bladder, the GI tract, the heart, and the iris/pupil.

In each case, attention is focused on identifying which factors govern variation in the activity of the respective autonomic branches. The approach taken here is not exhaustive nor could it be. It is offered to illustrate how the assertion of specific hypotheses concerning regulatory responsibilities of each branch can lead to novel, testable hypotheses regarding function. Where the physiological functions being regulated by the respective branches are intimately interrelated, we should expect to see intimate interrelationship in the autonomic regulation, and likely in the central circuitry governing activity in the two branches as well. Whether the relationship in the activity of each is oppositional or not, and the pattern of observed phase relationships in their activities, will depend on the specific circumstances, and the functional relationships between regulated factors.

The Bladder

It is helpful to begin with the bladder since its physiological functions are straightforward, and since the neurobiology of bladder control has been extensively mapped throughout the neuraxis [172,173].

The functional repertoire of the bladder is limited to two roles: storage and elimination. The bladder stores urine produced by the kidneys until such time as a decision is made to void, at which point it switches from a storage mode to a voiding mode of action. Urine production is sympathetically-regulated continuously, via sympathetic control of kidney function, which determines the composition and volume of the plasma [81]. Relaxation of the detrusor muscle of the bladder allows for filling while limiting the increase in intravesicular pressure resulting from the added volume, i.e. accommodation. Bladder accommodation is primarily regulated via sympathetic pathways [173], and it therefore seems reasonable to view the control of accommodation as related to and coordinated with the sympathetic control of urine production by the kidney.

A decision by the organism to urinate is accompanied by the movement of the body to the appropriate place and posture for urination. Voiding involves relaxation of the external urethral sphincter via withdrawal of ongoing tone in the somatic motor supply to it, and movements of the skeletal muscle of the pelvic floor. In coordination with these articulated changes in the pattern of somatic motor activity, a parasympathetically-mediated contraction of the detrusor muscle results from increased activity in cholinergic fibers, which increases urethral pressure. Concomitantly, relaxation of the internal urethral sphincter is stimulated by increased activity in nitrergic parasympathetic fibers [172,173]. Thus, bladder voiding is controlled by the parasympathetic innervation, acting in close coordination with the somatic motor system.

Transitions between the storage mode and voiding mode of the bladder are described as “switch-like” and the neural circuits controlling the lower urinary tract exhibit this switch-like behavior [172]. In the storage mode, parasympathetic influences on detrusor tone are inhibited by sympathetic inputs, and control of internal urethral sphincter tone is modulated by adrenergic fibers as part of a ‘guarding reflex’ which prevents inappropriate urination. During urination, parasympathetic output uncouples the sympathetic drive from the detrusor muscle, allowing the parasympathetic system to coordinate contraction of the bladder. We may think of it not so much as a sympathetic brake perhaps, but rather, as a sympathetic clutch.

Overall, then, it is possible to describe the storage function of the bladder as related to the rate of urine production and thus to regulation of whole-body fluid balance. Conversely, the voiding function involves coordinating smooth muscle activity of the bladder and internal sphincter with skeletal muscle activity in mediating exchanges with the outside world (i.e. micturition) episodically, and when appropriate. As these two functions - accommodation in concert with filling and

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contraction during voiding - are physically opposed processes, the systems are arranged so that one or the other is dominant, depending on circumstance.

GI Tract

In the bladder, filling is associated with the sympathetically-regulated production of urine by the kidney, and thus with regulation of the internal environment, while emptying is the result of conscious decisions to void. In the upper GI tract, in contrast, filling of the stomach results from conscious decisions involving the actions of skeletal muscles required to eat and drink. Vagal parasympathetic outflow coordinates smooth muscle and secretory activity with the movements of skeletal muscles involved in chewing and swallowing. This coordination allows for the passage of food to and through the lower esophagus, relaxation of the lower esophageal sphincter, and receptive relaxation of the gastric reservoir [30,128,174–176]. Thus, filling of the stomach, unlike filling of the bladder, involves parasympathetically-mediated coordination with the skeletal musculature during episodic exchanges with the outside world. Increased vagal cholinergic drive is responsible for stimulating gastric acid secretion and motility during the cephalic phase of digestion [177]. Vago-vagal reflexes, mediated by vagal afferent feedback, modulate the pattern of acid secretory activity and motility. It is worth emphasizing that the great majority of enterogastric vago-vagal reflexes are inhibitory [53], that is, they result in a reduction in vagal cholinergic drive to the stomach (and nitrergic drive to the pylorus) and a reduction in motility and acid secretion, not its stimulation [see for example [178].

Emptying of the gastric contents into the duodenum occurs through and is controlled by the motility of the antropyloric region of the stomach. Antropyloric coordination allows articulated control of the size distribution and composition of chyme that passes into the duodenum [179,180]. The vagus nerve coordinates both increases and decreases in gastric emptying, depending on circumstance. Increased vagal nitrergic drive to the pylorus and increased cholinergic drive to the antral region serve to propel contents into the duodenum by relaxing the pylorus and contracting the antrum, respectively, while vago-vagal reflexes evoked by a variety of duodenal stimuli inhibit both [178,179]. Such regulation is intimately related to the downstream digestive and absorptive capacity. However, the pylorus is also richly invested with sympathetic fibers, whose excitation results in increased pyloric pressure and reduced gastric emptying [181,182]. Given that both divisions of the ANS can and do restrict gastric emptying, we may ask, under which conditions is the activity of one or the other the more significant factor?

Gastric emptying is regulated in part via vago-vagal (i.e. parasympathetic) reflexes initiated by afferent input from the small intestine [178,183]. CCK released by duodenal enteroendocrine cells in response to and in proportion to the amount of protein and fat in the duodenum drives this reflex [178,184,185]. Interestingly, and in contrast, inhibition of gastric emptying due to the “ileal brake” is driven via inputs to the prevertebral sympathetic ganglia from intestinofugal primary afferent nerve fibers (IPANs) [182,186]. Rather than being driven by the response to recent gastric emptying of ingested nutrients into the duodenum, the ileal sympathetic brake appears to function in response to signals related to the processing of chyme over the full extent of the small intestine, which likely include factors related (but not limited) to the action of the microbiome on the ingesta and the associated changes in the hepatobiliary circulation. Inhibition of gastric motility in rats in response to certain pain stimuli is also sympathetically-mediated [187], as is the delay in gastric emptying associated with restraint stress [188].

Determining the relative roles of sympathetic vs. parasympathetic regulation of gastric emptying – or any other GI function – is not a simple matter. For example, in addition to mediating gastric motility and acid secretion in response to sham-feeding (i.e. cephalic phase responses), vagal motor pathways are responsible for many gastric effects of intracisternal TRH injection or of cold-restraint stress [189]. Vagal motor output also appears to be responsible for the aforementioned effects of hostile emotions on stomach [96]. Indeed, as noted previously, the complexity of the biology of the gastrointestinal tract and its relationship to the physiology of the rest of the body is so great

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that it would not do the subject justice here to do more than point out the value in framing each autonomic branch as responding to and governing qualitatively different aspects of the digestive process. A comprehensive summary of the literature concerning autonomic innervation of the gut is well beyond the scope of this article, but two points bear mentioning.

First, abundant evidence supports the view that it is the sympathetic system, not the parasympathetic, that regulates the massive fluid fluxes that occur in the intestines [11,13]. The now widely accepted view of the sympathetic system as intimately involved in this aspect of normal digestive function diverges from the traditional view of the sympathetic system as responsible for inhibiting digestive function generally. But it is wholly consistent with the view that the sympathetic system regulates whole-body fluid and salt balance, not only via renal regulation, but also via control of GI fluid fluxes and other processes, including sweating.

Second, the asymmetric innervation by the two extrinsic autonomic branches of the enteric nervous system and gut smooth muscle bears mentioning [13,190]. Recently, Walter et al. definitively showed that the great majority of individual postganglionic fibers originating in prevertebral (celiac and superior mesenteric) sympathetic ganglia emit collaterals so as to innervate both myenteric ganglia and enteric smooth muscle [191]. A small number of identified and mapped prevertebral postganglionic neurites were shown to innervate both myenteric blood vessels and the myenteric plexus. Overall, the arrangement suggests simultaneous sympathetic control of both enteric ganglionic signaling and the myenteric smooth muscle activity, as well as possibly coupled modulation of the perfusion of myenteric tissues. In contrast to the **postganglionic** sympathetic innervation of myenteric ganglia, the prevertebral sympathetic ganglion cells receive contacts from **preganglionic** vagal efferent fibers [192], and also projections from intestinofugal enteric neurons [11,193]. Thus, the neuroanatomical relationships between the extrinsic branches in the gut are quite asymmetric and reflect a complex set of functional interactions between the two, as might be expected given the inextricability of, for example, control of fluid fluxes with absorptive processes, regulation of the microbiome, and coordination of the supply of cardiac output to the gut with systemic demand for cardiac output.

Analyzing the situations in which one or the other extrinsic branch can be shown to exert dominant effects on gastric emptying, as well as the panoply of other GI functions under autonomic control, may reveal generalizations of value both conceptually and therapeutically. The important point remains that viewing the sympathetic and the parasympathetic innervation as responsible for qualitatively different aspects of regulation of tissues, within an overarching sphere of responsibilities for each, provides a basis for exploring the great variety of patterns of interaction between them. The existing caricature of a generic opposition does not.

The Heart

In the traditional autonomic pedagogy, the contrasting effects of sympathetic vs. parasympathetic excitation on heart rate are presented as a canonical example of a fundamental juxtaposition between the two branches. A typical example is as follows: “For example, the heart receives connections from both the sympathetic and parasympathetic divisions. One causes heart rate to increase, whereas the other causes heart rate to decrease,” [194]. As noted earlier, the notion that one or the other branch exists to adjust activity of the targeted tissue in only one direction, and the related but distinct misconception that the function of a nerve supply is identified only by the effect of increases in discharge, are both specious.

In exploring the relationship between the cardiac sympathetic and parasympathetic outflows, we have the advantage that there exists direct electrophysiological evidence on the point. In a series of investigations conducted over a number of years, Kollai and co-workers investigated autonomic control of the heart via simultaneous recordings in the cardiac sympathetic and vagal (parasympathetic) nerves during a variety of experimental manipulations [161–170,195]. Given the recording sites used in these experiments, the observed activity was from postganglionic sympathetic fibers and preganglionic vagal fibers, respectively. The studies were performed in chloralose-

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anesthetized dogs in which thoracotomy had been performed to allow access to the recording sites, thus requiring artificial (positive pressure) ventilation to maintain appropriate blood gas concentrations. As a result of the experimental preparation, the effects of the recorded nerve activity on physiological variables must have differed in important respects from what would be expected in an intact conscious behaving animal. Loss of homeostatic control, including hypothermia and hypotension, among other many other disruptions of homeostatic regulation, is a prominent effect of anesthesia. Further, thoracotomy and artificial ventilation cannot but profoundly influence the pattern of any autonomic activity involved in cardiorespiratory coordination, as it disrupts respiratory cyclicity of intrathoracic pressure changes and thus baroreceptor feedback, and uncouples blood gas level changes from changes in cardiac activity. Thus, direct extrapolation from such in vivo experimental findings to the situation in conscious humans is inadvisable. For example, a study performed by the same group indicated that early conclusions drawn from findings in freely breathing chloralose+urethane anesthetized dogs about the relationship between vagal tone, vagal modulation of respiratory sinus arrhythmia (RSA) and the magnitude of RSA do not appear to model the pattern of control in conscious humans [196–198]. Despite these caveats, this series of studies - in which changes in the phase relationships and the magnitude of impulse activity were recorded simultaneously along with various measures of physiological function (cardiac output, heart rate, BP, etc) in response to various forms of peripheral and central stimulation - shed considerable light on the subject of autonomic cardiac control and the relationship of activity between the sympathetic and parasympathetic cardiac supplies.

In their reports, Kollai and co-workers referred to patterns of activity in which vagal efferent (i.e. preganglionic parasympathetic) activity was inhibited during periods of sympathetic (postganglionic) excitation and vice-versa as “reciprocal.” Patterns in which this relationship did not hold were described as “non-reciprocal”, irrespective of the relative magnitudes of mean discharge rate changes in the two branches. For example, if mean discharge rates increased in both branches, but the pattern of discharge comprised alternation in firing between the two nerves (i.e. one active while the other silent), this was considered a “reciprocal” pattern of activity. It was found that baroreceptor-driven responses tended to evoke a strong “reciprocal” pattern of activity, while stimulation of carotid chemoreceptors elicited increased activation in both branches simultaneously [164]. Perturbations in the levels of blood gases elicited “non-reciprocal”, simultaneous activation, though the degree of activation differed between branches, as was also the case when right or left atrial stretch was used as a stimulus [167,169,170]. A variety of phase relationships between sympathetic and parasympathetic activities were observed in response to hypothalamic stimulation, depending on the site of stimulation. A strong “reciprocal” pattern of response was seen when hypothalamic stimulation elicited defense reactions, but very different patterns of response were elicited by stimulating other hypothalamic areas [166]. As the authors noted, “Between these two clear-cut, different reciprocal and non-reciprocal patterns, there are many reactions in which changes in vagal and sympathetic activity occur in the same or opposite direction, but to a different degree and with a different time course.” In this and their other studies the pattern of changes in cardiac performance and corresponding activity in the two branches were complex, and in no way stereotypic. Similar conclusions have been drawn by other authors [199–202]. Clearly, a range of phase and amplitude relationships between sympathetic and parasympathetic cardiac outflow may occur, depending on the specific physiological challenges being met. Thus, as noted with respect to the error of extrapolating from a vivid example to a general rule, the clear “reciprocal” pattern of activity observed in some states does not justify the assertion of a general rule regarding functional relationships between the branches supplying the heart.

This brings us to the question, then, of how to interpret the relative roles of each branch in cardiac regulation. If the two branches regulate different aspects of cardiac function, which of course must be coordinated, the question arises, what are these, respectively? Let us consider the regulatory challenges of cardiac control.

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Heart rate and stroke volume, and thus cardiac output, vary continuously. Over any given interval, enough blood must be pumped by the heart to meet the demands of all tissues for the appropriate level of perfusion at pressures appropriate for each. At the same time, cardiac activity must be coordinated with rapid fluctuations in intrathoracic pressure and position in the gravitational field (each of which influence preload, among many other factors) resulting from the activity of the skeletal muscles controlling respiratory and postural movements. It must also be coordinated with changes in preload and afterload resulting from changes in sympathetic regulation of the capacitance and resistance vessels, respectively [116].

Changes in ventilation, in position, and in the activity of the 'muscle pump' all vary the rate of venous return continuously, leading to mismatches in right and left ventricular filling and output that, since the system is a closed loop, must be balanced over time, but which are not matched instantaneously [203–205]. Guz et al. found that cardiac pacing in dogs increased swings in left and right stroke volume with the respiratory cycle, indicating that respiratory sinus arrythmia (RSA) may modulate such variations [203], at least in this paradigm. Dynamic changes in venous return due to changes in ventilation, position, and the activity of the muscle pump are not directly related to the total systemic demand for cardiac output. These factors vary much more rapidly than does demand for cardiac output by the tissues supplied by the systemic circulation. Given a common total demand for cardiac output but a difference in movement and position within the gravitational field and/or the respiratory cycle, cardiac activity will differ.

The proposed alternative narrative suggests that we view cardiac sympathetic regulation as concerned with adjustments of cardiac function related to and integrated with changes in sympathetically-mediated vasoconstrictor drive to resistance and capacitance vessels, and changes in systemic demand for cardiac output generally. In contrast, parasympathetic drive can be seen as relating to cardiorespiratory coordination and coordination with postural/positional changes, i.e. with the rapid variations in intrathoracic pressure associated with skeletal muscular activity and movement. These two spheres of regulation are intimately intertwined. As just one example, it is clear that parasympathetically-mediated variations in heart rate have effects on arterial pressure waves at the respiratory and slower frequencies (e.g. Mayer waves) and on sympathetic rhythmicity [15,206]. It is therefore unsurprising that the two systems would show a high degree of central convergence [207–211].

What is the evidence in support of this proposal concerning the 'division of labor' in cardiovascular autonomic control? One clear line of evidence concerns the role of the two branches in varying heart rate with the respiratory cycle, i.e. RSA. As Grossman and Kollai noted:

"A plethora of research over the last five decade has demonstrated that respiratory sinus arrhythmia is exclusively or overwhelmingly mediated by the parasympathetic branch of the autonomic nervous system, at least within the normal physiological range of breathing frequencies (e.g., Anrep, Pascual, & Rössler, 1936a. 1936b: Katona & Jih, 1975: Raczkowska, Eckberg, & Ebert, 1983). Thus, inspiratory cardiac acceleration mirrors vagal inhibitory influences upon the sinus node. Conversely, expiratory cardiac deceleration reflects vagal excitatory influence upon the heart via the sinus node," [197].

Interestingly, while increased vagal drive is consistently associated with reductions in heart rate, its relationship to changes in stroke volume and cardiac output are not consistent. That is, changes in mass cardiac activity cannot be used to predict changes in the amount of blood provided to the systemic circulation. For example, Koiziumi et al. found that electrical vagal stimulation caused cardiac output to drop if simultaneous sympathetic activation was absent, but was enhanced compared with appropriate controls by the same pattern of vagal stimulation if sympathetic activation was present [165]. Thus, the nature of the relationships between parasympathetic activity and cardiac function differs depending on the particular variable/endpoint considered (e.g. chronotropy, inotropy, dromotropy, cardiac output, etc.) and the physiological state or background against which observed changes occur [165,199]. Here it must again be emphasized that autonomic activity in any nerve trunk is not a unitary variable. The detailed patterns of activity within and

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between various fiber types within each type of supply to the heart are certain to be meaningful functionally [64,212,213].

Numerous experiments have demonstrated that the heart rate changes more promptly in response to changes in parasympathetic drive than to changes in sympathetic drive. Immediate slowing of the heart in response to vagal activation and comparatively lagged increases in heart rate in response to sympathetic activation have been observed in numerous studies in which the effects of electrical stimulation of each nerve was monitored [214–217]. Warner and Russell (1969) concluded, "that any sudden change in heart rate within one or two heart beats cannot be brought about through direct effect of variations in frequency of sympathetic action potentials arriving at the S-A node". Brown et al. similarly noted, "Although sympathetic nerve traffic also fluctuates at respiratory frequencies (9, 30), R-R interval responses to such rapid changes of sympathetic activity are small because of the sluggishness of adrenergically mediated sinus node responses" [218]. In reviewing the dynamic changes in stroke volume and heart rate occurring with variations in the respiratory cycle and with postural changes Rowell (1993) summarized evidence supporting the view that neural factors are responsible for adjustments which maintain the stroke outputs of the ventricles in phase and in balance during postural change [219], and noted that, "The most rapid neural response is vagal and affects primarily heart rate, whereas the sympathetic responses affecting myocardial contractile force are much slower. The 5 to 10 seconds required for a sympathetic response is far too slow to account for the balancing of ventricular outputs in response to breathing and postural change [204]." Koizumi et al (1985) also noted the more rapid responsiveness of the sinus node to parasympathetic than to sympathetic drive. They analyzed changes in pulse period as a function of changes in autonomic activity recorded during baroreceptor stimulation and found that changes in vagal (i.e. preganglionic) discharge affected cycle length during the same cardiac cycle, while changes in sympathetic (i.e. postganglionic) discharge affected the next cycle [163]. Brown and Eccles observed slowing of heart rate within a few hundred milliseconds following a single shock applied to the cervical vagus in decerebrate cats [220]. Hill-Smith and Purves observed that iontophoretic application of acetylcholine or carbachol slowed the beating of clustered of cultured rat ventricular muscle cells with a minimum latency of 250 ms, while the minimum latency for adrenergic agonists (adrenaline, noradrenaline, isoprenaline) to accelerate the beating of such cells was 3-6 sec, and found similar responses in intact rat atria [221]. The effects of the muscarinic agonists were short-lived (6-12 sec) while those of the adrenergic agonists were long-lived (20-30 sec to reach a peak, decaying from there with a half-life of 40-120 sec). These authors cited a number of prior studies with comparable results. It should be noted that in the cases of vagal stimulation, the activated fibers were preganglionic, while when stimulating sympathetic nerves, the activated fibers were postganglionic. Thus, in the former case, transit of a ganglionic synapse was necessary. Nonetheless, the functional responses occurred many times faster than for the latter case. Thus, cholinergic signaling appears better suited to mediating responses to rapidly varying conditions than does adrenergic signaling.

Eckberg (1983) noted that the correlation between base-line heart rate and the level of parasympathetic cardiac efferent activity is weak. In contrast, evidence of variation in the level of parasympathetic activity with the respiratory cycle is strong. RSA is driven by cyclic variation in the cardiac parasympathetic outflow [61,62,65,198]. This cyclic variation is modulated by baroreceptor input, while the basic rhythmicity is generated centrally [61,62]. With short breathing intervals, the acceleration of heart rate in man begins just prior to the beginning of inspiration, indicating that it anticipates rather than reacts to lowered intrathoracic pressure [65]. However, the pattern of regulation varies depending on context, and many factors modulate the pattern of RSA, in complex ways [222,223].

Consistent with Eckberg's point regarding the weak relationship between base line heart rates and parasympathetic activity, Warner and Russell demonstrated that with continued vagal nerve stimulation in the presence of ongoing sympathetic drive over ~90 s, the initial reduction in heart rate evoked by vagal stimulation wanes and heart rate rises toward pre-stimulus levels, while in the

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absence of simultaneous sympathetic stimulation, heart rate remains depressed with continued vagal stimulation [215]. That is, the phasic effects of vagal drive are much more pronounced than are the tonic effects in the presence of coincident sympathetic drive.

Interactions between the activities of the two extrinsic autonomic branches in cardiovascular regulation are, of course, profoundly intertwined, as are the physical factors involved in the linkages between heart rate, cardiac output, and arterial pressures. An extensive network of central cardiorespiratory regulatory centers regulate vagal and sympathetic outflows controlling systemic pressure and flow continuously, across a range of very different, very dynamic patterns of ventilation and intrathoracic pressure changes [224]. The essential coupling of these systems is reflected in many ways, including in the prominent respiratory modulation of the firing pattern of sympathetic fibers innervating the systemic vasculature. Indeed, the presence and pattern of respiratory modulation of firing is used as a criterion for identifying functional classes of vascular efferent sympathetic fibers in in vivo electrophysiological studies [225,226]. Powerful respiratory modulation of sympathetic outflow is also prominently seen in recordings of nerve activity in conscious human subjects [227], though the functional significance of such modulation remains a subject of debate.

What is critical to keep in mind when considering autonomic regulation of cardiovascular and cardiorespiratory coordination is that the nature of the task being performed is multidimensional and highly varied. As a result, those cases in which we can clearly observe a consistent predominant role for one or the other branch in a given phenomenon may be fewer in number than those cases in which we cannot. For example, in a study of supine young adults, Toska and Eriksen found that variations in intrathoracic pressure at the respiratory frequency were reflected in variations in stroke volume (SV), which was the main source of variation in cardiac output (CO), while being inversely related to variations in R-R interval [228]. Atropine administration eliminated the heart rate variability but not the respiratory-associated variations in SV, with the effect that respiratory associations between CO and mean arterial pressure (MAP) increased. Their results suggested that in this model RSA functioned to buffer the effects of intrathoracic pressure changes on the swings in CO and MAP, a finding consistent with those of others before and since. However, Taylor and Eckberg, taking a different approach to eliminate heart rate variability - cardiac pacing from an intraesophageal electrode rather than blocking RSA by systemic atropine - obtained a different result in subjects breathing at a controlled frequency [206]. They found that eliminating R-R interval fluctuations by pacing in the supine position reduced, rather than increased, arterial pressure fluctuations at the respiratory frequency. However, they found that in subjects tilted at 40° rather than supine, the same procedure resulted in increased arterial pressure fluctuations. These results demonstrate that the effects of vagal modulation of heart rate and its impacts on cardiac output and mean arterial pressure depend on multiple physical factors in complex ways. Thus, generalizations must be made with great care, and only based on extensive study in many model systems. As noted, the regulatory demands of cardiovascular/cardiorespiratory regulation are highly complex. The key assertion of the proposed schema is that it is the parasympathetic innervation that is most immediately responsive to the rapid changes in intrathoracic pressure and body position, which themselves are determined by musculoskeletal and somatic motor activities.

It may be argued that the formulation proposed here for describing the respective regulatory roles of sympathetic and parasympathetic innervation of the heart is too speculative to serve as the foundation of introductory teaching of the subject. However, introducing the established facts concerning the functional asymmetry and the non-stereotypic relationship between sympathetic and parasympathetic activity first, followed by a frank admission that the extrapolated theory is just that, a theory, seems far preferable to the current use of a misleading caricature of vagal and sympathetic drive to the pacemaker as reciprocal and counterbalanced, i.e. to claiming that the sympathetic innervation increases heart rate and the parasympathetic system lowers it, which is clearly false but remains the basis of present teaching.

Assertion of the alternative schema proposed here promotes the formulation of testable hypotheses. For example, the relationship between requirements for cardiac output and for total

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ventilation also may differ depending on the proportion of cardiac output needed for thermoregulation, renal filtration, digestion, or exercise, respectively, since each of these functions consumes different amounts of oxygen for a given level of cardiac output. Similarly, the assertion that sympathetic cardiac drive should be viewed as related to the sympathetic regulation of preload and afterload may guide experimental work directed to explore this hypothesis.

There is value in posing the question, irrespective of how near or far we may be to or from an answer. Viewing each branch of the system as responsible for distinct aspects of cardiac function is likely to shed light on the significance of observed changes in heart rate variability in various physiological contexts [6,15,224]. If we view the two divisions as regulating different things, then we need not think in terms of a generally "optimal" level or pattern of heart rate variability, a metric that has been used to estimate the ratio of the mass activity in the two motor pathways supplying the pacemaker. Rather, the level of activity in each branch is likely to depend on the specifics of the physiological situation [229]. While for any given type of physical activity certain consistent patterns of relationship between mass discharge in the two branches may be discernible and/or be demonstrably optimal, there is no reason to suppose that the magnitude of bulk activity in the two branches must reflect some generalized global state of optimality any more than, say, the ratio of total movement of the wrist to the activity of the quadriceps muscle, or the arms to the legs for that matter, might be considered optimal. Such ratios may be informative in certain situations – say for example in evaluating performance during bicycling, swimming, tennis, pitching or batting – but it would be surprising to find that particular ratios were optimal across all physical states, or that they served as some sort of broad measure of physiological balance or well-being. Specific hypotheses about why the level of activity in each branch changes as it does in various situations may help us crack the code of HRV and thus make much more effective clinical use of HRV data [230–232].

The Eye

Autonomic control of the pupil is another of the canonical examples used to illustrate a supposed fundamental reciprocal relationship between parasympathetic and sympathetic activity. Yet, as with the systems already reviewed, there is ample evidence of marked asymmetry in the regulatory responsibilities of the sympathetic and parasympathetic innervation of the eye. This again emphasizes that the question of which aspects of pupillary responsiveness each branch governs should be the focus of inquiry.

Pupil diameter is determined by the combined activity of the sphincter pupillae and the (radial) dilator pupillae muscles. The autonomic innervation of these muscles is highly asymmetric. There is a rich parasympathetic innervation and sparse sympathetic innervation of the sphincter, while the reverse is true of the innervation of the radial muscle [66,233]. Parasympathetic oculomotor innervation is supplied by preganglionic fibers originating in the Edinger-Westphal nucleus, which travel via the third cranial nerve to synapse in the ciliary ganglion. Postganglionic fibers emerging from the ciliary ganglion reach the eye via the short ciliary nerves. Postganglionic sympathetic fibers originating in the superior cervical ganglion reach the eye in both the short and long ciliary nerves [233,234].

In summarizing the factors that determine pupillary dynamics, Davson noted that:

"the state of the pupil at any moment is determined by a variety of synergistic and antagonistic nervous influences; in general, external circumstances – light, and proximity of the fixation point – tend to cause constriction whilst the internal factors of sensation, and psychic activity generally, cause dilatation. The continual interplay between these opposing forces results in a constant state of pupillary activity – the pupil is restless – and the size of the pupil under any given conditions is a fluctuating quantity" [235].

Again, the subtle point is easily missed and is typically ignored. That is, it is *increases* in light or *increased* proximity of the fixation point that are associated with constriction of the pupil. Nothing is said of the dilation of the pupil in response to decreased illumination or lengthening of focal distance, or the mechanisms by which these occur. Similar logic applies to the points about

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psychic activity and the mechanisms by which reduced arousal results in narrowing of the pupil. To say that muscarinic agonists constrict the pupil, while adrenergic agonists dilate it, and that the respective antagonists have the opposite effects, is not the same as saying that the parasympathetic innervation is generically responsible for narrowing the pupil and the sympathetic innervation is generically responsible for widening it. The autonomic nerves supplying the eye are tonically active, and thus changes in the ongoing level of activity in either branch may alter pupillary diameter in either direction, for the same reason that agonists of the respective transmitters have effects opposite to those of the antagonists, it being only a question of whether it is the agonist or antagonist that is responsible for constriction or dilation. Thus, in a primate, McDougal and Gamlin recorded sinusoidal variation in pupil diameter and the discharge rate of a pupil-related Edinger-Westphal neuron evoked by sinusoidal variations in light intensity [66].

If we treat the traditional autonomic narrative as an hypothesis, that hypothesis holds that the two branches of the autonomic system are generically responsible, respectively, for narrowing or widening of the pupil, irrespective of the stimulus driving the response. This hypothesis can be confidently rejected, as will be described. The alternative approach proposed here hypothesizes that each autonomic branch regulates changes in pupillary diameter, whether constriction or dilation, in response to distinct factors, for example, the level of illumination, or the level of arousal. Let us consider the evidence.

A great deal of work demonstrates that the parasympathetic innervation plays the predominant if not exclusive role in driving dynamic pupillary changes associated with discriminative aspects of the visual task. Sympathetic activity appears to be involved primarily by setting baseline levels of tone, but it plays at best a minor role in dynamic responses to light, as discussed below.

It is long established that pupillary diameter varies with the overall luminance in the visual field [236]. Dynamic changes in pupillary diameter in response to changes in illumination are controlled by the third cranial nerve. Parasympathetic denervation results in pupillary immobility (tonic pupile) and abolition of the pupillary light reflex (PLR) [66,237,238]. Sympathetic denervation or adrenergic blockade results in smaller tonic pupil sizes but does not greatly alter the temporal profile of pupillary responses to light [238–241]. The secondary redilation of the pupil following the initial pupillary contraction during the PLR was initially thought to be sympathetically mediated, but Heller et al. found no evidence of adrenergic participation in this reflex [242]. In rhesus monkeys, Clarke et al (2003) found that sympathetic denervation or blocking α1-adrenergic signaling in the iris altered the steady-state pupillary diameter but did not influence the dynamics of the PLR. They concluded that "the parasympathetic pupilloconstrictor input is most important dynamically but that the sympathetic pupillodilator input nevertheless acts slowly to modulate pupil diameter under steady-state conditions."

As noted by Mathôt et al. in a paper entitled, "The pupillary light response reflects eye movement preparation, "the PLR is a dynamic movement that is tightly linked to visual attention and eye-movement preparation." [243]. Thus, parasympathetic pathways control not just the rapid pupillary responses to dynamic changes in light reaching the eye but are also responsible for anticipatory adjustments in pupillary diameter ahead of altered stimulus conditions, a key aspect of the visual task.

As evidence supporting an important role for sympathetic control of pupillary responses to light, many authors commonly cite early electrophysiological studies from two groups, in which responses to light were recorded from a small number of sympathetic efferent fibers. One set of studies involved recordings made from preganglionic sympathetic fibers at a recording site in the sympathetic chain immediately proximal to the superior cervical ganglion [244–246]. This work was motivated by earlier recordings of sympathetic activity recorded from postganglionic fibers in the long ciliary nerves [247,248]. In the later studies, preganglionic fibers were identified that were excited by a light stimulus, while in the earlier studies, postganglionic fibers were found that were inhibited by a light stimulus. Detailed temporal analyses of the responses of the sort typical in quantitative studies of the PLR were not performed in either sets of studies. However, the published figures suggest that the

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latencies to alterations of activity in at least some of these fibers was too long to account for the prompt pupillary responses to light. It is also important to note that when recording from the central cut ends of efferent fibers, it is impossible to know the fibers' projective fields, i.e. the specific tissues supplied by the fiber whose activity is being recorded. Some light-responsive preganglionic fibers supplying the superior cervical ganglion may innervate ganglion cells that project to targets other than the eye, and some that project to the eye may be involved in phenomena other than control of pupil diameter. More importantly, even those postganglionic fibers projecting in the long ciliary nerves cannot be assumed to innervate the radial muscles of the iris, as a sympathetic supply to the sphincter, though sparser than that to the radial muscles, has also been demonstrated [249]. Further, both excitatory and inhibitory adrenoreceptors have been demonstrated in both muscles [249]. Thus, the effects of the excitation or inhibition of light-sensitive sympathetic fibers - whose targets are not known - cannot be inferred with any confidence. Any number of combinations are possible. Only functional studies can identify the physiological significance of this nerve supply. As noted above, careful functional studies have established that the dynamic pupillary responses to light are controlled predominantly if not wholly by the parasympathetic supply. That is, given the available data, it is justified to assert a marked asymmetry in the functional responsibilities of the sympathetic and parasympathetic innervation in the control of pupillary changes in response to variations in lighting, with the parasympathetic supply having by far the more important role.

Pupillary diameter varies not only with changes in luminance, but also with changes in the fixation point of the gaze. Pupillary constriction during near vision serves to increase the depth of focus and is coordinated with both changes in lens curvature (accommodation) via action of the ciliary muscle, and with the action of the internal recti muscles, particularly the medial rectus, which alter the fixation point [102]. Each of these three components of the near response (pupillary constriction, accommodation, convergence), known as the near triad, is mediated via distinct subnuclei of the third cranial nerve nucleus, with convergence mediated by somatic motor fibers. The fiber population in the third cranial nerve, and the central pathways that mediate the pupillary responses to light are demonstrably distinct from those that mediate the components of the near response, including the pupillary component [233,250]. In reviewing over a century of literature concerning the respective roles of the parasympathetic and sympathetic innervation in controlling accommodation, Gilmartin proposed that, "the rapid changes in accommodative response which are required for normal visual tasks are solely under parasympathetic control, whereas sustained visual tasks involving high levels of cognitive demand (e.g. prolonged viewing of visual display units) involve both parasympathetic and sympathetic control" [251]. Such a formulation is consistent with the respective effects of the two autonomic branches on dynamic vs tonic levels of activity discussed above for the control of heart rate. So too is the demonstration that parasympathetically-mediated changes in accommodation were much more rapid than the much smaller effects resulting from changes in sympathetic activity by Tornqvist, who concluded that sympathetic activity plays at best a minor role in "desaccommodation" [252]. The integrative action of the near triad clearly demonstrates the intimate functional relationship between the parasympathetically-controlled iris and ciliary muscles responsible for accommodation and pupillary changes with somatic motoneuron-controlled vergence movements, and with saccadic movements that typically accompany changes in fixation point [253,254].

While the sympathetic supply to the muscles of the iris seems not to play a critical role in the dynamic responses to varying illumination and changes in the focal length, it plays a dominant role in controlling other types of activity of the iris dilator (radial) muscle, particularly in pupillary reflex dilation. In Chapter 6 of her authoritative monograph, The Pupil (1999), Loewenfeld reviews and resolves a vast, at times ambiguous, conflicting, and often contentious literature concerning the dilator response to arousing stimuli. In reviewing this literature she notes that, "[p]upillary reflex dilation has been embroiled in more controversies than any other pupillary movement," [233].

In introducing the subject, Loewenfeld points out that, "Any sensory stimulus (with the exception of light) can elicit pupillary dilation; and spontaneous thoughts and emotions have the

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same effect as sensory stimuli. In other words, any somatic or visceral afferent nerve as well as all central connections involved in sensation or in general arousal responses can serve as afferent path for pupillary reflex dilation. There is no single, specialized afferent path for this reaction as has been claimed," [233].

Her critical review of the extensive historical literature is too involved to be reprised here, but it can be summarized as follows. Pupillary reflex dilation is driven centrally by hypothalamic premotor neurons projecting to preganglionic neurons in the thoracic cord whose projections synapse in the superior cervical ganglion (SCG) [233]. Fibers emerging from the SCG in turn project via the long ciliary nerves to innervate the radial muscles of the iris. Excitation of these sympathetic pathways is primarily responsible for reflex dilation of the pupil, particularly the most rapid aspects of the response. Interruption of this pathway (e.g. by sectioning the sympathetic nerves or by instilling adrenergic antagonists) abolishes most of the dilator response, although a smaller, slower residual component remains. This residual response is primarily attributable to central inhibition of parasympathetic activity originating in the Edinger-Westphal nucleus, carried via the third cranial nerve to the ciliary ganglion, and from there via the short ciliary nerves to the pupillary sphincter muscle. Loewenfeld notes that both the sphincter and dilator muscles each receive a dual innervation, but that the sympathetic supply to the sphincter and the parasympathetic supply to the dilator muscles are sparse. While such sparse innervation may play a facilitatory role, neither is believed responsible for the major components of these responses [233].

It is interesting that Loewenfeld describes the respective roles of the sympathetic and parasympathetic pathways in the reciprocal contraction and relaxation of the radial and sphincter muscles, respectively, "as a classic example of Sherrington's reciprocal innervation." Her own narrative emphasizes the asymmetry in the relative magnitudes and time courses of the sympathetic and parasympathetic contributions to reflex dilation. While changes observed in this reflex are indeed reciprocal, the relationship is not stereotypic, in that the same pattern is not observed in the case of the PLR or the near response described above.

To summarize, it is unjustified to consider the parasympathetic system as responsible, generically, for pupillary constriction and the sympathetic system as responsible, generically, for pupillary dilation. Rather, abundant evidence supports the view that the two branches regulate distinct aspects of pupillary function. Variation in the activity of either branch may widen or narrow of the pupil, the response depending on whether tonic activity is waxing or waning or vice versa, and which branch is responsible for the effect. Thus, parasympathetic pathways relax the sphincter muscle and widen the pupil in response to reduced luminance, and sympathetic pathways may relax the radial muscle leading to narrowing of the pupil in response to reduced arousal, each by reducing tonic impulse activity in the respective postganglionic fibers (along with whatever reciprocal and facilitatory influences each exerts simultaneously). Again, the function of a nerve supply is not defined by the effect of excitation only, but rather by the factors that recruit changes in its activity. Exploring and defining these respective regulatory spheres of responsibility should be our focus, rather than the effect of excitation per se.

Based on the available evidence it is reasonable to describe the parasympathetic supply as responsible for coordinating the activity of the ciliary and pupillary muscles in concert with the demands of the changing visual field, including changes in luminance and fixation point. The activity of the ciliary muscle and iris smooth muscles must be integrated with skeletal muscular control of vergence, saccadic and other eye movements [253,254]. In contrast, the sympathetic supply appears to have the dominant responsibility for regulating pupillary responses associated with various types of 'arousal' [233], although this term is so broad, covering so many different conditions, that care should be taken to better define this category. Arousal is too vague a term to allow for a confident attribution of the neural pathways responsible for all forms of what we might call arousal. The claim regarding arousal, though asserted rather forcefully by Loewenfeld, may be an oversimplification because several studies indicate a greater role for central inhibition of parasympathetic drive – sometimes referred to as central sympathetic inhibition due to its adrenergic nature. But in broad

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outline, describing the two branches as responsible for distinct aspects of regulation is more productive than treating them simply as antagonistic. The functional antagonism between sympathetically-dominant dilator muscle activity and parasympathetically-dominant sphincter activity can be thought of as resembling the similar functional antagonism between accommodation and voiding in the bladder, though in the pupil a much wider array of phase relationships in their activities must occur, due to the essentially infinite potential combinations of the need to respond to the visual field and to arousal of various sorts.

Application of the Hypothesis to Other Tissues

A great deal of experimental work on autonomic control in tissues receiving a dual innervation has focused on how excitation in one or the other branch influences measured physiological variables (endpoints). To repeat, the more important question – and the more difficult question to address - concerns which factors drive changes in the activities of the respective branches, i.e. which branch is responsible for what, functionally.

Asserting a theory of the functional spheres of responsibility of the two divisions of the ANS generally provides a lens through which to consider their possible respective functions in specific tissues beyond those in which more definitive statements can be made. Taking a position on functional responsibilities leads to the formation of testable hypotheses that are more enlightening than statements about the polarity of responses to excitation.

Endocrine Pancreas and Liver

Consider the autonomic innervation of the pancreatic islets, and the autonomic regulation of insulin and glucagon secretion. Acetylcholine stimulates insulin release from β-cells while noradrenaline inhibits it [255]. Given ongoing modulation of glucose-dependent insulin release and tonic discharge, either branch may cause either increases or decreases in insulin secretion, depending on the direction of change in discharge rates in the respective nerve supplies. The schema proposed here leads naturally to viewing the parasympathetic regulation of the islets as related to changes in blood sugar associated with feeding, digestion, and absorption. In contrast, sympathetic regulation may be more important in regulating blood sugar to meet current and anticipated demand of tissues for metabolic supply. The fact that cholinergic stimulation increases both insulin release from beta cells and glucagon release from alpha cells indicates that the parasympathetic supply to and control of each must be distinct, and must be differentially regulated [106,256,257]. The situations in which changes in parasympathetic activity might stimulate release of insulin vs. glucagon are presumably quite different, though in each case the effects may be related to particular phases of the digestive process. Such interpretations are of course speculative, and difficult to address experimentally, but the point is that forming the hypotheses in this way, against the background of a broader pattern of observations, permits the design of experiments that can address the question.

Similarly, if we consider the autonomic innervation of the liver [94], we might consider parasympathetic control of hepatic function to be concerned with postabsorptive adjustments in glucose storage, while sympathetic innervation may be concerned with glucose regulation related to expected systemic demand for energy, both in concert with the corresponding regulation of the activity of the pancreatic islets. Further, we may hypothesize that the hepatic parasympathetic innervation may be involved more broadly in anticipatory alterations in bile production and other events related to the digestive process. In contrast, we might expect the sympathetic supply to be concerned with regulating production of the many plasma proteins such as albumin, clotting factors, kallikreins, angiotensinogen, etc., in addition to the regulation of metabolic supply needed to meet anticipated demand, and other aspects of hepatic function related to the homeostatic functions generally under sympathetic control. In the case of control of blood glucose and fatty acids/lipoprotein levels, a complex interplay between both branches of the ANS in controlling these processes is to be expected.

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Parasympathetically-Innervated Vascular Beds

The traditional autonomic narrative does not address the observation that while parasympathetic innervation of the vasculature is absent from the bulk of the systemic circulation, specific vascular beds are parasympathetically innervated. These include the pulmonary vasculature, the genital vasculature, the cerebral vasculature, the vascular supply of exocrine tissues (tear ducts, liver and pancreas, salivary glands, etc.) and other secretory tissues such as the ocular choroid [94,258–262]. The proposed alternative narrative holds that the sympathetic innervation of the vasculature should be seen as related to the regulation of supply to meet anticipated metabolic demand, and that, in contrast, the parasympathetic vascular supply (PVS) should be seen as related to anticipated interactions and exchanges with the exterior (including various lumens), often involving rapidly varying musculoskeletal activity.

The potential physiological purpose of the pulmonary PVS has already been addressed. The alternative schema suggests that the PVS of secretory tissues [262] be seen as related to the need to supply adequate fluid volume to support such secretions, i.e. what we might call the tissues' hydraulic needs, rather than to their metabolic needs. A similar argument could be made that the genital PVS [263–265] is concerned with providing adequate perfusion to drive the engorgement of the erectile tissues of the genitals, and again, is not related to the metabolic needs of the tissue.

The situation for the cerebral circulation is somewhat more obscure. The Monro-Kellie doctrine holds that, "because the brain is enclosed in the skull, there must be an equilibrium between its volumetric components (brain parenchyma, interstitial and cerebrospinal fluid, and arterial and venous blood volume)," [266]. Due to the fixed volume of the cranium, cerebral blood flow (CBF) must be tightly regulated. In reviewing CBF control, Claassen et al. divided the mechanisms responsible for regulating CBF into four broad categories: autoregulation (changes in vascular resistance resulting from changes in perfusion pressure), vascular reactivity to vasoactive stimuli, neuronal regulation, and endothelium-dependent responses. In his review of the ANS regulation of the cerebral circulation, Goadsby wrote that, "[a]lthough there have been considerable advances in understanding the basic capabilities and connectivity of the parasympathetic innervation of the cerebral circulation, there is no clear physiological role for the system. The nerves are not involved directly in the most basic cerebrovascular responses, such as hypoxic or hypercapnic vasodilatation, nor do they appear to play a role in autoregulation," – a point later echoed by Claassen et al. [266]. Goadsby also categorically asserted that the cerebral PVS is uninvolved in regulating cerebral blood flow to meet metabolic needs [266,267].

Claassen et al. [266] noted that the existence of a dynamic component of autoregulation - responsible for changes in CBF in response to rapid changes in BP - was only recognized once experimental methods for monitoring CBF with high temporal resolution became available, commenting that, "[a]utoregulation is strongly affected by the rate at which BP changes," (a fact that might have relevance to RSA, although this is not something they address). They further noted that "[u]nder physiological conditions, cerebral perfusion pressure is mainly determined by arterial BP and body posture (supine or prone vs. seated or standing in humans)," [266]. Hamner et al. noted that autoregulation is less effective at buffering higher frequency changes in BP [268]. They demonstrated that muscarinic cholinergic blockade (i.v. glycopyrrolate) reduced the effectiveness of autoregulation in healthy human subjects in response to oscillatory lower body pressure at frequencies above 0.04 Hz. That work was motivated by an interest in the possibility of autonomic effects on autoregulation, and their work supported this hypothesis.

Together, these observations are consistent with the view that the cerebral PVS may play an important role in adjusting the reactivity of the cerebral vasculature to imminent (with possibly fractions of a second) pressure changes resulting from parasympathetically-driven variations in heart rate and potentially rapidly varying changes in body and head position resulting from either changes in musculoskeletal activity or awareness of changing outside circumstances (e.g. recognizing the imminence of a fall).

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To explore such hypotheses, it is not enough to demonstrate that stimulation of a given nerve supply produces a given effect. The more significant questions concern when such effects are relevant. Such questions are difficult to address. Even in cases where the goal is limited to identifying the therapeutic potential of mass activation (for example by an implanted stimulator device), understanding the regulatory significance of the activity is important for interpreting and addressing the possibility of potential sequelae of any given stimulation regime.

Experiments designed to probe specific hypotheses regarding each branch's sphere of regulatory responsibility are likely to lead to advance development of overarching concepts. Since it is typically much more difficult to discern clear functional responsibilities than it is to demonstrate the effects of changes in mass activity on endpoints, situating experimental work in the context of a broader theory can help justify the effort and funding required.

Anticipation and Dynamic Regulation

The emphasis on the concepts of homeostasis and negative feedback that forms the basis of much teaching of physiology focuses attention on how responses to imposed perturbations or manipulations act to restore some physiological variable to a range that is considered normal and stable, i.e. toward some resting 'set-point'. This emphasis is also traceable to Cannon, whose coinage of the term homeostasis was intended to elaborate on and improve upon the then-dominant principle of the constancy of the internal milieu that Claude Bernard had asserted fifty years earlier [269]. Cannon proposed his neologism to account for the observed variation in physiological parameters in the 'resting state', and to draw attention to the mechanisms called into play both to maintain certain variables within a "normal range" during action as well as those that act to restore the resting state after the organism has acted. As previously noted, Cannon's lab demonstrated that the organism can survive total sympathectomy [33]. This begs the question, why do we need sympathetic nerves at all? Put another way, why does the organism commit vast resources to maintaining this network, if it can survive in its absence?

Autonomic innervation allows the organism to adjust the activity of innervated tissues not only in response to stimuli, but in anticipation of need, i.e. before an error signal is present. It permits integrative activity with a high degree of spatial and temporal patterning. Feed-forward mechanisms allow for experience and learning to improve performance. The importance of emphasizing anticipatory change and flexibility of action led Sterling and Eyer, in the 1980's, to coin a new term, allostasis, which they proposed as a superior framework for understanding physiological regulation [270]. The principle of allostasis emphasizes not the stability of physiological variables and the mechanisms of negative feedback, but rather fluidity of physiological change, how feedforward signaling and positive feedback facilitate such fluidity, and the role of anticipation in physiological regulation.

That the autonomic system plays a key role in mediating physiological changes that anticipate action was well-established since before the work of Pavlov on conditioning [32]. The recognition of the importance of "feed-forward" or central command-driven adjustments in cardiorespiratory function has a long history. Waldrop et al. trace it back at least as far as the late 19th century [271], citing Johansson's hypothesis that a central command mechanism could account for the rapid circulatory changes accompanying onset of exercise [272,273]. Later studies demonstrated that stimulation of discrete central loci can elicit coordinated behavioral responses, along with physiological changes that anticipate demand [119,274]. Eckberg (2003) highlighted the long history of research into the variations in heart rate associated with respiratory sinus arrythmia (RSA). Such variations were shown by Frédéricq [275] to persist in the absence of associated changes in intrathoracic pressure (during open chest surgery), and by Heymans [276] to persist after pulmonary denervation. These findings suggested, and more recent studies confirm, that respiratory-associated variations in parasympathetic drive to the cardiac pacemaker are initiated by a central pattern generator, whose output is modified by peripheral input from baroreceptors and other sources [223]. For the ENS, where our knowledge of the pattern of connectivity and the properties of the network

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elements is extensive, modeling of the coordination of peristaltic activity in isolated gut has illustrated the value and flexibility of feedforward regulation [52]. There is no reason to suppose that this finding is unique to the intrinsic network of the gut.

Challenges to Discerning the Significance and Nature of Autonomic Function

It is somewhat remarkable that despite decades of interest and study, we still lack explanations for the physiological importance of the prominent parasympathetic nerve supplies of the pulmonary and cerebral vasculature and that of airway smooth muscle, of widely studied parasympathetically-mediated phenomena such as RSA, of many of the varied prominent frequency components apparent in sympathetic nerve activity, and many other notable features of autonomic signaling. Why is this?

Two reasons stand out. One has to do with limitations in the spatiotemporal resolution with which we can monitor and discern dynamic changes in physiological activity of various sorts under 'normal' conditions. The other concerns functional redundancy.

Claassen et al. recently addressed both these points in their review of cerebral blood flow (CBF) regulation. Concerning the latter point, they wrote,

"An important characteristic of CBF regulation is mechanistic redundancy, i.e., overlapping mechanisms contribute to maintaining CBF under highly challenging conditions. Studies exploring the regulation of CBF are importantly impacted by this, because the overlap in pathways makes it difficult to explore the relative importance of individual pathways or identify key contributors. From a teleological perspective, this redundancy makes the regulation of CBF a robust system where multiple strategies are present to ensure precise control and thus protect against potential brain damage" [266].

Distributed regulation is difficult if not impossible to monitor effectively with experimental approaches that lack adequate spatial and/or temporal resolution. This was already discussed earlier, in the context of the problem of quantifying coordinated patterns of GI motility using simple measures such as intraluminal pressure. There are many examples, of course, of high-resolution methods opening new vistas of inquiry and understanding. In the same review on CBF, Claassen et al. pointed out that it was only with the advent of high-resolution methods for measuring rapid changes in CBF that a dynamic component of autoregulation was finally discerned [266]. It may require the development of the ability to measure blood pressure and flow simultaneously with broad spatial and high temporal resolution in a behaving subject to permit experimental investigation of the question of whether the cerebral PVS adjusts vascular reactivity immediately in advance of or simultaneous with arterial pressure changes resulting from anticipated voluntary movements of the head and trunk. The same holds true for exploring the proposals made here concerning the regulatory roles of the pulmonary PVS and the parasympathetic innervation of the airways in ventilation-perfusion matching throughout the respiratory tree with high spatial resolution under dynamic conditions, with the addition that it would also be necessary to monitor airflow and pressure in the airways at the same time.

Such challenges raise questions of the physiological importance of proposed mechanisms that require elaborate and sensitive methods to detect their action, especially if other mechanisms can substitute in their absence to achieve organismal goals. Are these mechanisms and systems then superfluous? The problem posed is similar to that presented by Cannon's findings on the effects of total sympathectomy in animals maintained in the lab, and his interpretation regarding the significance of sympathetic function generally [33].

Again, the key point concerns the value of the capacity not only to respond to an imposed change of conditions, but to anticipate imminent changes, to pre-act, and to learn over time how to optimize function, even as the "equipment" changes with age and state. Negative feedback requires an error signal that is then corrected, and a time lag for its correction. Biological systems have multiple reinforcing mechanisms for achieving negative feedback locally. But feedforward systems that allow for adjustment of a system in preparation for an anticipated change can reduce or eliminate such error signals before they occur, enabling a level of flexibility and fluidity not possible in their absence.

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Autonomic nerves provide a pathway for such feedforward regulation, based on learning and experience.

We easily recognize the importance of learned pre-action in producing the fluidity of trained movements, such as handwriting, or artistic, musical or athletic performance. We also immediately recognize various disorders of somatic motor control based on sometimes subtle, sometimes glaring disruptions of 'normal' movements of the body in those afflicted. Yet many impairments caused by motor disorders are overcome by those afflicted to the extent that they are able to perform desired tasks at a level that could not be distinguished from 'normal' by simple measurements. Various basal-ganglia related movement disorders can be distinguished from each other and from cerebellar disorders by noting characteristic movement patterns, some of which can be quite subtle and require medical training and specific characteristic tests to notice. Yet measurements of the time afflicted subjects might take to move from one point to another, or of the skill with which they could cook a meal, or play a musical instrument could easily fail to detect these differences, or perhaps any impairment at all. Conversely, imagine two musicians of unimpaired motor capacity, one professional, another an amateur of average skill, each playing a given sequence of notes. What quantitative measure of performance could be used to distinguish virtuosity? The number of notes played per minute? The mean duration between notes struck or the variability in these intervals? Variations in amplitude?

We recognize physical virtuosity immediately because we have an everyday familiarity with the patterns it produces. It emerges from ceaseless repetition and thus, effective anticipation of and adjustment in preparation for what is about to occur. It cannot be captured easily with simple measures. In contrast, we typically have no such familiarity with what constitutes what might be called physiological virtuosity and fluidity, no way to recognize it, and we therefore are ignorant of its importance. We struggle to identify the pathways responsible for producing it, because we do not know how to manipulate or characterize it. Yet this does not mean such virtuosity or the pathways responsible for producing it are not important, nor that they are only important under exceptionally demanding circumstances. Indeed, the feeling of vibrant good health and the sense of well-being that arises with and from it may reflect such virtuosity. Conversely, states of malaise and many syndromes that we identify as functional disorders may reflect impaired feedforward function for which these systems may be responsible.

Until the advent of recording and analysis methods that will allow us to discern directly the articulated spatiotemporal patterning that an autonomic nerve supply may orchestrate, hypotheses about such regulation may not be directly testable. And even with such capacity, many challenges to recognizing these effects may remain, as the example of the difficulty of discerning musical virtuosity by objective measures of performance makes clear. Perhaps the only system equal to the task of monitoring the effects of autonomic activity with appropriate spatiotemporal resolution is the ensemble of afferent fibers whose combined activity likely contributes to the pleasing sensations and emotions associated with autonomic virtuosity, or the aversive ones associated with autonomic dysregulation. While we await technological developments that can allow us to investigate these things experimentally, thought experiments, reasonable guesses and theory can help guide our thinking. What is certainly the case is that a nerve supply is a biologically costly apparatus, and its persistence throughout phylogeny argues strongly for its importance, even when we remain ignorant of the ways in which it is important. We should not fail to point out our admitted blind spots when describing what we do and do not know, and it is helpful to be clear on the reasons for our areas of ignorance.

Possible Objections to the Proposed Pedagogy

Any proposal that departs so markedly from tradition as that offered here is bound to be controversial. It may well elicit objections from specialists in each of the fields on which it touches, particularly given the prevailing concepts that have driven autonomic research the and interpretations of results over the past century. And it would be surprising if experts in each of the

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areas surveyed above could not point to questionable interpretations of the literature or facts not addressed here, calling into question this proposed framing. As just one example, the fact that ejaculation requires an intact sympathetic supply [277] might be seen as contradicting the general thesis that it is the parasympathetic innervation that is responsible for coordinating exchanges of material with the outside world. Further, eccrine sweating, clearly under sympathetic control, obviously involves interchanges of material with the outside world, though not via orifices surrounded by striated muscle, nor coordinated with specific detailed patterns of musculoskeletal activity. Yet coordination with specific patterns of musculoskeletal activity is also unlikely to be involved in some types of parasympathetically-mediated secretory activity, e.g. the exocrine activity of the pancreas.

Similarly, the fact that cardiac output, systemic blood pressure and sympathetic vasoconstrictor activity all clearly vary with the respiratory pattern might cause some to object that in this way the sympathetic system is just as bound up with coordinating exchanges with the outside world as is the parasympathetic system, though perhaps in different, less instantaneously responsive, ways. A similar argument could be made for the sympathetically-mediated cephalic phase cardiovascular changes associated with feeding behavior. And so perhaps the rubrics suggested here deserve refinement so as to avoid confusion about the which aspects of "interactions with the outside world" fall within the parasympathetic sphere of responsibility.

Other, more challenging examples may be found that might call for these summary descriptions to be revised. And there are undoubtedly a great variety of situations in which the interactions between the functional responsibilities of the two branches are so intimately linked that it may be extremely difficult to disentangle and assign to one or the other specific responsibilities as definitive as those seen in the cases of the pupillary light reflex or of respiratory sinus arrhythmia.

Finally, it may be objected that the description of the sympathetic sphere of responsibility does not adequately capture its role in the allostatic adjustment of setpoints of targeted processes.

Ideally, objections to the present proposal and any ensuing debate will lead to refinements of it or to proposal of a superior alternative, culminating in a consensus narrative that can represent robustly the opinions of the community of experts. However, whatever objections may be raised to the present proposal, it is hoped that, sooner rather than later, a consensus can be reached that the popular view of the sympathetic and parasympathetic divisions as generically oppositional and counterbalanced must be replaced *in toto*, and that in order to overcome a century of inertia in this area an active and categorical repudiation of the traditional narrative will be required. It is further to be hoped that discussions on these topics may motivate increased research interest and funding directed toward basic studies designed to address these questions. It is difficult in the present funding environment to get such basic, theoretically-oriented work funded. Much of it is painstaking, and its implications will frequently be open to further debate. It can be difficult to reach definitive conclusions – often, experimental work will simply reveal greater complexity, and in the present environment such complexity is not always welcomed.

Still, consider that perhaps billions of dollars' worth of both public and commercial funding have gone into and continue to go into the measurement and analysis of cardiac sympathovagal balance, in the thought that the ratio of total sympathetic to parasympathetic drive to the cardiac pacemaker (in those cases where the measurement can be shown to reflect this ratio robustly) is somehow a reflection of an overall state of physiological well-being, i.e. a balance between arousal and repose. This specious idea – still widely propagated - should be recognized as based on a speculative story originally proposed over a hundred years ago by Walter Cannon, based on relatively sparse data, and later rejected by him based on further information [1,33]. If instead we see sympathetic and parasympathetic drives as responsible for different aspects of physiological regulation, then their ratio takes on no more general a significance than any other ratio of disparate though possibly related activities, e.g. the ratio of the motion of the wrist to the contractile activity of the hamstring muscle, or of the movements of the arms to those of the legs. Such ratios may indeed be informative. In specific spheres of application they may be quite useful proxies of state. But to

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confer on such a ratio a broader meaning in representing an overall state of musculoskeletal coordination would be a mistake.

We should of course be careful not to take such matters too far. The nervous system did not evolve to have its various pathways adhere to some design principle, but rather to solve problems necessary for survival. And Blessing's point - that it is the nervous system as a whole rather than any component of it that is ultimately responsible for solving such problems – still holds [7]. Nonetheless, the attempt to develop more apt descriptions of functional relationships cannot but improve our ability to judge the potential value of various therapeutic approaches.

Summary and Conclusions

The default, nearly ubiquitous view of the respective functions of the sympathetic and parasympathetic branches of the ANS, and of the relationships between them, remain those originally advanced by Walter Cannon in his 1915 monograph, Bodily Changes in Pain, Hunger, Fear and Rage [1], despite repeated critiques by autonomic neuroscientists over many decades. The schema that Cannon laid out and that persists to this day rested fundamentally on a juxtaposition between conditions that were "favorable" to gastric motor and secretory activity to those that were "unfavorable". Excitation of the vagus nerve was known to stimulate gastric motor and secretory activity, and adrenaline secretion and sympathetic activation to inhibit it. Further, adrenaline secretion and sympathetic activation had been shown to mediate diverse physiological changes associated with greatly increased demand from skeletal muscle during periods of intense emotional arousal. From a consideration of these facts was extrapolated the now familiar narrative, which holds that the sympathetic system exists for the purpose of mediating catabolic activity and physiological correlates of states of arousal (fight-or-flight), that the parasympathetic system exists for the purpose of mediating anabolic activity and physiological correlates of states repose (rest-and-digest), and that homeostasis depends on balancing the activity of these two counterposed systems.

This traditional autonomic narrative rests on and perpetuates a variety of logical and interpretive errors. It omits and obscures many facts that do not fit the pattern. The principles it claims as foundational do not represent simplified but otherwise useful first approximations to physiologic reality. They do not form an appropriate basis for introducing or understanding autonomic regulation. Rather, they are fundamentally misleading ideas whose familiarity, allure and simplicity continue to undermine popular and medical understanding of autonomic regulation.

As has been discussed at length in this work, the errors and distortions of the traditional narrative are numerous. They include:

- Inappropriate generalization from limited examples. While it is true that sympathetic activation during what Cannon called 'emergency' conditions inhibit digestive activity and mobilize metabolic resources and processes necessary to support intense skeletal muscular activity, sympathetic activity is also involved in diverse aspects of normal digestive activity and is continuously involved regulating processes such as the appropriate distribution of blood flow. It is an error to consider sympathetic activity and parasympathetic activity as either monolithic or consistently antagonistic. It is also an error to conclude that any example, no matter how vivid nor how commonplace, characterizes the essential nature of a system. Basing our view of autonomic function fundamentally on a dichotomy between states favorable and unfavorable to gastric motor and secretory activity cannot bear the burden of accurately organizing thinking about these systems.
- Conflation of effects of excitation with essential function. Introductory texts commonly provide tables or lists indicating, among other binaries, that the sympathetic **system** accelerates heart rate, and the parasympathetic **system** decelerates it. This is not the case. It is not a fiber population that produces the described effects, it is **excitation** of that fiber population that does

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so. Increased sympathetic drive to the pacemaker accelerates the heart, but decreased sympathetic drive to the pacemaker decelerates it. The reverse holds true for the parasympathetic supply. Tonically active nerve fibers may alter their activity in either direction, so we cannot say that a given nerve supply, even if consisting of only a single fiber type communicating with only a single receptor type, exists only to drive activity of target tissues in a single direction. For example, parasympathetic cardiac output regulates the cyclical modulation, both acceleration and deceleration, of heart rate that produces RSA. Similarly, the parasympathetic supply to the iris, and not the sympathetic, is responsible for the dynamic modulation of pupillary diameter, both increases and decreases, with sinusoidal variations in the light regime [66,278,279]. Neither the sympathetic nor the parasympathetic supplies are generically responsible for increasing or decreasing heart rate or pupillary diameter. Each can cause either effect depending on the circumstances, and the factors to which each respond are different. To understand the function of a nerve supply one must investigate the factors that elicit changes in its activity and for what purpose, not just how an increase in activity affects the target. The effect of excitation does not define the regulatory purpose of the respective pathways. To understand neural function, one must look not at the effects of mass activation but at how the respective systems are engaged in specific physiological contexts, and across a variety of such contexts.

- Conflation of the effects of intense, mass activation with essential function. The existence in any nerve trunk of diverse subpopulations of fibers with distinct targets, of various neurotransmitter receptor subtypes in target tissues, as well as the presence of multiple neuromodulatory co-transmitters, all contribute to the ability of a nerve supply to elicit a pattern of changes in target tissue function that is highly articulated both spatially and temporally. Indeed, articulated coordination of function is the very purpose of a nerve supply. To speak solely in terms of increases or decreases in the activity of targeted tissues simply because of limits in the resolution with which simple endpoints are measured is to overlook the essential regulatory functions of a given nerve supply. Further, the action of a system at its maximum intensity does not define its essential purpose and it is a logical error to assume that it does. The fact that sympathetic discharge is maximal when there is a physiological need to maximally raise cardiac output, increase energy availability (blood glucose, fatty acids, etc) and increase the rate of heat dissipation does not mean that the system exists fundamentally to respond to maximal demand, nor does the fact that impairment of the system has the greatest impact in situations of maximal demand imply this.
- The widespread emphasis on the role of the sympathetic division of the ANS with so-called fight-or-flight responses is among the most pernicious of the distortions of the traditional narrative. The sympathetic division provides the sole innervation of the kidney and the sympathetic supply to all parts of the nephron indicates a role for this system in the regulation of all the physiological functions of the kidneys. The same can be said of the sole sympathetic innervation of the great bulk of the systemic vasculature with respect to the distribution of blood flow [6], or the sole sympathetic innervation of adipose tissue [83–89]. Elegant experiments have directly demonstrated the reciprocal variation in the firing of premotor neurons that control adrenaline and noradrenaline release from the adrenal medulla in response to even slight changes in the normal range of blood glucose and blood pressure, respectively [71]. The sympathetic division is also involved in important aspects of normal digestive function,

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including regulation of associated cardiovascular changes associated, intestinal fluid fluxes, and feedback from the distal gut that influence gastric emptying and relaxation [13,82]. Postganglionic sympathetic fibers innervating the pineal gland - which arise from the superior cervical ganglion and are driven by inputs from the superchiasmatic nucleus of the hypothalamus - regulate pineal melatonin secretion and thus, the sleep-wake cycle [91,92]. Again, to insistently focus on the actions of elevated sympathetic activity under conditions of intense demand or its expectation is akin to teaching that the voice is fundamentally an emergency alerting system, that the limbs are stress limbs, or that the heart is an emergency hydraulic pump since each is maximally engaged under duress.

- The rubric of rest-and-digest to describe broadly parasympathetic regulatory responsibilities and a primary association of parasympathetic regulation with anabolic states is similarly problematic. The parasympathetic division certainly regulates a range of digestive activities, but as just noted, the sympathetic plays important roles in various aspects of digestion as well. Parasympathetic regulation of anabolic activity in the post-prandial state is not in question, but its role in other aspects of anabolism – for example the development of skeletal muscle mass or the regulation of adipose tissue mass and cellularity - is questionable at best. Cannon's argument that the narrowing of the pupil in the presence of light functions to protect the retina and is thus an example of a generalized conservative or restorative role for the parasympathetic division is not as persuasive as is the view that parasympathetically-controlled variations in pupil diameter in response to light, and both lens curvature and pupil diameter in response to the nearness of the fixation point, are all aspects of parasympathetic participation in the visual task per se. These functions are just as important in intense emotional states as they are in the restful states, possibly moreso. Further, evidence that parasympathetic effects on cardiac function relate to dynamic aspects of cardiorespiratory coordination suggest that this innervation is likely to be relevant across the full range of physiological states. The rest-and-digest rubric does not seem to account for the functional significance of the innervation of specific vascular beds – pulmonary, genital, ocular choroid, cerebral and others – and such innervation is unlikely to be only or even primarily relevant to digestive or restful states or anabolism. The predominant parasympathetic innervation of the airways along with the parasympathetic innervation of the pulmonary vasculature is highly suggestive of a possible role in coordinating localized ventilation-perfusion matching throughout the respiratory tree, and if so, is likely again to be important across a range of physiological states, and perhaps of greatest importance during extreme exertion, where minimization of physiologic dead space may be critical to performance. Finally, Cannon himself discussed the role of parasympathetic activity in mediating engorgement of the genitals during sexual excitement. All these observations suggest that we should abandon the description of the parasympathetic system as primarily responsible for 'rest-and-digest' functions. The available evidence suggests that both divisions of the ANS cooperate in diverse physiological processes and states including those of digestion and rest, and that our concern ought to be focused on the nature of that cooperation rather than on a litany of questionable dichotomies.

Given that autonomic neuroscientists and other physiologists have been pointing out the flaws in the traditional pedagogy for decades without making a substantial dent in how it is (mis)taught, and despite the advent of reviews that avoid these distorting caricatures [10,12,13], something more must be needed if we are to displace the traditional, false, narrative.

A central premise of the present work is that the persistence of the traditional narrative and pedagogy - in the face of an extensive body of evidence to the contrary and decades of commentary

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by experts in the field pointing out its errors - results from the absence of an alternative framing of the respective roles of the sympathetic and parasympathetic divisions that is 1) more realistic and corresponds to what we know of the regulatory responsibilities of each, 2) is easily described, and 3) is widely supported and advocated broadly by knowledgeable authorities. Unfortunately, the persistence of the traditional narrative obscures the need for an alternative and undermines the effort to imagine one.

The present work offers such an alternative for consideration and debate by experts in the field, with the goal of developing a broad consensus approach that can displace the current narrative.

The Proposed Alternative Narrative

The alternative schema proposed here centers known and significant facts that are typically excluded from and are inconsistent with the traditional functional narrative. Starting from those physiological phenomena whose regulation can be shown with confidence to be the sole or predominant province of one or the other division of the ANS, hypotheses concerning the qualitatively distinct spheres of regulatory responsibility of each are developed. These hypotheses are then used to interpret the actions of each branch in tissues receiving dual innervation.

The key features of the proposed schema are as follows:

- It argues against seeing the typically opposed effects of mass cholinergic vs. adrenergic stimulation or blockade as evidence of an essential oppositional relationship between the systems. It holds that respective divisions of the ANS use different final neurotransmitters to regulate different aspects of physiological regulation, and that the polarity of response to mass activation of each is not indicative of regulatory function per se.
- It develops a description of sympathetic regulatory responsibilities by considering first tissues that only or predominantly receive a sympathetic innervation, including the kidney, adipose tissue, the bulk of the systemic vasculature, sweat glands, the piloerector muscles, and the adrenal medulla (the first two of which are typically overlooked). It associates sympathetic function generally with the continuous regulation of the internal milieu, as Cannon aptly pointed out [20], across all behavioral states and not just aggressive/defensive states.
- In contrast, it describes parasympathetic regulation broadly as concerned with secretory and smooth muscle activity involved in coordinating interactions and exchanges with the outside world—eating, breathing, speaking, voiding, looking, mating, moving, etc—often closely articulated with associated somatic motor activity. This view dovetails with the proximity of nuclei containing parasympathetic preganglionic neurons with those of somatic motor neurons, and of the much lower latencies of the responses of target tissues to cholinergic compared to adrenergic signaling. Both may be related to the demand for rapid, fine coordination of musculoskeletal activity with various parasympathetically-controlled smooth muscle and secretory activities. This approach to understanding parasympathetic regulatory responsibilities is then applied to the interpretation of the potential functional importance of parasympathetic nerve supplies whose significance remains a topic of controversy or ignorance, including those of the pulmonary circulation and airway smooth muscle, or the cerebral circulation, among others.
- It advocates an emphasis on the unique capacity of autonomic outflow to mediate anticipatory adjustments in smooth muscle and secretory activity and deprecates seeing this outflow as solely responsible for responding to changed circumstances after they occur.

The proposed alternative re-orients common observations of the traditional narrative and suggests more straightforward associations in other cases. For example, the proposed alternative

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holds that what is similar about parasympathetically-mediated cardiac and pupillary regulation is not supposed "conservative" functions. Instead, it highlights a parasympathetic role in regulating smooth muscle and secretory activity associated with interactions with the outside world in which the somatic system also participates. In contrast, it notes the frequent finding in many tissues of a more slowly varying sympathetic drive governing tonic levels of activity over which dynamic parasympathetically-mediated modulation is superimposed. It sees parasympathetic regulation of the exocrine secretions of the GI tract as comparable to those of the respiratory, lacrimal and other systems, involving exchanges with the outside world and requiring increased blood supply to meet secretory fluid demands involved in such interactions rather than to meet metabolic needs, as opposed to any overarching "rest-and-digest" or conservative sphere of responsibility.

Interestingly, the proposed schema turns the association of sympathetic activation with outward exertion and the parasympathetic with inward regulation somewhat on its head, or perhaps more properly, on its side. That is, it frames sympathetic activity as primarily concerned with regulating the conditions of the internal milieu for both visceral and somatic tissues, and parasympathetic activity as coordinating internal smooth muscle and secretory activity with specific patterns of somatic motor activity associated with largely conscious acts as noted above, i.e. the decision to consume, to void, to mate, to breathe, to move, to look, etc. This view is consistent with the anatomical locations along the rostrocaudal axis of the preganglionic cell bodies, i.e. the location of the sympathetic cell bodies in the thoracolumbar spinal segments and the parasympathetic cell bodies in the cranial nerve nuclei and pelvic spinal segments. Langley's original rationale for the term parasympathetic was anatomical, and the alternative interpretation suggested here harmonizes with that distinction.

It is hoped that the proposed approach will stimulate demand for experiments designed to clarify which aspects of regulation of a target tissue receiving dual innervation is the primary responsibility of each respective branch. Hopefully, the broad functional labels of quartermaster and coordinator proposed here to summarize the actions of the sympathetic and parasympathetic divisions, respectively, are neutral enough to avoid introducing strong biases that would make revision of these concepts difficult in the face of contrary experimental results, as has been the case for the traditional functional narrative. The nervous system did not evolve with the primary aim of allowing its various functions to be summarized succinctly, and it is important not to try to force facts to fit a narrative. Rather, narratives must be adjusted to encompass the facts.

The proposed schema seeks to contribute to the replacement of the traditional narrative that now dominates. It is unlikely to be able to succeed in this effort without concerted and persistent effort on the part of a broad swath of experts in various fields. What is needed is a consensus-building process of refinement, followed by widespread dissemination of the resulting consensus. While objections may be raised to various aspects of what has been proposed here, it is hoped that such objections will stimulate productive discussion, with the aim of improving or identifying a superior alternative to this proposal. The need to do so is urgent.

I know of no other branch of science in which the basis of its pedagogy is so widely acknowledged by experts to be fallacious, yet which has nonetheless doggedly resisted revision. The challenge to any change in thinking on the subject is in part the vast existing infrastructure of texts, study materials, test questions and so on that reinforce the current view, and in part the deep popular entrenchment of the story and the biases it has produced. Knowledge of the canonical examples and their traditional interpretations remains a criterion for demonstrating competency on professional licensing exams. Thus, being steeped in these distortions is a requirement for becoming a biomedical professional. The system thus reproduces itself, even in the face of over fifty years of commentary by the most knowledgeable authorities in the field that the story does not hold.

Teaching students that the traditional narrative is incorrect will lead to problems if, when they take entry or qualifying exams to continue in their field or seek study materials online, they are confronted with the errors of that narrative, presented as truth. Displacing the existing mass of misleading pedagogical tools and test questions will not be easy, and it cannot be accomplished by

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any small group of advocates. It does no good to eliminate one of these errors in a single textbook. The whole mutually reinforcing panoply of study materials and the tests they are designed to prepare for must be revised. This is a challenge that must be taken on by the field generally, and taken on *in toto*, if we are to correct and uproot the persistent errors and distortions that lie at the heart of current misunderstandings of autonomic function.Acknowledgments: The author would like to thank James Gibbs, Jen Yu Wei, Mary Townsley and James A. McRoberts, and Jane Borden for their helpful suggestions and contributions, and Marcus Gallagher-Jones, Muriel Larauche, Joseph Reeve Jr. and Million Mulugeta for their ongoing encouragement. The author would also like to thank Yvette Taché and Million Mulugeta for the opportunity of collaboration, without which this work could not have been accomplished. This work was wholly self-funded, without institutional financial support. It is dedicated, with gratitude, to Jen Yu Wei, who taught the author how to record from visceral nerve fibers and, over many years of productive discussions and work, why it mattered.

References

1. Cannon WB. Bodily changes in pain, hunger, fear and rage : An account of recent researches into the function of emotional excitement. New York: D. Appleton; 1915.
2. State OO. Divisions of the autonomic nervous system. Anatomy & Physiology. Corvallis, OR: Oregon State University; 2017. p. Chapter 16.1.
3. Teff KL. Visceral nerves: vagal and sympathetic innervation. JPEN J Parenter Enteral Nutr. 2008;32(5):569-71. doi: 10.1177/0148607108321705. PubMed PMID: 18753395.
4. Scott-Solomon E, Hsu Y-C. Neurobiology, Stem Cell Biology, and Immunology: An Emerging Triad for Understanding Tissue Homeostasis and Repair. Annual Review of Cell and Developmental Biology. 2022;38(1):419-46. doi: 10.1146/annurev-cellbio-120320-032429. PubMed PMID: 36201298.
5. Jänig W, McLachlan EM. Neurobiology of the autonomic nervous system. In: Mathias CJ, Bannister SR, editors. Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System. 4th ed ed. Oxford: Oxford University Press; 1999. p. 0.
6. Malpas SC. Sympathetic nervous system overactivity and its role in the development of cardiovascular disease. Physiol Rev. 2010;90(2):513-57. doi: 10.1152/physrev.00007.2009. PubMed PMID: 20393193.
7. Blessing WW. Inadequate frameworks for understanding bodily homeostasis. Trends Neurosci. 1997;20(6):235-9. Epub 1997/06/01. PubMed PMID: 9185301.
8. Langley JN. The autonomic nervous system, Part 1. Cambridge, Eng.: W. Heffer; 1921. 2 leaves, 80 p. p.
9. Jänig W. The integrative action of the autonomic nervous system : neurobiology of homeostasis. Cambridge, United Kingdom ; New York, NY: Cambridge University Press,; 2022.
10. Gibbins I. Functional organization of autonomic neural pathways. Organogenesis. 2013;9(3):169-75. Epub 20130606. doi: 10.4161/org.25126. PubMed PMID: 23872517; PubMed Central PMCID: PMCPMC3896588.
11. Furness JB. The enteric nervous system and neurogastroenterology. Nat Rev Gastroenterol Hepatol. 2012;9(5):286-94. Epub 20120306. doi: 10.1038/nrgastro.2012.32. PubMed PMID: 22392290.
12. Jänig W, McLachlan EM. Neurobiology of the autonomic nervous system. In: Mathias CJ, Bannister SR, editors. Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System: Oxford University Press; 2013. p. 0.
13. Furness JB, Callaghan BP, Rivera LR, Cho H-J. The Enteric Nervous System and Gastrointestinal Innervation: Integrated Local and Central Control. In: Lyte M, Cryan JF, editors. Microbial Endocrinology: The Microbiota-Gut-Brain Axis in Health and Disease. New York, NY: Springer New York; 2014. p. 39-71.
14. Langley JN. The autonomic nervous system. Brain. 1903;26(1):1-26.
15. Malpas SC. Neural influences on cardiovascular variability: possibilities and pitfalls. American Journal of Physiology-Heart and Circulatory Physiology. 2002;282(1):H6-H20. doi: 10.1152/ajpheart.2002.282.1.H6.
16. Gaskell WH. On the Structure, Distribution and Function of the Nerves which innervate the Visceral and Vascular Systems. J Physiol. 1886;7(1):1-80.9. doi: 10.1113/jphysiol.1886.sp000207. PubMed PMID: 16991419; PubMed Central PMCID: PMCPMC1484971.
17. Winslow JB. Exposition anatomique de la structure du corps humain : suivie du discours de Nicolaus Steno sur l'anatomie du cerveau. Paris: G. Desprez et J. Desessartz; 1732.

 doi:10.20944/preprints202510.1768.v3

18. von Euler US. The presence of a sympathomimetic substance in extracts of mammalian heart. J Physiol. 1946;105:38-44. PubMed PMID: 20994069.
19. von Euler US. A Specific Sympathomimetic Ergone in Adrenergic Nerve Fibres (Sympathin) and its Relations to Adrenaline and Nor-Adrenaline. Acta Physiologica Scandinavica. 1946;12(1):73-97. doi: https://doi.org/10.1111/j.1748-1716.1946.tb00368.x.
20. Cannon WB. The wisdom of the body. New York,: W.W. Norton & Company; 1932. xv p., 1 l., 19-312 p. p.
21. Cannon WB, de la Paz D. Emotional stimulation of adrenal secretion. Am J Physiol. 1911;28(1):64-70. doi: https://doi.org/10.1152/ajplegacy.1911.28.1.64.
22. Cannon WB. The emergency function of the adrenal medulla in pain and the major emotions. American Journal of Physiology. 1914;33(2):356-72.
23. McDougall W. An introduction to social psychology. London,: Methuen & co.; 1908. 2 p. l., vii-xv, 355, 1 p. p.
24. Cannon WB, Shohl AT, Wright WS. Emotional glycosuria. Am J Physiol. 1911;29(2):280-7. doi: https://doi.org/10.1152/ajplegacy.1911.29.2.280.
25. Nervous or emotional glycosurias. Journal of the American Medical Association. 1914;LXIII(6):485-6. doi: 10.1001/jama.1914.02570060045017.
26. Cannon WB, Nice LB. The effect of adrenal secretion on muscular fatigue. American Journal of Physiology-Legacy Content. 1913;32(1):44-60. doi: 10.1152/ajplegacy.1913.32.1.44.
27. Cannon WB, Gray H. Factors affecting the coagulation time of the blood II. The hastening or retarding of coagulation by adrenalin injections. Am J Physiol. 1914;34(2):232-42. doi: https://doi.org/10.1152/ajplegacy.1914.34.2.232.
28. Cannon WB, Mendenhall WL. Factors affecting the coagulation time of the blood IV. The hastening of coagulation in pain and emotional excitement. Am J Physiol. 1914;34(2):251-61. doi: https://doi.org/10.1152/ajplegacy.1914.34.2.251.
29. Cannon WB, Mendenhall WL. Factors affecting the coagulation time of the blood III. The hastening of coagulation by stimulating the splanchnic nerves. Am J Physiol. 1914;34(2):243-50. doi: https://doi.org/10.1152/ajplegacy.1914.34.2.243.
30. Cannon WB, Lieb CW. The receptive relaxation of the stomach. American Journal of Physiology-Legacy Content. 1911;29(2):267-73. doi: 10.1152/ajplegacy.1911.29.2.267.
31. Cannon WB, Washburn AL. An explanation of hunger. American Journal of Physiology-Legacy Content. 1912;29(5):441-54. doi: 10.1152/ajplegacy.1912.29.5.441.
32. Pavlov IP, Thompson WH. The work of the digestive glands : lectures. London: Charles Griffin & Company; 1902. xii, 196, 35, 1 p. p.
33. Cannon WB, Newton HF, Bright EM, Menkin V, Moore RM. Some aspects of the physiology of animals surviving complete exclusion of sympathetic nerve impulses. Am J Physiol. 1929;89(1):84-107. doi: https://doi.org/10.1152/ajplegacy.1929.89.1.84.
34. Cybulski N, Szymonowicz W. O funkcyi nadnercza. Gazeta Lekarska. 1895;12:299-308.
35. Oliver G, Schäfer EA. The physiological effects of extracts of the suprarenal capsules. J Physiol. 1895;18(3):230-76. doi: https://dx.doi.org/10.1113%2Fjphysiol.1895.sp000564.
36. Bayliss WM, Starling EH. The mechanism of pancreatic secretion. The Journal of Physiology. 1902;28(5):325-53. doi: https://doi.org/10.1113/jphysiol.1902.sp000920.
37. Starling EH. The Croonian Lectures ON THE CHEMICAL CORRELATION OF THE FUNCTIONS OF THE BODY - Lecture IV. The Lancet. 1905;166(4278):579-83. doi: https://doi.org/10.1016/S0140-6736(00)68108-4.
38. Barman SM, Yates BJ. Deciphering the Neural Control of Sympathetic Nerve Activity: Status Report and Directions for Future Research. Frontiers in Neuroscience. 2017;11. doi: 10.3389/fnins.2017.00730.
39. Ramchandra R, Barrett CJ, Guild SJ, Malpas SC. Evidence of differential control of renal and lumbar sympathetic nerve activity in conscious rabbits. Am J Physiol Regul Integr Comp Physiol. 2006;290(3):R701-8. Epub 20051020. doi: 10.1152/ajpregu.00504.2005. PubMed PMID: 16239371.
40. Malpas S, Guild SJ, Evans R. Responsiveness of the renal vasculature: relating electrical stimulation to endogenous nerve activity is problematic. Am J Physiol Renal Physiol. 2003;284(3):F594-5; author reply 5-6. doi: 10.1152/ajprenal.00374.2002. PubMed PMID: 12556367.

 doi:10.20944/preprints202510.1768.v3

41. Malpas S, McAllen R. Electrical stimulation of the renal nerve neither replicates its natural burst pattern nor proves the importance of that pattern for renal function. Am J Physiol Regul Integr Comp Physiol. 2000;279(1):R355-6. doi: 10.1152/ajpregu.2000.279.1.R355. PubMed PMID: 11012294.
42. Malpas SC, Evans RG. Do different levels and patterns of sympathetic activation all provoke renal vasoconstriction? Journal of the Autonomic Nervous System. 1998;69(1):72-82. doi: https://doi.org/10.1016/S0165-1838(98)00010-1.
43. McAllen RM, Malpas SC. Sympathetic burst activity: characteristics and significance. Clin Exp Pharmacol Physiol. 1997;24(11):791-9. doi: 10.1111/j.1440-1681.1997.tb02693.x. PubMed PMID: 9363359.
44. Janssen B, Burke S, Malpas S, Head G. How are beat to beat changes in sympathetic activity coupled to beat to beat changes in organ blood flow: data from conscious rabbits. Fundamental & Clinical Pharmacology. 1997;11(S1):109s-s. doi: https://doi.org/10.1111/j.1472-8206.1997.tb00895.x.
45. Malpas SC, Ninomiya I. A new approach to analysis of synchronized sympathetic nerve activity. Am J Physiol. 1992;263(4 Pt 2):H1311-7. doi: 10.1152/ajpheart.1992.263.4.H1311. PubMed PMID: 1415779.
46. DiBona GF. Physiology in perspective: The Wisdom of the Body. Neural control of the kidney. Am J Physiol Regul Integr Comp Physiol. 2005;289(3):R633-41. doi: 10.1152/ajpregu.00258.2005. PubMed PMID: 16105818.
47. Barman SM, Fadel PJ, Vongpatanasin W, Victor RG, Gebber GL. Basis for the cardiac-related rhythm in muscle sympathetic nerve activity of humans. Am J Physiol Heart Circ Physiol. 2003;284(2):H584-97. Epub 20021024. doi: 10.1152/ajpheart.00602.2002. PubMed PMID: 12399256.
48. Barman SM. What can we learn about neural control of the cardiovascular system by studying rhythms in sympathetic nerve activity? Int J Psychophysiol. 2016;103:69-78. Epub 20150211. doi: 10.1016/j.ijpsycho.2015.02.015. PubMed PMID: 25681532; PubMed Central PMCID: PMCPMC4532667.
49. Barman SM. Sympathetic nerve activity has more character than you may think. J Physiol. 2009;587(Pt 20):4767-8. doi: 10.1113/jphysiol.2009.181222. PubMed PMID: 19828523; PubMed Central PMCID: PMCPMC2770145.
50. Julien C, Malpas SC, Stauss HM. Sympathetic modulation of blood pressure variability. J Hypertens. 2001;19(10):1707-12. doi: 10.1097/00004872-200110000-00002. PubMed PMID: 11593088.
51. Das M, Gebber GL, Barman SM, Lewis CD. Fractal properties of sympathetic nerve discharge. J Neurophysiol. 2003;89(2):833-40. doi: 10.1152/jn.00757.2002. PubMed PMID: 12574461.
52. Thomas EA, Bertrand PP, Bornstein JC. Genesis and role of coordinated firing in a feedforward network: a model study of the enteric nervous system. Neuroscience. 1999;93(4):1525-37. doi: 10.1016/s0306-4522(99)00243-2. PubMed PMID: 10501477.
53. Furness JB. The Enteric Nervous System. Malden, MA: Blackwell Publishing, Inc.; 2006.
54. Lewis CD, Gebber GL, Larsen PD, Barman SM. Long-term correlations in the spike trains of medullary sympathetic neurons. J Neurophysiol. 2001;85(4):1614-22. doi: 10.1152/jn.2001.85.4.1614. PubMed PMID: 11287485.
55. Osanlouy M, Bandrowski A, de Bono B, Brooks D, Cassarà AM, Christie R, et al. The SPARC DRC: Building a Resource for the Autonomic Nervous System Community. Frontiers in Physiology. 2021;Volume 12 - 2021. doi: 10.3389/fphys.2021.693735.
56. Levick JR. An introduction to cardiovascular physiology. 5th ed. London: Hodder Arnold; 2010. xii, 414 p. p.
57. Malpas SC. What sets the long-term level of sympathetic nerve activity: is there a role for arterial baroreceptors? Am J Physiol Regul Integr Comp Physiol. 2004;286(1):R1-r12. doi: 10.1152/ajpregu.00496.2003. PubMed PMID: 14660468.
58. Malpas SC, Leonard BL. Neural regulation of renal blood flow: a re-examination. Clin Exp Pharmacol Physiol. 2000;27(12):956-64. doi: 10.1046/j.1440-1681.2000.03386.x. PubMed PMID: 11117231.
59. Schiller AM, Pellegrino PR, Zucker IH. Renal nerves dynamically regulate renal blood flow in conscious, healthy rabbits. Am J Physiol Regul Integr Comp Physiol. 2016;310(2):R156-66. Epub 20151104. doi: 10.1152/ajpregu.00147.2015. PubMed PMID: 26538235; PubMed Central PMCID: PMCPMC4747893.
60. Guyenet PG. The sympathetic control of blood pressure. Nature Reviews Neuroscience. 2006;7(5):335-46. doi: 10.1038/nrn1902.

 doi:10.20944/preprints202510.1768.v3

61. Anrep GV, Pascual W, Rossler R. Respiratory Variations of the Heart Rate. I.--The Reflex Mechanism of the Respiratory Arrhythmia. Proceedings of the Royal Society of London Series B, Biological Sciences. 1936;119(813):191-217.
62. Anrep GV, Pascual W, Rossler R. Respiratory Variations of the Heart Rate. II.--The Central Mechanism of the Respiratory Arrhythmia and the Inter-Relations between the Central and the Reflex Mechanisms. Proceedings of the Royal Society of London Series B, Biological Sciences. 1936;119(813):218-30.
63. Katona PG, Poitras JW, Barnett GO, Terry BS. Cardiac vagal efferent activity and heart period in the carotid sinus reflex. Am J Physiol. 1970;218(4):1030-7. doi: 10.1152/ajplegacy.1970.218.4.1030. PubMed PMID: 5435400.
64. Kunze DL. Reflex discharge patterns of cardiac vagal efferent fibres. J Physiol. 1972;222(1):1-15. doi: 10.1113/jphysiol.1972.sp009784. PubMed PMID: 4338691; PubMed Central PMCID: PMCPMC1331413.
65. Eckberg DL. Human sinus arrhythmia as an index of vagal cardiac outflow. J Appl Physiol Respir Environ Exerc Physiol. 1983;54(4):961-6. doi: 10.1152/jappl.1983.54.4.961. PubMed PMID: 6853303.
66. McDougal DH, Gamlin PD. Autonomic control of the eye. Compr Physiol. 2015;5(1):439-73. Epub 2015/01/16. doi: 10.1002/cphy.c140014. PubMed PMID: 25589275; PubMed Central PMCID: PMCPMC4919817.
67. Loewenfeld IE. Mechanisms of reflex dilatation of the pupil; historical review and experimental analysis. Doc Ophthalmol. 1958;12:185-448. doi: 10.1007/BF00913471. PubMed PMID: 13609524.
68. Mathôt S, van der Linden L, Grainger J, Vitu F. The Pupillary Light Response Reveals the Focus of Covert Visual Attention. PLOS ONE. 2013;8(10):e78168. doi: 10.1371/journal.pone.0078168.
69. Mathôt S. Pupillometry: Psychology, Physiology, and Function. J Cogn. 2018;1(1):16. Epub 20180221. doi: 10.5334/joc.18. PubMed PMID: 31517190; PubMed Central PMCID: PMCPMC6634360.
70. Cryer PE. Glucose counterregulation in man. Diabetes. 1981;30(3):261-4. doi: 10.2337/diab.30.3.261. PubMed PMID: 6110601.
71. Verberne AJ, Sartor DM. Rostroventrolateral medullary neurons modulate glucose homeostasis in the rat. Am J Physiol Endocrinol Metab. 2010;299(5):E802-7. Epub 2010/09/03. doi: 10.1152/ajpendo.00466.2010. PubMed PMID: 20807841.
72. Sartor DM, Verberne AJ. Cholecystokinin selectively affects presympathetic vasomotor neurons and sympathetic vasomotor outflow. Am J Physiol Regul Integr Comp Physiol. 2002;282(4):R1174-84. Epub 2002/03/15. doi: 10.1152/ajpregu.00500.2001. PubMed PMID: 11893623.
73. Granger DN, Holm L, Kvietys P. The Gastrointestinal Circulation: Physiology and Pathophysiology. Compr Physiol. 2015;5(3):1541-83. doi: 10.1002/cphy.c150007. PubMed PMID: 26140727.
74. Sartor DM, Shulkes A, Verberne AJ. An enteric signal regulates putative gastrointestinal presympathetic vasomotor neurons in rats. Am J Physiol Regul Integr Comp Physiol. 2006;290(3):R625-33. Epub 2005/10/22. doi: 10.1152/ajpregu.00639.2005. PubMed PMID: 16239368.
75. Vatner SF, Franklin D, Van Citters RL. Mesenteric vasoactivity associated with eating and digestion in the conscious dog. Am J Physiol. 1970;219(1):170-4. doi: 10.1152/ajplegacy.1970.219.1.170. PubMed PMID: 4393203.
76. Fronek K, Stahlgren LH. Systemic and regional hemodynamic changes during food intake and digestion in nonanesthetized dogs. Circ Res. 1968;23(6):687-92. doi: 10.1161/01.res.23.6.687. PubMed PMID: 4882287.
77. Joyner MJ, Charkoudian N, Wallin BG. Sympathetic nervous system and blood pressure in humans: individualized patterns of regulation and their implications. Hypertension. 2010;56(1):10-6. Epub 20100524. doi: 10.1161/hypertensionaha.109.140186. PubMed PMID: 20497993; PubMed Central PMCID: PMCPMC2891078.
78. Charkoudian N, Joyner MJ, Johnson CP, Eisenach JH, Dietz NM, Wallin BG. Balance between cardiac output and sympathetic nerve activity in resting humans: role in arterial pressure regulation. The Journal of Physiology. 2005;568(1):315-21. doi: https://doi.org/10.1113/jphysiol.2005.090076.
79. Norvell JE, Anderson JM. Assessment of possible parasympathetic innervation of the kidney. J Auton Nerv Syst. 1983;8(3):291-4. Epub 1983/07/01. doi: 10.1016/0165-1838(83)90112-1. PubMed PMID: 6668390.

 doi:10.20944/preprints202510.1768.v3

80. Maeda S, Kuwahara-Otani S, Tanaka K, Hayakawa T, Seki M. Origin of efferent fibers of the renal plexus in the rat autonomic nervous system. J Vet Med Sci. 2014;76(5):763-5. Epub 20140116. doi: 10.1292/jvms.13-0617. PubMed PMID: 24430660; PubMed Central PMCID: PMCPMC4073349.
81. Kopp UC. Neural Control of Renal Function. Integrated Systems Physiology: from Molecule to Function to Disease. San Rafael (CA)2011.
82. Kvietys PR. The Gastrointestinal Circulation. San Rafael (CA): Morgan & Claypool Life Sciences Copyright © 2010 by Morgan & Claypool Life Sciences.; 2010.
83. Bartness TJ, Vaughan CH, Song CK. Sympathetic and sensory innervation of brown adipose tissue. Int J Obes (Lond). 2010;34 Suppl 1(0 1):S36-42. doi: 10.1038/ijo.2010.182. PubMed PMID: 20935665; PubMed Central PMCID: PMCPMC3999344.
84. Bartness TJ, Shrestha YB, Vaughan CH, Schwartz GJ, Song CK. Sensory and sympathetic nervous system control of white adipose tissue lipolysis. Molecular and Cellular Endocrinology. 2010;318(1):34-43. doi: https://doi.org/10.1016/j.mce.2009.08.031.
85. Bartness TJ, Song CK. Thematic review series: adipocyte biology. Sympathetic and sensory innervation of white adipose tissue. J Lipid Res. 2007;48(8):1655-72. Epub 20070425. doi: 10.1194/jlr.R700006-JLR200. PubMed PMID: 17460327.
86. Giordano A, Song CK, Bowers RR, Ehlen JC, Frontini A, Cinti S, et al. White adipose tissue lacks significant vagal innervation and immunohistochemical evidence of parasympathetic innervation. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2006;291(5):R1243-R55. doi: 10.1152/ajpregu.00679.2005. PubMed PMID: 16809481.
87. Berthoud H-R, Fox EA, Neuhuber WL. Rebuttal: controversial white adipose tissue innervation by the vagus nerve: seeing is believing. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2007;293(1):R553-R4. doi: 10.1152/ajpregu.00249.2007.
88. Shi H, Song CK, Giordano A, Cinti S, Bartness TJ. Sensory or sympathetic white adipose tissue denervation differentially affects depot growth and cellularity. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2005;288(4):R1028-R37. doi: 10.1152/ajpregu.00648.2004. PubMed PMID: 15550613.
89. Bowers RR, Festuccia WT, Song CK, Shi H, Migliorini RH, Bartness TJ. Sympathetic innervation of white adipose tissue and its regulation of fat cell number. Am J Physiol Regul Integr Comp Physiol. 2004;286(6):R1167-75. doi: 10.1152/ajpregu.00558.2003. PubMed PMID: 15142857.
90. Morrison SF, Blessing WW. Central Nervous System Regulation of Body Temperature. In: Llewellyn-Smith IJ, Verberne AJM, editors. Central Regulation of Autonomic Functions: Oxford University Press; 2011. p. 0.
91. Larsen PJ. Tracing autonomic innervation of the rat pineal gland using viral transneuronal tracing. Microsc Res Tech. 1999;46(4-5):296-304. doi: 10.1002/(SICI)1097-0029(19990815/01)46:4/5<296::AID-JEMT6>3.0.CO;2-C. PubMed PMID: 10469465.
92. Larsen PJ, Enquist LW, Card JP. Characterization of the multisynaptic neuronal control of the rat pineal gland using viral transneuronal tracing. Eur J Neurosci. 1998;10(1):128-45. doi: 10.1046/j.1460-9568.1998.00003.x. PubMed PMID: 9753120.
93. Schomerus C, Korf H. Mechanisms Regulating Melatonin Synthesis in the Mammalian Pineal Organ. Annals of the New York Academy of Sciences. 2005;1057(1):372-83. doi: https://doi.org/10.1196/annals.1356.028.
94. Jensen KJ, Alpini G, Glaser S. Hepatic nervous system and neurobiology of the liver. Compr Physiol. 2013;3(2):655-65. doi: 10.1002/cphy.c120018. PubMed PMID: 23720325; PubMed Central PMCID: PMCPMC3733049.
95. Sartor DM, Verberne AJ. The sympathoinhibitory effects of systemic cholecystokinin are dependent on neurons in the caudal ventrolateral medulla in the rat. Am J Physiol Regul Integr Comp Physiol. 2006;291(5):R1390-8. Epub 2006/06/24. doi: 10.1152/ajpregu.00314.2006. PubMed PMID: 16793934.
96. Wolf S, Wolff HG. Human gastric function, an experimental study of a man and his stomach [by] Stewart Wolf ... and Harold G. Wolff ... with a foreword by Walter B. Cannon. London, New York etc.: Oxford University Press; 1947. xvi, 262 p. incl. illus., plates, diagrs. p.

97. Wolf S, Andrus WD. The effect of vagotomy on gastric function as determined in a fistulous human subject. Proc Am Fed Clin Res. 1947;3:66. PubMed PMID: 18909338.
98. Wolf S. The stomach. New York,: Oxford University Press; 1965. 321 p. p.
99. Kaneko H, Taché Y, Kusugami K. Importance of medullary thyrotropin-releasing hormone in brain-gut circuits regulating gastric integrity: preclinical studies. J Gastroenterol. 2002;37 Suppl 14:128-32. doi: 10.1007/bf03326431. PubMed PMID: 12572880.
100. Lumsden SC, Clarkson AN, Cakmak YO. Neuromodulation of the Pineal Gland via Electrical Stimulation of Its Sympathetic Innervation Pathway. Front Neurosci. 2020;14:264. Epub 20200402. doi: 10.3389/fnins.2020.00264. PubMed PMID: 32300290; PubMed Central PMCID: PMCPMC7145358.
101. Moller M, Baeres FM. The anatomy and innervation of the mammalian pineal gland. Cell Tissue Res. 2002;309(1):139-50. Epub 20020518. doi: 10.1007/s00441-002-0580-5. PubMed PMID: 12111544.
102. Davson H. Accommodation. Physiology of the Eye. London: Macmillan Education UK; 1990. p. 767-82.
103. Loewenfeld IE, Lowenstein O. The pupil : anatomy, physiology, and clinical applications. 1st ed. Ames Detroit: Iowa State University Press ; Wayne State University Press; 1993.
104. Raczkowska M, Eckberg DL, Ebert TJ. Muscarinic cholinergic receptors modulate vagal cardiac responses in man. J Auton Nerv Syst. 1983;7(3-4):271-8. doi: 10.1016/0165-1838(83)90080-2. PubMed PMID: 6875192.
105. Ahren B, Taborsky GJ, Jr. The mechanism of vagal nerve stimulation of glucagon and insulin secretion in the dog. Endocrinology. 1986;118(4):1551-7. doi: 10.1210/endo-118-4-1551. PubMed PMID: 3512257.
106. Taborsky GJ, Jr. The physiology of glucagon. J Diabetes Sci Technol. 2010;4(6):1338-44. Epub 20101101. doi: 10.1177/193229681000400607. PubMed PMID: 21129328; PubMed Central PMCID: PMCPMC3005043.
107. Ahren B, Taborsky GJ, Jr., Porte D, Jr. Neuropeptidergic versus cholinergic and adrenergic regulation of islet hormone secretion. Diabetologia. 1986;29(12):827-36. Epub 1986/12/01. PubMed PMID: 2883061.
108. Osborn JW, Tyshynsky R, Vulchanova L. Function of Renal Nerves in Kidney Physiology and Pathophysiology. Annual Review of Physiology. 2021;83(1):429-50. doi: 10.1146/annurev-physiol-031620-091656. PubMed PMID: 33566672.
109. Guild SJ, Austin PC, Navakatikyan M, Ringwood JV, Malpas SC. Dynamic relationship between sympathetic nerve activity and renal blood flow: a frequency domain approach. Am J Physiol Regul Integr Comp Physiol. 2001;281(1):R206-12. doi: 10.1152/ajpregu.2001.281.1.R206. PubMed PMID: 11404295.
110. Netter FH. The Ciba Collection of Medical Illustrations, Vol. 1: Nervous System : a Compilation of Paintings on the Normal and Pathologic Anatomy, with a Supplement on the Hypothalamus. Summit, New Jersey: CIBA Pharmaceutical Company; 1977.
111. Barajas L, Wang P. Demonstration of acetylcholinesterase in the adrenergic nerves of the renal glomerular arterioles. J Ultrastruct Res. 1975;53(2):244-53. doi: 10.1016/s0022-5320(75)80141-9. PubMed PMID: 1195453.
112. Barajas L, Wang P, De Santis S. Light and electron microscopic localization of acetylcholinesterase activity in the rat renal nerves. Am J Anat. 1976;147(2):219-34. doi: 10.1002/aja.1001470206. PubMed PMID: 970352.
113. Guyton AC. Long-term arterial pressure control: an analysis from animal experiments and computer and graphic models. Am J Physiol. 1990;259(5 Pt 2):R865-77. doi: 10.1152/ajpregu.1990.259.5.R865. PubMed PMID: 2240271.
114. Barajas L, Powers K, Wang P. Innervation of the renal cortical tubules: a quantitative study. Am J Physiol. 1984;247(1 Pt 2):F50-60. doi: 10.1152/ajprenal.1984.247.1.F50. PubMed PMID: 6742205.
115. Malpas SC, Head GA, Anderson WP. Renal responses to increases in renal sympathetic nerve activity induced by brainstem stimulation in rabbits. J Auton Nerv Syst. 1996;61(1):70-8. doi: 10.1016/0165-1838(96)00060-4. PubMed PMID: 8912256.
116. Browning KN, Zheng Z, Kreulen DL, Travagli RA. Two populations of sympathetic neurons project selectively to mesenteric artery or vein. Am J Physiol. 1999;276(4):H1263-72. doi: 10.1152/ajpheart.1999.276.4.H1263. PubMed PMID: 10199851.
117. Blaszkiewicz M, Willows JW, Johnson CP, Townsend KL. The Importance of Peripheral Nerves in Adipose Tissue for the Regulation of Energy Balance. Biology. 2019;8(1):10. PubMed PMID: doi:10.3390/biology8010010.

118. Bandler R, Carrive P. Integrated defence reaction elicited by excitatory amino acid microinjection in the midbrain periaqueductal grey region of the unrestrained cat. Brain Res. 1988;439(1-2):95-106. doi: 10.1016/0006-8993(88)91465-5. PubMed PMID: 3359200.
119. Bandler R, Carrive P, Zhang SP. Integration of somatic and autonomic reactions within the midbrain periaqueductal grey: viscerotopic, somatotopic and functional organization. Prog Brain Res. 1991;87:269-305. doi: 10.1016/s0079-6123(08)63056-3. PubMed PMID: 1678189.
120. Carrive P, Bandler R. Viscerotopic organization of neurons subserving hypotensive reactions within the midbrain periaqueductal grey: a correlative functional and anatomical study. Brain Res. 1991;541(2):206-15. doi: 10.1016/0006-8993(91)91020-2. PubMed PMID: 2054638.
121. Carrive P, Bandler R. Control of extracranial and hindlimb blood flow by the midbrain periaqueductal grey of the cat. Exp Brain Res. 1991;84(3):599-606. doi: 10.1007/BF00230972. PubMed PMID: 1864330.
122. Carrive P, Bandler R, Dampney RA. Somatic and autonomic integration in the midbrain of the unanesthetized decerebrate cat: a distinctive pattern evoked by excitation of neurones in the subtentorial portion of the midbrain periaqueductal grey. Brain Res. 1989;483(2):251-8. doi: 10.1016/0006-8993(89)90169-8. PubMed PMID: 2706518.
123. Ruffolo RR. [Alpha]-adrenoceptors : molecular biology, biochemistry, and pharmacology. Basel ; New York: Karger; 1991. xiii, 225 p. p.
124. Ruffolo RR. [Beta]-adrenoceptors : molecular biology, biochemistry, and pharmacology. Basel ; New York: Karger; 1991. xii, 240 p. p.
125. Vatner SF, Franklin D, Van Citters RL. Coronary and visceral vasoactivity associated with eating and digestion in the conscious dog. Am J Physiol. 1970;219(5):1380-5. doi: 10.1152/ajplegacy.1970.219.5.1380. PubMed PMID: 5473122.
126. Ostrin LA, Glasser A. Autonomic drugs and the accommodative system in rhesus monkeys. Exp Eye Res. 2010;90(1):104-12. Epub 20090924. doi: 10.1016/j.exer.2009.09.015. PubMed PMID: 19782072; PubMed Central PMCID: PMCPMC3637388.
127. Pedersen E. Regulation of bladder and colon--rectum in patients with spinal lesions. J Auton Nerv Syst. 1983;7(3-4):329-38. doi: 10.1016/0165-1838(83)90086-3. PubMed PMID: 6135730.
128. Miolan JP, Roman C. The role of oesophageal and intestinal receptors in the control of gastric motility. J Auton Nerv Syst. 1984;10(3-4):235-41. doi: 10.1016/0165-1838(84)90018-3. PubMed PMID: 6481090.
129. Bieger D. The brainstem esophagomotor network pattern generator: a rodent model. Dysphagia. 1993;8(3):203-8. doi: 10.1007/bf01354539. PubMed PMID: 8102966.
130. Rogers RC, Hermann GE, Travagli RA. Brainstem pathways responsible for oesophageal control of gastric motility and tone in the rat. J Physiol. 1999;514 (Pt 2)(Pt 2):369-83. doi: 10.1111/j.1469-7793.1999.369ae.x. PubMed PMID: 9852320; PubMed Central PMCID: PMCPMC2269075.
131. Krassioukov A, Elliott S. Neural Control and Physiology of Sexual Function: Effect of Spinal Cord Injury. Top Spinal Cord Inj Rehabil. 2017;23(1):1-10. doi: 10.1310/sci2301-1. PubMed PMID: 29339872; PubMed Central PMCID: PMCPMC5340504.
132. Nadel JA. Parasympathetic nervous control of airway smooth muscle. Ann N Y Acad Sci. 1974;221:99-102. doi: 10.1111/j.1749-6632.1974.tb28204.x. PubMed PMID: 4522567.
133. Richardson JB. Nerve supply to the lungs. Am Rev Respir Dis. 1979;119(5):785-802. doi: 10.1164/arrd.1979.119.5.785. PubMed PMID: 110183.
134. van der Velden VH, Hulsmann AR. Autonomic innervation of human airways: structure, function, and pathophysiology in asthma. Neuroimmunomodulation. 1999;6(3):145-59. Epub 1999/04/24. doi: 10.1159/000026376. PubMed PMID: 10213912.
135. Jordan D. Central nervous pathways and control of the airways. Respir Physiol. 2001;125(1-2):67-81. Epub 2001/03/10. PubMed PMID: 11240153.
136. Canning BJ. Reflex regulation of airway smooth muscle tone. J Appl Physiol (1985). 2006;101(3):971-85. Epub 20060525. doi: 10.1152/japplphysiol.00313.2006. PubMed PMID: 16728519.
137. Canning BJ, Woo A, Mazzone SB. Neuronal modulation of airway and vascular tone and their influence on nonspecific airways responsiveness in asthma. J Allergy (Cairo). 2012;2012:108149. Epub 2012/11/15. doi: 10.1155/2012/108149. PubMed PMID: 23150736; PubMed Central PMCID: PMCPMC3485909.

 doi:10.20944/preprints202510.1768.v3

138. Mazzone SB, Canning BJ. Evidence for differential reflex regulation of cholinergic and noncholinergic parasympathetic nerves innervating the airways. Am J Respir Crit Care Med. 2002;165(8):1076-83. Epub 2002/04/17. doi: 10.1164/ajrccm.165.8.2001121270c. PubMed PMID: 11956048.
139. Hahn HL, Graf PD, Nadel JA. Effect of vagal tone on airway diameters and on lung volume in anesthetized dogs. J Appl Physiol. 1976;41(4):581-9. doi: 10.1152/jappl.1976.41.4.581. PubMed PMID: 985405.
140. Karczewski W, Widdicombe JG. The effect of vagotomy, vagal cooling and efferent vagal stimulation on breathing and lung mechanics of rabbits. J Physiol. 1969;201(2):259-70. doi: 10.1113/jphysiol.1969.sp008754. PubMed PMID: 5780543; PubMed Central PMCID: PMCPMC1351607.
141. Doidge JM, Satchell DG. Adrenergic and non-adrenergic inhibitory nerves in mammalian airways. J Auton Nerv Syst. 1982;5(2):83-99. doi: 10.1016/0165-1838(82)90030-3. PubMed PMID: 6806348.
142. Coburn RF. Peripheral airway ganglia. Annu Rev Physiol. 1987;49:573-82. doi: 10.1146/annurev.ph.49.030187.003041. PubMed PMID: 3032077.
143. Barnes PJ, Nadel JA, Skoogh BE, Roberts JM. Characterization of beta adrenoceptor subtypes in canine airway smooth muscle by radioligand binding and physiological responses. Journal of Pharmacology and Experimental Therapeutics. 1983;225(2):456-61.
144. Carstairs JR, Nimmo AJ, Barnes PJ. Autoradiographic visualization of beta-adrenoceptor subtypes in human lung. Am Rev Respir Dis. 1985;132(3):541-7. doi: 10.1164/arrd.1985.132.3.541. PubMed PMID: 2864008.
145. Barnes PJ. Beta-adrenoceptors on smooth muscle, nerves and inflammatory cells. Life Sci. 1993;52(26):2101-9. doi: 10.1016/0024-3205(93)90725-i. PubMed PMID: 8389953.
146. Otis AB. A perspective of respiratory mechanics. J Appl Physiol Respir Environ Exerc Physiol. 1983;54(5):1183-7. doi: 10.1152/jappl.1983.54.5.1183. PubMed PMID: 6345491.
147. Gabella G. Anatomy of airways smooth muscle. In: Raeburn D, Giembycz MA, editors. Airways Smooth Muscle: Structure, Innervation and Neurotransmission. Basel: Birkhäuser Verlag; 1994. p. 1-28.
148. Belmonte KE. Cholinergic pathways in the lungs and anticholinergic therapy for chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2005;2(4):297-304; discussion 11-2. doi: 10.1513/pats.200504-043SR. PubMed PMID: 16267352.
149. Townsley MI. Structure and composition of pulmonary arteries, capillaries, and veins. Compr Physiol. 2012;2(1):675-709. Epub 2012/01/01. doi: 10.1002/cphy.c100081. PubMed PMID: 23606929; PubMed Central PMCID: PMCPMC3630377.
150. Barnes PJ, Liu SF. Regulation of pulmonary vascular tone. Pharmacol Rev. 1995;47(1):87-131. PubMed PMID: 7784481.
151. Kummer W. Pulmonary vascular innervation and its role in responses to hypoxia: size matters! Proc Am Thorac Soc. 2011;8(6):471-6. Epub 2011/11/05. doi: 10.1513/pats.201101-013MW. PubMed PMID: 22052922.
152. Amenta F, Cavallotti C, Ferrante F, Tonelli F. Cholinergic innervation of the human pulmonary circulation. Acta Anat (Basel). 1983;117(1):58-64. doi: 10.1159/000145771. PubMed PMID: 6637373.
153. Barnes PJ. Neural control of human airways in health and disease. Am Rev Respir Dis. 1986;134(6):1289-314. doi: 10.1164/arrd.1986.134.5.1289. PubMed PMID: 3538958.
154. Allen KM, Wharton J, Polak JM, Haworth SG. A study of nerves containing peptides in the pulmonary vasculature of healthy infants and children and of those with pulmonary hypertension. Br Heart J. 1989;62(5):353-60. doi: 10.1136/hrt.62.5.353. PubMed PMID: 2686736; PubMed Central PMCID: PMCPMC1224833.
155. Partanen M, Laitinen A, Hervonen A, Toivanen M, Laitinen LA. Catecholamine- and acetylcholinesterase-containing nerves in human lower respiratory tract. Histochemistry. 1982;76(2):175-88. doi: 10.1007/BF00501920. PubMed PMID: 7161145.
156. Petersson J, Glenny RW. Gas exchange and ventilation–perfusion relationships in the lung. European Respiratory Journal. 2014;44(4):1023-41. doi: 10.1183/09031936.00037014.
157. Slobod D, Damia A, Leali M, Spinelli E, Mauri T. Pathophysiology and clinical meaning of ventilation-perfusion mismatch in the acute respiratory distress syndrome. Biology. 2023;12(1):67. PubMed PMID: doi:10.3390/biology12010067.

 doi:10.20944/preprints202510.1768.v3

158. Mazzone SB, Undem BJ. Vagal Afferent Innervation of the Airways in Health and Disease. Physiol Rev. 2016;96(3):975-1024. doi: 10.1152/physrev.00039.2015. PubMed PMID: 27279650; PubMed Central PMCID: PMCPMC4982036.
159. Hesser CM, Lind F. Role of airway resistance in the control of ventilation during exercise. Acta Physiol Scand. 1984;120(4):557-65. doi: 10.1111/j.1748-1716.1984.tb07421.x. PubMed PMID: 6485829.
160. Betts JG, Wise J, Young KA, Desaix P, Johnson E, Johnson JE, et al. Anatomy and physiology: OpenStax College; 2017.
161. Koizumi K, Kollai M. Multiple modes of operation of cardiac autonomic control: development of the ideas from Cannon and Brooks to the present. J Auton Nerv Syst. 1992;41(1-2):19-29. doi: 10.1016/0165-1838(92)90123-x. PubMed PMID: 1491113.
162. Kollai M, Koizumi K. Cardiac vagal and sympathetic nerve responses to baroreceptor stimulation in the dog. Pflugers Arch. 1989;413(4):365-71. doi: 10.1007/BF00584485. PubMed PMID: 2928088.
163. Koizumi K, Terui N, Kollai M. Effect of cardiac vagal and sympathetic nerve activity on heart rate in rhythmic fluctuations. J Auton Nerv Syst. 1985;12(2-3):251-9. doi: 10.1016/0165-1838(85)90065-7. PubMed PMID: 3998390.
164. Koizumi K, Terui N, Kollai M. Neural control of the heart: significance of double innervation re-examined. J Auton Nerv Syst. 1983;7(3-4):279-94. doi: 10.1016/0165-1838(83)90081-4. PubMed PMID: 6875193.
165. Koizumi K, Terui N, Kollai M, Brooks CM. Functional significance of coactivation of vagal and sympathetic cardiac nerves. Proc Natl Acad Sci U S A. 1982;79(6):2116-20. doi: 10.1073/pnas.79.6.2116. PubMed PMID: 6952259; PubMed Central PMCID: PMCPMC346134.
166. Koizumi K, Kollai M. Control of reciprocal and non-reciprocal action of vagal and sympathetic efferents: study of centrally induced reactions. J Auton Nerv Syst. 1981;3(2-4):483-501. doi: 10.1016/0165-1838(81)90082-5. PubMed PMID: 6792258.
167. Kollai M, Koizumi K. Cardiovascular reflexes and interrelationships between sympathetic and parasympathetic activity. J Auton Nerv Syst. 1981;4(2):135-48. doi: 10.1016/0165-1838(81)90091-6. PubMed PMID: 7276446.
168. Kollai M, Koizumi K. The mechanisms of differential control in the sympathetic system studied by hypothalamic stimulation. J Auton Nerv Syst. 1980;2(4):377-89. doi: 10.1016/0165-1838(80)90035-1. PubMed PMID: 7252057.
169. Kollai M, Koizumi K. Reciprocal and non-reciprocal action of the vagal and sympathetic nerves innervating the heart. J Auton Nerv Syst. 1979;1(1):33-52. doi: 10.1016/0165-1838(79)90004-3. PubMed PMID: 553085.
170. Kollai M, Koizumi K, Yamashita H, Brooks CM. Study of cardiac sympathetic and vagal efferent activity during reflex responses produced by stretch of the atria. Brain Res. 1978;150(3):519-32. doi: 10.1016/0006-8993(78)90817-x. PubMed PMID: 678988.
171. Saper CB, Stornetta RL. Chapter 23 - Central Autonomic System. In: Paxinos G, editor. The Rat Nervous System (Fourth Edition). San Diego: Academic Press; 2015. p. 629-73.
172. de Groat WC, Griffiths D, Yoshimura N. Neural control of the lower urinary tract. Compr Physiol. 2015;5(1):327-96. doi: 10.1002/cphy.c130056. PubMed PMID: 25589273; PubMed Central PMCID: PMCPMC4480926.
173. Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci. 2008;9(6):453-66. doi: 10.1038/nrn2401. PubMed PMID: 18490916; PubMed Central PMCID: PMCPMC2897743.
174. Tack J, Demedts I, Meulemans A, Schuurkes J, Janssens J. Role of nitric oxide in the gastric accommodation reflex and in meal induced satiety in humans. Gut. 2002;51(2):219-24. Epub 2002/07/16. PubMed PMID: 12117883.
175. Paterson CA, Anvari M, Tougas G, Huizinga JD. Nitrergic and cholinergic vagal pathways involved in the regulation of canine proximal gastric tone: an in vivo study. Neurogastroenterol Motil. 2000;12(4):301-6. Epub 2000/07/08. doi: nmo209 [pii]. PubMed PMID: 10886672.
176. Hermann GE, Travagli RA, Rogers RC. Esophageal-gastric relaxation reflex in rat: dual control of peripheral nitrergic and cholinergic transmission. Am J Physiol Regul Integr Comp Physiol. 2006;290(6):R1570-6. Epub 2006/01/28. doi: 00717.2005 [pii]10.1152/ajpregu.00717.2005. PubMed PMID: 16439669.
177. Powley TL. Vagal circuitry mediating cephalic-phase responses to food. Appetite. 2000;34(2):184-8. Epub 2000/04/04. doi: 10.1006/appe.1999.0279S0195-6663(99)90279-9 [pii]. PubMed PMID: 10744908.

 doi:10.20944/preprints202510.1768.v3

178. Okano-Matsumoto S, McRoberts JA, Tache Y, Adelson DW. Electrophysiological evidence for distinct vagal pathways mediating CCK-evoked motor effects in the proximal versus distal stomach. J Physiol. 2011;589(Pt 2):371-93. Epub 20101115. doi: 10.1113/jphysiol.2010.196832. PubMed PMID: 21078593; PubMed Central PMCID: PMCPMC3043539.
179. Goyal RK, Guo Y, Mashimo H. Advances in the physiology of gastric emptying. Neurogastroenterology & Motility. 2019;31(4):e13546. doi: https://doi.org/10.1111/nmo.13546.
180. Ramkumar D, Schulze KS. The pylorus. Neurogastroenterology & Motility. 2005;17(s1):22-30. doi: https://doi.org/10.1111/j.1365-2982.2005.00664.x.
181. Zalecki M. Localization and neurochemical characteristics of the extrinsic sympathetic neurons projecting to the pylorus in the domestic pig. Journal of Chemical Neuroanatomy. 2012;43(1):1-13. doi: https://doi.org/10.1016/j.jchemneu.2011.08.004.
182. Zhang T, Perkins MH, Chang H, Han W, de Araujo IE. An inter-organ neural circuit for appetite suppression. Cell. 2022;185(14):2478-94.e28. doi: https://doi.org/10.1016/j.cell.2022.05.007.
183. Harper AA, Kidd C, Scratcherd T. Vago-vagal reflex effects on gastric and pancreatic secretion and gastrointestinal motility. J Physiol. 1959;148:417-36. Epub 1959/10/01. PubMed PMID: 14399886.
184. Raybould HE, Zittel TT, Holzer HH, Lloyd KC, Meyer JH. Gastroduodenal sensory mechanisms and CCK in inhibition of gastric emptying in response to a meal. Dig Dis Sci. 1994;39(12 Suppl):41S-3S. Epub 1994/12/01. PubMed PMID: 7995213.
185. Raybould HE, Lloyd KC. Integration of postprandial function in the proximal gastrointestinal tract. Role of CCK and sensory pathways. Ann N Y Acad Sci. 1994;713:143-56. Epub 1994/03/23. PubMed PMID: 8185155.
186. Van Citters GW, Lin HC. Ileal brake: neuropeptidergic control of intestinal transit. Curr Gastroenterol Rep. 2006;8(5):367-73. doi: 10.1007/s11894-006-0021-9. PubMed PMID: 16968603.
187. Bojo L, Cassuto J, Nellgard P. Pain-induced inhibition of gastric motility is mediated by adrenergic and vagal non-adrenergic reflexes in the rat. Acta Physiol Scand. 1992;146(3):377-83. doi: 10.1111/j.1748-1716.1992.tb09432.x. PubMed PMID: 1481692.
188. Nakade Y, Tsuchida D, Fukuda H, Iwa M, Pappas TN, Takahashi T. Restraint stress delays solid gastric emptying via a central CRF and peripheral sympathetic neuron in rats. Am J Physiol Regul Integr Comp Physiol. 2005;288(2):R427-32. Epub 20040930. doi: 10.1152/ajpregu.00499.2004. PubMed PMID: 15458973.
189. Tache Y, Yang H, Miampamba M, Martinez V, Yuan PQ. Role of brainstem TRH/TRH-R1 receptors in the vagal gastric cholinergic response to various stimuli including sham-feeding. Auton Neurosci. 2006;125(1-2):42-52. Epub 20060306. doi: 10.1016/j.autneu.2006.01.014. PubMed PMID: 16520096; PubMed Central PMCID: PMCPMC8086327.
190. Powley TL. Vagal input to the enteric nervous system. Gut. 2000;47 Suppl 4:iv30-2; discussion iv6. Epub 2000/11/15. PubMed PMID: 11076904.
191. Walter GC, Phillips RJ, McAdams JL, Powley TL. Individual sympathetic postganglionic neurons coinnervate myenteric ganglia and smooth muscle layers in the gastrointestinal tract of the rat. Journal of Comparative Neurology. 2016;524(13):2577-603. doi: https://doi.org/10.1002/cne.23978.
192. Berthoud HR, Powley TL. Interaction between parasympathetic and sympathetic nerves in prevertebral ganglia: morphological evidence for vagal efferent innervation of ganglion cells in the rat. Microsc Res Tech. 1996;35(1):80-6. Epub 1996/09/01. doi: 10.1002/(SICI)1097-0029(19960901)35:1<80::AID-JEMT7>3.0.CO;2-W [pii]10.1002/(SICI)1097-0029(19960901)35:1<80::AID-JEMT7>3.0.CO;2-W. PubMed PMID: 8873061.
193. Anderson RL, Jobling P, Matthew SE, Gibbins IL. Development of convergent synaptic inputs to subpopulations of autonomic neurons. Journal of Comparative Neurology. 2002;447(3):218-33. doi: https://doi.org/10.1002/cne.10222.
194. Betts JG, Wise J, Young KA, Desaix P, Johnson E, Johnson JE, et al. Divisions of the Autonomic Nervous System. 2020.
195. Kollai M, Koizumi K. Reciprocal effects of the steroid anesthetic (Althesin) on autonomic nerves innervating the heart. J Auton Nerv Syst. 1981;4(1):93-100. doi: 10.1016/0165-1838(81)90009-6. PubMed PMID: 7264206.

 doi:10.20944/preprints202510.1768.v3

196. Kollai M, Mizsei G. Respiratory sinus arrhythmia is a limited measure of cardiac parasympathetic control in man. J Physiol. 1990;424:329-42. doi: 10.1113/jphysiol.1990.sp018070. PubMed PMID: 2391653; PubMed Central PMCID: PMCPMC1189816.
197. Grossman P, Kollai M. Respiratory sinus arrhythmia, cardiac vagal tone, and respiration: within- and between-individual relations. Psychophysiology. 1993;30(5):486-95. doi: 10.1111/j.1469-8986.1993.tb02072.x. PubMed PMID: 8416075.
198. Katona PG, Jih F. Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control. J Appl Physiol. 1975;39(5):801-5. doi: 10.1152/jappl.1975.39.5.801. PubMed PMID: 1184518.
199. Levy MN. Cardiac sympathetic-parasympathetic interactions. Fed Proc. 1984;43(11):2598-602. PubMed PMID: 6745448.
200. Sunagawa K, Kawada T, Nakahara T. Dynamic nonlinear vago-sympathetic interaction in regulating heart rate. Heart Vessels. 1998;13(4):157-74. doi: 10.1007/bf01745040. PubMed PMID: 10442397.
201. Iriuchijima J, Kumada M. Activity of Single Vagal Fibers Efferent to the Heart. Jpn J Physiol. 1964;14:479-87. doi: 10.2170/jjphysiol.14.479. PubMed PMID: 14216693.
202. Iriuchijima J, Kumada M. On the cardioinhibitory reflex originating from the superior laryngeal nerve. Jpn J Physiol. 1968;18(4):453-61. doi: 10.2170/jjphysiol.18.453. PubMed PMID: 5304336.
203. Guz A, Innes JA, Murphy K. Respiratory modulation of left ventricular stroke volume in man measured using pulsed Doppler ultrasound. J Physiol. 1987;393:499-512. doi: 10.1113/jphysiol.1987.sp016836. PubMed PMID: 3328782; PubMed Central PMCID: PMCPMC1192406.
204. Hoffman JI, Guz A, Charlier AA, Wilcken DE. Stroke volume in conscious dogs; effect of respiration, posture, and vascular occlusion. J Appl Physiol. 1965;20(5):865-77. doi: 10.1152/jappl.1965.20.5.865. PubMed PMID: 5319998.
205. Rowell LB. Human cardiovascular control. New York: Oxford University Press; 1993. xv, 500 p. p.
206. Taylor JA, Eckberg DL. Fundamental relations between short-term RR interval and arterial pressure oscillations in humans. Circulation. 1996;93(8):1527-32. doi: 10.1161/01.cir.93.8.1527. PubMed PMID: 8608621.
207. Loewy AD, Spyer KM. Central regulation of autonomic functions. New York: Oxford University Press; 1990. xii, 390 p. p.
208. Spyer KM. Central nervous integration of cardiovascular control. J Exp Biol. 1982;100:109-28. doi: 10.1242/jeb.100.1.109. PubMed PMID: 6294210.
209. Blessing WW. The lower brainstem and bodily homeostasis. New York: Oxford University Press; 1997. xiv, 575 p.
210. Ciriello J, Caverson MM, Polosa C, Society for Neuroscience. Meeting. The Central neural organization of cardiovascular control. Amsterdam ; New York New York, NY, USA: Elsevier ; Sole distributors for the USA and Canada, Elsevier Science Pub. Co.; 1989. xviii, 334 p. p.
211. Smith JC, Abdala AP, Borgmann A, Rybak IA, Paton JF. Brainstem respiratory networks: building blocks and microcircuits. Trends Neurosci. 2013;36(3):152-62. Epub 20121217. doi: 10.1016/j.tins.2012.11.004. PubMed PMID: 23254296; PubMed Central PMCID: PMCPMC4080795.
212. Kollai M, Koizumi K. Patterns of single unit activity in sympathetic postganglionic nerves. J Auton Nerv Syst. 1980;1(3):305-12. doi: 10.1016/0165-1838(80)90025-9. PubMed PMID: 7440899.
213. Jewett DL. Activity of Single Efferent Fibres in the Cervical Vagus Nerve of the Dog, with Special Reference to Possible Cardio-Inhibitory Fibres. J Physiol. 1964;175:321-57. doi: 10.1113/jphysiol.1964.sp007520. PubMed PMID: 14241836; PubMed Central PMCID: PMCPMC1357140.
214. Levy MN, Zieske H. Autonomic control of cardiac pacemaker activity and atrioventricular transmission. Journal of Applied Physiology. 1969;27(4):465-70. doi: 10.1152/jappl.1969.27.4.465. PubMed PMID: 5822553.
215. Warner HR, Russell R. Effect of combined sympathetic and vagal stimulation on heart rate in the dog. Circulation Research. 1969;24(4):567-73. doi: doi:10.1161/01.RES.24.4.567.
216. Warner HR, Cox A. A mathematical model of heart rate control by sympathetic and vagus efferent information. Journal of Applied Physiology. 1962;17(2):349-55. doi: 10.1152/jappl.1962.17.2.349. PubMed PMID: 14005012.

 doi:10.20944/preprints202510.1768.v3

217. Ng GA, Brack KE, Coote JH. Effects of direct sympathetic and vagus nerve stimulation on the physiology of the whole heart--a novel model of isolated Langendorff perfused rabbit heart with intact dual autonomic innervation. Exp Physiol. 2001;86(3):319-29. doi: 10.1113/eph8602146. PubMed PMID: 11471534.
218. Brown TE, Beightol LA, Koh J, Eckberg DL. Important influence of respiration on human R-R interval power spectra is largely ignored. J Appl Physiol (1985). 1993;75(5):2310-7. doi: 10.1152/jappl.1993.75.5.2310. PubMed PMID: 8307890.
219. Franklin DL, Van Citters RL, Rushmer RF. Balance between right and left ventricular output. Circ Res. 1962;10:17-26. doi: 10.1161/01.res.10.1.17. PubMed PMID: 13894676.
220. Brown GL, Eccles JC. The action of a single vagal volley on the rhythm of the heart beat. J Physiol. 1934;82(2):211-41. doi: 10.1113/jphysiol.1934.sp003176. PubMed PMID: 16994580; PubMed Central PMCID: PMCPMC1394249.
221. Hill-Smith I, Purves RD. Synaptic delay in the heart: an ionophoretic study. J Physiol. 1978;279:31-54. doi: 10.1113/jphysiol.1978.sp012329. PubMed PMID: 209176; PubMed Central PMCID: PMCPMC1282600.
222. Stankovski T, Cooke WH, Rudas L, Stefanovska A, Eckberg DL. Time-frequency methods and voluntary ramped-frequency breathing: a powerful combination for exploration of human neurophysiological mechanisms. J Appl Physiol (1985). 2013;115(12):1806-21. Epub 20131010. doi: 10.1152/japplphysiol.00802.2013. PubMed PMID: 24114700; PubMed Central PMCID: PMCPMC3882935.
223. Eckberg DL. The human respiratory gate. J Physiol. 2003;548(Pt 2):339-52. Epub 20030307. doi: 10.1113/jphysiol.2002.037192. PubMed PMID: 12626671; PubMed Central PMCID: PMCPMC2342859.
224. Guyenet PG. Cardiorespiratory Integration. In: Llewellyn-Smith IJ, Verberne AJM, editors. Central Regulation of Autonomic Functions: Oxford University Press; 2011. p. 0.
225. Janig W, Habler HJ. Specificity in the organization of the autonomic nervous system: a basis for precise neural regulation of homeostatic and protective body functions. Prog Brain Res. 2000;122:351-67. Epub 2000/03/29. doi: 10.1016/s0079-6123(08)62150-0. PubMed PMID: 10737070.
226. Janig W, McLachlan EM. Specialized functional pathways are the building blocks of the autonomic nervous system. J Auton Nerv Syst. 1992;41(1-2):3-13. Epub 1992/11/01. doi: 10.1016/0165-1838(92)90121-v. PubMed PMID: 1491114.
227. Katayama K, Dominelli PB, Foster GE, Kipp S, Leahy MG, Ishida K, et al. Respiratory modulation of sympathetic vasomotor outflow during graded leg cycling. Journal of Applied Physiology. 2021;131(2):858-67. doi: 10.1152/japplphysiol.00118.2021. PubMed PMID: 34197231.
228. Toska K, Eriksen M. Respiration-synchronous fluctuations in stroke volume, heart rate and arterial pressure in humans. J Physiol. 1993;472:501-12. doi: 10.1113/jphysiol.1993.sp019958. PubMed PMID: 8145156; PubMed Central PMCID: PMCPMC1160498.
229. Paton JFR, Boscan P, Pickering AE, Nalivaiko E. The yin and yang of cardiac autonomic control: Vago-sympathetic interactions revisited. Brain Research Reviews. 2005;49(3):555-65. doi: https://doi.org/10.1016/j.brainresrev.2005.02.005.
230. Frasch MG. Heart Rate Variability Code: Does It Exist and Can We Hack It? Bioengineering (Basel). 2023;10(7). Epub 20230710. doi: 10.3390/bioengineering10070822. PubMed PMID: 37508849; PubMed Central PMCID: PMCPMC10375964.
231. Frasch MG, Giussani DA. Heart during acidosis: Etiology and early detection of cardiac dysfunction. EClinicalMedicine. 2021;37:100994. Epub 20210713. doi: 10.1016/j.eclinm.2021.100994. PubMed PMID: 34286236; PubMed Central PMCID: PMCPMC8280510.
232. Frasch MG. Fetal heart rate variability: An ocean of meanings beyond ups and downs. BJOG. 2023. Epub 20230206. doi: 10.1111/1471-0528.17391. PubMed PMID: 36746779.
233. Loewenfeld IE, Lowenstein O. The pupil : anatomy, physiology, and clinical applications. Boston: Butterworth-Heinemann; 1999.
234. Davson H. Physiology of the eye. 5th ed. New York: Pergamon Press; 1990. xii, 830 p. p.
235. Davson H. The Pupil. Physiology of the Eye. London: Macmillan Education UK; 1990. p. 754-66.
236. De Groot SG, Gebhard JW. Pupil size as determined by adapting luminance. J Opt Soc Am. 1952;42(7):492-5. doi: 10.1364/josa.42.000492. PubMed PMID: 14939111.

 doi:10.20944/preprints202510.1768.v3

237. Lowenstein O, Loewenfeld IE. Role of sympathetic and parasympathetic systems in reflex dilation of the pupil; pupillographic studies. Arch Neurol Psychiatry. 1950;64(3):313-40. doi: 10.1001/archneurpsyc.1950.02310270002001. PubMed PMID: 15433651.
238. Clarke RJ, Zhang H, Gamlin PD. Characteristics of the pupillary light reflex in the alert rhesus monkey. J Neurophysiol. 2003;89(6):3179-89. Epub 20030115. doi: 10.1152/jn.01131.2002. PubMed PMID: 12611973.
239. Lowenstein O, Loewenfeld IE. Mutual role of sympathetic and parasympathetic in shaping of the pupillary reflex to light; pupillographic studies. Arch Neurol Psychiatry. 1950;64(3):341-77. doi: 10.1001/archneurpsyc.1950.02310270030002. PubMed PMID: 15433652.
240. Ury B, Gellhorn E. Role of the sympathetic system in reflex dilatation of pupil. Journal of Neurophysiology. 1939;2(4):268-75. doi: 10.1152/jn.1939.2.4.268.
241. Anderson HK. Reflex pupil-dilatation by way of the cervical sympathetic nerve. J Physiol. 1903;30(1):15-24. doi: 10.1113/jphysiol.1903.sp000978. PubMed PMID: 16992685; PubMed Central PMCID: PMCPMC1540656.
242. Heller PH, Perry F, Jewett DL, Levine JD. Autonomic components of the human pupillary light reflex. Invest Ophthalmol Vis Sci. 1990;31(1):156-62. PubMed PMID: 2137115.
243. Mathôt S, van der Linden L, Grainger J, Vitu F. The pupillary light response reflects eye-movement preparation. J Exp Psychol Hum Percept Perform. 2015;41(1):28-35. doi: 10.1037/a0038653. PubMed PMID: 25621584.
244. Passatore M. Physiological characterization of efferent cervical sympathetic fibers influenced by changes of illumination. Experimental Neurology. 1976;53(1):71-81. doi: https://doi.org/10.1016/0014-4886(76)90282-X.
245. Passatore M, Pettorossi VE, Casoni RP. Sympathetic preganglionic pupillodilator fibres in the light reflex. Experientia. 1977;33(2):218-9. doi: 10.1007/BF02124076. PubMed PMID: 844562.
246. Passatore M, Pettorossi VE. Efferent fibers in the cervical sympathetic nerve influenced by light. Exp Neurol. 1976;52(1):66-82. doi: 10.1016/0014-4886(76)90201-6. PubMed PMID: 954912.
247. Okada H, Nakano O, Okamoto K, Nakayama K, Nisida I. The central path of the light reflex via the sympathetic nerve in the cat. Jpn J Physiol. 1960;10:646-58. doi: 10.2170/jjphysiol.10.646. PubMed PMID: 13730563.
248. Nisida I, Okada H, Nakano O. The activity of the ciliospinal centers and their inhibition in pupillary light reflex. Jpn J Physiol. 1960;10:73-84. doi: 10.2170/jjphysiol.10.73. PubMed PMID: 14427324.
249. Yoshitomi T, Ito Y. Double reciprocal innervations in dog iris sphincter and dilator muscles. Invest Ophthalmol Vis Sci. 1986;27(1):83-91. PubMed PMID: 2867064.
250. Karplus JP, Kreidl A. Über die Bahn des Pupillarreflexes. Pfluegers Arch Ges Physiol. 1912;149:115-55.
251. Gilmartin B. A review of the role of sympathetic innervation of the ciliary muscle in ocular accommodation. Ophthalmic Physiol Opt. 1986;6(1):23-37. PubMed PMID: 2872644.
252. Tornqvist G. The relative importance of the parasympathetic and sympathetic nervous systems for accommodation in monkeys. Invest Ophthalmol. 1967;6(6):612-7. PubMed PMID: 4965325.
253. Mays LE, Gamlin PD. Neuronal circuitry controlling the near response. Curr Opin Neurobiol. 1995;5(6):763-8. doi: 10.1016/0959-4388(95)80104-9. PubMed PMID: 8805411.
254. May PJ, Billig I, Gamlin PD, Quinet J. Central mesencephalic reticular formation control of the near response: lens accommodation circuits. J Neurophysiol. 2019;121(5):1692-703. Epub 20190306. doi: 10.1152/jn.00846.2018. PubMed PMID: 30840529; PubMed Central PMCID: PMCPMC6589714.
255. Ahren B. Autonomic regulation of islet hormone secretion--implications for health and disease. Diabetologia. 2000;43(4):393-410. doi: 10.1007/s001250051322. PubMed PMID: 10819232.
256. Bloom SR, Vaughan NJ, Russell RC. Vagal control of glucagon release in man. Lancet. 1974;2(7880):546-9. doi: 10.1016/s0140-6736(74)91875-3. PubMed PMID: 4140268.
257. Gilon P, Henquin JC. Mechanisms and physiological significance of the cholinergic control of pancreatic beta-cell function. Endocr Rev. 2001;22(5):565-604. doi: 10.1210/edrv.22.5.0440. PubMed PMID: 11588141.
258. Neuhuber W, Schrödl F. Autonomic control of the eye and the iris. Autonomic Neuroscience. 2011;165(1):67-79. doi: https://doi.org/10.1016/j.autneu.2010.10.004.
259. Jin K, Imada T, Hisamura R, Ito M, Toriumi H, Tanaka KF, et al. Identification of Lacrimal Gland Postganglionic Innervation and Its Regulation of Tear Secretion. Am J Pathol. 2020;190(5):1068-79. Epub 20200219. doi: 10.1016/j.ajpath.2020.01.007. PubMed PMID: 32084368.

 doi:10.20944/preprints202510.1768.v3

260. Morris JL, Kondo M, Gibbins IL. Selective innervation of different target tissues in guinea-pig cranial exocrine glands by sub-populations of parasympathetic and sympathetic neurons. J Auton Nerv Syst. 1997;66(1-2):75-86. Epub 1997/10/23. PubMed PMID: 9334996.
261. Makhmutova M, Caicedo A. Optical Imaging of Pancreatic Innervation. Frontiers in Endocrinology. 2021;Volume 12 - 2021. doi: 10.3389/fendo.2021.663022.
262. Holmgren S, Olsson C. Autonomic control of glands and secretion: a comparative view. Auton Neurosci. 2011;165(1):102-12. Epub 20101204. doi: 10.1016/j.autneu.2010.10.008. PubMed PMID: 21130712.
263. Azadzoi KM, Siroky MB. Neurologic Factors in Female Sexual Function and Dysfunction. Korean J Urol. 2010;51(7):443-9.
264. Toesca A, Stolfi VM, Cocchia D. Immunohistochemical study of the corpora cavernosa of the human clitoris. J Anat. 1996;188 (Pt 3)(Pt 3):513-20. PubMed PMID: 8763468; PubMed Central PMCID: PMCPMC1167479.
265. Giuliano F, Rampin O. Neural control of erection. Physiol Behav. 2004;83(2):189-201. doi: 10.1016/j.physbeh.2004.08.014. PubMed PMID: 15488539.
266. Claassen J, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. Physiol Rev. 2021;101(4):1487-559. Epub 20210326. doi: 10.1152/physrev.00022.2020. PubMed PMID: 33769101; PubMed Central PMCID: PMCPMC8576366.
267. Goadsby PJ. Chapter 16 - Autonomic nervous system control of the cerebral circulation. In: Buijs RM, Swaab DF, editors. Handbook of Clinical Neurology. 117: Elsevier; 2013. p. 193-201.
268. Hamner JW, Tan CO, Tzeng Y-C, Taylor JA. Cholinergic control of the cerebral vasculature in humans. The Journal of Physiology. 2012;590(24):6343-52. doi: https://doi.org/10.1113/jphysiol.2012.245100.
269. Cannon WB. Organization for physiological homeostasis. Physiological Reviews. 1929;9(3):399-431. doi: https://doi.org/10.1152/physrev.1929.9.3.399.
270. Sterling P, Eyer J. Allostasis: A new paradigm to explain arousal pathology. In: Fisher S, Reason J, editors. Handbook of life stress, cognition and health. New York: John Wiley & Sons; 1988. p. 629-49.
271. Waldrop TG, Eldridge FL, Iwamoto GA, Mitchell JH. Central Neural Control of Respiration and Circulation During Exercise. Comprehensive Physiology2011. p. 333-80.
272. Zuntz N, Geppert J. Uber die Natur der normalen Atemreize und den Ort ihrer Wirkung. Arch Ges Physiol. 1886;38:337-8.
273. Johansson JE. Uber die Einwirkung der Musdeltatigkeit auf die Atmun und die Herztatigkeit. Skand Arch Physiol. 1893;5:20-66.
274. Hess WR, Brügger M. The Subcortical Center of the Affective Defense Reaction. In: Akert K, editor. Biological Order and Brain Organization: Selected Works of WRHess. Berlin, Heidelberg: Springer Berlin Heidelberg; 1981. p. 183-202.
275. Fredericq L. De l'influence de la respiration sur la circulation. Première partie : Les oscillations respiratoires de la pression artérielle chez le chien. Arch Biol Paris. 1882;3:55-100.
276. Heymans C. Über die Physiologie und Pharmakologie des Herz-Vagus-Zentrums. Ergebnisse der Physiologie. 1929;28(1):244-311. doi: 10.1007/BF02322304.
277. Marson L. Autonomic Regulation of Sexual Function. In: Llewellyn-Smith IJ, Verberne AJM, editors. Central Regulation of Autonomic Functions: Oxford University Press; 2011. p. 0.
278. Takagi M, Abe H, Toda H, Usui T. Accommodative and pupillary responses to sinusoidal target depth movement. Ophthalmic Physiol Opt. 1993;13(3):253-7. doi: 10.1111/j.1475-1313.1993.tb00467.x. PubMed PMID: 8265166.
279. Clarke RJ, Ikeda H. Luminance detectors in the olivary pretectal nucleus and their relationship to the pupillary light reflex in the rat. II. Studies using sinusoidal light. Exp Brain Res. 1985;59(1):83-90. doi: 10.1007/BF00237669. PubMed PMID: 4018200.