

# **The Lower Brainstem and Bodily Homeostasis**

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## **Preface**

Maintenance of the internal environment, the process of bodily homeostasis as conceived by Bernard and Cannon, involves a complex interaction between behavior and physiology, coordinated by the nervous system. Accounts of the neural coordination usually place the hypothalamus on center stage as a link between the limbic system in the forebrain and the autonomic nervous system in the periphery. This book approaches homeostatic regulation from the standpoint of the lower brainstem. This is the brain region most intimately related to those primary afferent and efferent nerves concerned with the housekeeping functions of the body, yet a region that is often neglected in accounts of neural regulation of bodily homeostasis.

In this book the autonomic nervous system is viewed not as a separate functional entity, but as a collection of neurons (afferent and efferent) that link the central nervous system with visceral effectors. These linking neurons have little overall integrative function in their own right. There is no separate functional autonomic nervous system. In a related sense, there is no separate cardiovascular system, respiratory system or gastrointestinal system. As Sherrington told us and as Langley recognized, the brain integrates all bodily processes, visceral and somatic, in accordance with the economy of the whole individual.

Brainstem regions important to bodily homeostasis include those constituting the reticular formation, a concept introduced to represent the parts of the brainstem relevant to arousal and the maintenance of awareness. There has been an unfortunate tension between physiological and neuroanatomical accounts of the reticular formation. Now that modern procedures are confirming the neurochemical and functional specificities of brainstem neuroanatomical connections, a holistic concept of the reticular formation is no longer tenable. Similarly, in this book the limbic system is viewed, through Brodal's eyes, as a foggy concept that should be removed from the scientific stage.

The bias of this book is toward studies that characterize specific neural pathways in specific regions of the brain, especially the lower brainstem, with the aim of elucidating their natural function in bodily homeostasis. Studies purporting to deal with "the central cholinergic system" or "the central dopaminergic system," thereby assuming a global function for particular neurotransmitter candidates, have generally been excluded from consideration. The brain is not the liver.

Decerebrate animals, and humans with little or no forebrain function, demonstrate complex behavioral and visceral regulation, emphasizing the complexity of neural circuitry in the lower brainstem and blurring the distinction between simple reflexes and complex purposive behavior. These issues are discussed in an introductory chapter. The different neuroscientific methods and their limitations are then considered. A neuroanatomical description of the lower brainstem stresses the importance of connectivity, neurotransmitter content, and physiological function in the classification of neuronal groups. An atlas of the rat brainstem is included. The subsequent account of bodily homeostasis deals with the afferent and efferent signals that link the brain with the different bodily organs and with the

central pathways that integrate this linkage. The chapters on control of breathing and blood flow aim to interpret the traditional "centers" in terms of anatomically characterized neural circuitry. The account of breathing attempts a coherent synthesis of work from different laboratories that use different terminologies to refer to the relevant brainstem areas. The chapter on cardiovascular regulation stresses regional blood flow as the major variable controlled by the brain. Emphasis is placed on the cardiovascular role of particular neuronal groups in the medulla oblongata. The possible importance of neural control in the regulation of cerebral blood flow is considered in some detail, since the second-to-second dependence of the brain on oxygen and glucose supply is a most important factor in cardiovascular regulation.

Stimuli eliciting arousal and focusing of attention have important brainstem relays, enabling coordination of visceral and cardiovascular components of the alerting reaction at the brainstem level. Inputs to the nucleus tractus solitarius from respiratory, cardiovascular, and visceral sources may alter the level of arousal. Descriptions of these pathways are integrated with the account of the neural basis of the sleep-wake cycle. Brainstem nuclei involved in the processing of nociceptive inputs are described. In the chapter on eating and metabolism, evidence is presented for locating the "glucostat" in the lower brainstem rather than in the hypothalamus. The importance of vagal afferents is emphasized, particularly their role in transmitting satiation signals from the gastrointestinal tract to the brain. The role of vagal afferents and the area postrema in nausea and vomiting and in conditioned taste aversions is described, as is the secretion of neurohypophyseal hormones in response to gastrointestinal stimuli that cause vomiting and abdominal malaise. A final chapter focuses on the human medulla, with examples of the manner in which various disease processes affecting this structure alter bodily functions. Photomicrographs of a series of transverse sections through the human brainstem are included, integrated with magnetic resonance images as a guide to the brainstem level.

The book considers the primary evidence and thus should prove useful to graduate students and research scientists interested in how the nervous system coordinates physiological functions. Cognitive scientists and neural network theorists may discover interesting raw data. Physicians, especially psychiatrists, neurologists, neurosurgeons, gastroenterologists, endocrinologists, as well as respiratory, cardiac, and hypertension specialists may find the book illuminating, as may adventurous medical students. A detailed account of the lower brainstem has the potential to shed light on many presently mysterious aspects of bodily function.

The emphasis on integrative physiology in the book is especially important given the predominant molecular and intracellular temper of many contemporary neuroscience studies. Moreover, investigators in different fields frequently study the same brainstem regions, assigning them different functions and different names. The book attempts to integrate studies ranging vertically from intracellular to behavioral levels and laterally from one physiological function to another. Although it is difficult for a single author to cover all this material, the attempt increases the likelihood of a coherent account.

Many of the figures in the book are modified from original sources, using scanning and computer graphics procedures. I thank Alan Bentley in Media and Illustration at Flinders Medical Centre for

much helpful advice. Robyn Flook corrected many typographical errors. My colleague Weiping Gai contributed many hours to the construction of both the rat and the human lower brainstem atlases, and I thank him for sharing his knowledge of computer-based image analysis. Peter Blumbergs supplied the sections for the human brainstem atlas. For material concerning the patients discussed in Chapter 8, Clinicopathological Case Studies of Brainstem Dysfunction, I thank Dr. R. Burns, Director of Neurology, Flinders Medical Centre; Professor M. Sage, Director of Diagnostic Imaging, Flinders Medical Centre and Dr. P. Blumbergs, Director of Neuropathology, Institute of Medical and Veterinary Science.

My interest in the lower brainstem was sparked by John Chalmers at Flinders University and nurtured by Donald Reis at Cornell University Medical College. John Furness and Marcello Costa emphasized that neuroscience techniques are important for answering physiological questions, not as ends in themselves. Over the years it has been a pleasure to converse with Robin McAllen, Roger Dampney, and Antonio Granata, with colleagues in the Centre for Neuroscience, Flinders University, and with my clinical colleagues Richard Burns and John Willoughby. My friend Marcello Costa provided constructive critical input to my efforts, both academic and otherwise. The foundations for this book were laid during my time as a Visiting Scholar at the Center for Neural Science at New York University, and I thank Joseph LeDoux for his hospitality. Jeffrey House of Oxford University Press patiently encouraged my efforts, and my family, Sue, Anita, and Esther, persevered while I sat at the keyboard. Gerry Smith, Gary Aston-Jones, Robin McAllen, Roger Dampney, Janusz Lipski, Qijian Sun, Jamie Polson, and Kevin McKenna critically assessed different chapters; but if there is flak to be caught, I am the catcher.

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**Neuroanatomical Abbreviations Used in Blessing's Figures**

A5	A5 group of catecholamine neurons	LVe	lateral vestibular nucleus
Acen	central nucleus of the amygdala	MB	mammillary body
AP	area postrema	mcp	middle cerebellar peduncle
aq	aqueduct	ml	medial lemniscus
Arc	arcuate nucleus	mlf	median longitudinal fasciculus
Bar	Barrington's nucleus	MPO	medial preoptic area
BNST	bed nucleus of stria terminalis	MR	median raphe nucleus
cc	central canal	MVe	medial vestibular nucleus
CM	center median nucleus of thalamus	nA	nucleus ambiguus
Co	cochlear nucleus	nTS	nucleus tractus solitarius
CP	choroid plexus	nTScom	commissural nucleus tractus solitarius
Cu	cuneate nucleus	ot	optic tract
Cun	cuneiform nucleus	PAG	periaqueductal grey
DLT	dorsolateral tegmental nucleus	PB	parabrachial nucleus
DMH	dorsomedial nucleus of hypothalamus	PBl	lateral division of parabrachial nucleus
DR	dorsal raphe nucleus	PBm	medial division of parabrachial nucleus
DT	dorsal tegmental nucleus	pdx	pyramidal decussation
ECu	external cuneate nucleus	PGi	paragigantocellularis neuron
Gr	gracile nucleus	Pn	pontine nuclei
gVII	genu of facial nerve	PPT	pedunculo-pontine tegmental nucleus
ic	internal capsule	PrP	nucleus prepositus hypoglossi
IC	inferior colliculus	PVH	paraventricular nucleus of hypothalamus
icp	inferior cerebellar peduncle	py	pyramidal tract
IML	intermediolateral column	RM	nucleus raphe magnus
In	intermediate (intercalated) nucleus	RN	red nucleus
int arc	internal arcuate fibers	RO	raphe obscurus
IO	inferior olive	RP	raphe pallidus
IVe	inferior vestibular nucleus	rst	rubrospinal tract
KF	Kölliker-Fuse nucleus	RTN	retrotrapezoid nucleus
L	lateral thalamic nucleus	scp	superior cerebellar peduncle
lat lem	lateral lemniscus	scpx	decussation of superior cerebellar peduncle
LC	locus coeruleus	sct	spinocerebellar tract
LG	lateral geniculate nucleus of thalamus		
LHA	lateral hypothalamic area		
LRN	lateral reticular nucleus		

SN	substantia nigra	Vn	trigeminal nerve
SO	superior olive	VP	ventral nucleus of thalamus, posterior part
SON	supraoptic nucleus	VPTI	paratrigeminal islands
SpVe	vestibulospinal nucleus	Vroot	trigeminal nerve root
SubC	subcoeruleus nucleus	Vsen	principal sensory trigeminal nucleus
SVe	superior vestibular nucleus	Vsp	spinal nucleus of the trigeminal nerve
tb	trapezoidal body	Vspt	spinal tract of the trigeminal nerve
TB	nucleus of trapezoidal body	VI	abducens nucleus
ts	tractus solitarius	VIIn	abducens nerve
tst	tectospinal tract	VII	facial nucleus
VMH	ventromedial nucleus of hypothalamus	VIIIn	facial nerve
III	oculomotor nucleus	VIIIIn	vestibulocochlear nerve
IV	trochlear nucleus	X	dorsal motor nucleus of the vagus
Vmes	mesencephalic nucleus of trigeminal nerve	XII	hypoglossal nucleus
Vmest	mesencephalic tract of trigeminal nerve	XIIIn	hypoglossal nerve
VMo	motor nucleus of the trigeminal nerve		

## Bessing, Chapter 1. Introduction: Just One Nervous System

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Oxford University Press. pp.1-18.]

On a hot day the dog keeps cool not only by distributing blood to its tongue, ears, and paws, where heat exchange occurs, and by salivating and panting, but also by moving into the shade. The complexity of the behavioral contribution to temperature control was emphasized by Richter (1942) when he demonstrated that rats use more or less paper to construct a nest, according to the ambient temperature. Hibernation and migration anticipate winter's onset; growth of hair and secretion of thyroid hormone also vary with the season. In herbivorous mammals, physiological mechanisms for conserving sodium are complemented by sophisticated behavioral strategies whereby salt intake is regulated (Denton, 1982). The nervous system thus maintains bodily homeostasis by coordinating internal physiological processes with the individual's interaction with the external environment. As the *milieu interieur* is maintained, the brain coordinates the contraction of striated and smooth muscles, as well as the secretions of endocrine and exocrine glands.

Homeostasis may proceed remarkably normally in mammals without functioning cerebral hemispheres, as demonstrated by the decerebrate dog that Goltz maintained for 18 months (Bazett and Penfield, 1922). The dog could walk. It would eat and drink when brought close to food and water. Basic respiratory and cardiovascular functions were normal. Temperature control was intact, with the animal shivering when placed in a cold room. When the brain of this dog was examined at autopsy, the basal forebrain, hypothalamus, and portions of the thalamus were intact (Holmes, 1901). Since neuronal circuitry in these regions is important for many homeostatic processes, the contribution of lower brainstem regions might be better assessed in animals decerebrated at the midbrain collicular level. In such animals many bodily homeostatic functions can be quite well maintained (Bazett and Penfield, 1922; Bard and Macht, 1958; Woods, 1964; Lovick, 1972; Tenney and Ou, 1977; Davis, 1984; Berntson, 1988). Depending on the species, the chronically decerebrate mammal may move about in its cage, groom itself, eat and drink relatively normally when food or water is closely presented, or reject bitter-tasting food. Auditory stimuli continue to elicit startle responses. Such animals show evidence of sleep-wake cycles. Complex nociceptive behavior occurs. Rats struggle during passage of a feeding tube, pushing at the tube with both forepaws and uttering loud cries. Cats display marked behavioral arousal in response to hypoxia. Cardiovascular, respiratory, gastrointestinal, metabolic, renal, and bladder function maintain the *milieu interieur* sufficiently well for survival in the laboratory situation.

Similarly, infant humans born without the cerebral hemispheres (incorrectly labeled "anencephalics") and mature humans with loss of forebrain function can survive, sometimes for years, in a so-called vegetative state (Celesia, 1993). Such individuals sleep and wake, cry and smile, startle in response to a loud sound, become restless with hunger and hypoxia, and reject certain foods. Respiratory, cardiovascular, metabolic, and eliminative functions are reasonably normal, although incontinence occurs. Surviving hypothalamic and basal forebrain circuitry may contribute to these processes so

that, as for experimental animals deprived of their cerebral hemispheres, the contribution of the lower brainstem is difficult to assess. However, Neilsen and Sedgwick (1949) described an anencephalic infant who proved to have no neural tissue above the midbrain when autopsied after 85 days survival.

The patient startled in the presence of loud noises... If we handled the patient roughly he cried weakly, but otherwise like any other infant, and when we cuddled him he showed contentment and settled down in our arms. When a finger was placed into his mouth he sucked vigorously.... He would sleep after feeding and awaken when hungry, expressing his hunger by crying.

The brainstem thus contains neural circuitry sufficiently complex to regulate the maintenance of bodily homeostasis in a laboratory or hospital setting. Indeed, the complexity has probably been underestimated because the name stem was bestowed in deference to the supposed all pervasive role of the cerebral hemispheres, presumably the nervous system flower. The brainstem contains many of the premotor and motor neurons responsible for homeostatic control; it receives primary visceral and cardiovascular-respiratory afferents; it contains complex interneuronal circuitry relevant to the coordination of homeostasis.

This book reviews neural control of mammalian homeostatic function from the standpoint of the lower brainstem, hopefully providing a counterbalance to other accounts that emphasize the upper brainstem and the forebrain.

One only has to consider the behavior of a unicellular organism, such as a paramecium, to appreciate the subtlety and complexity of function already apparent at the cellular level. Coordination of the multiple cells that make up a mammal is achieved largely by the nervous system. One's scientific attention can focus on relevant subcellular or molecular events. Complex changes in ionic conductances in nerve cell membranes are now illuminated by the achievements of molecular biologists in sequencing and synthesizing functionally relevant membrane receptors and ion channels. Knowledge of how intracellular calcium ions are sequestered or mobilized has extended our understanding of how individual cells function. Active regulation of transcription and translation processes selectively alters protein synthesis so that neuronal function is modified over time periods from hours to years. Reference is made to such processes in the present book, but the author's ability to evaluate intracellular physiology critically is limited.

At a more integrated level, one may focus on groups of neurons regulating those physiological and behavioral activities that maintain the *milieu interieur*. Such an account requires an appreciation of human and animal behavior, an understanding of integrated organ system physiology, and familiarity with the neural pathways, neurotransmitters, and cellular mechanisms underlying bodily homeostasis. This is the type of account attempted in the present book.

A framework for the global neural regulation of bodily function was provided by Hughlings Jackson (1884, 1931), a clinical neurologist who formulated the principle of "evolution and dissolution," according to which the same bodily region is regulated at increasing degrees of complexity by neural circuitry in more recently evolved regions of the nervous system. There are multiple nervous system

"representations" of bodily parts. In the case of the somatic motor system, the lowest representation level—the anterior horn cell—controls the contraction of individual muscle fibers. The highest representation level—the premotor frontal neocortex—controls those finely coordinated movements that occur in complex behaviors such as blowing a kiss or playing the piano. Damage to a higher center causes less actual paralysis than occurs after damage to a lower center. Damage to the premotor cortex may make it impossible to play the piano, yet individual finger movements may still be executed. Damage to the motor cortex eliminates voluntary movement, but postural support functions of the limb are preserved, as are reflexly induced movements. Damage to the appropriate anterior horn cells eliminates all voluntary and reflex movement. Jackson realized that the cortex normally controls movements, not individual muscles. Without special training it is usually very difficult for us to contract an individual muscle. Thus, paradoxically, we do not normally have direct control over our "voluntary" muscles; we have control over our movements.

Jackson included visceral function in his concept of multiple representations. Noting the emotional manifestations that may precede a seizure (pallor of face, increased flow of saliva), he concluded that the arteries and the viscera are also represented in the cerebral cortex. Visceral muscle has its own intrinsic contraction, independent of neural input. More useful function is ensured by nerve cells in the viscera and in the various peripheral ganglia. Additional complexity is provided by the action of preganglionic visceral neurons in the spinal cord and the brainstem. The brainstem and basal forebrain contain additional coordinating centers, including neural circuitry integrating somatic behavior with visceral function. The basal forebrain and the cerebral hemispheres add the final levels of complexity.

The central command process involved in voluntarily moving a limb may also alter the contraction of vascular smooth muscle so that blood flow to the appropriate striated muscles increases ahead of demand. Gandevia and colleagues (1993) demonstrated that the effort to make a voluntary movement in a paralyzed (but fully conscious) human alters cardiovascular parameters, presumably via a central command process. Pavlov (1927) documented how readily salivation and gastric secretion can be conditioned to occur in response to environmental cues. Such processes are presumably part of the normal regulation of glandular function.

### **Affective Experiences and Purposive Behavior Are Part of the Homeostatic Process**

Many internal physiological processes, for example, the maintenance of erythrocyte numbers or the secretion of cerebrospinal fluid, are regulated unconsciously, with no emotional component.

However, other homeostatic processes, particularly those dependent on interactions between external and internal environments, involve intense affective experiences, each linked with an urge to behave in a particular manner.

Sherrington (1900) noted that cutaneous stimulation produces particularly strong affective tones, provoking behavior in a "curiously imperative manner." Reactions to painful stimuli are obvious, but other sensations are also linked with behavioral responses. On a cold day we approach the fire and enjoy its warmth. On a hot day we seek out the pleasant cool of the shade. The behavior contributes to control of body temperature. Respiratory inadequacy may be associated with the unpleasant

sensation of dyspnea, with associated arousal and vigorous attempts to breathe. As thirst increases, the idea of water begins to dominate our consciousness. The dryness of the mouth disappears as we drink, and the water no longer seems so attractive. When hunger occurs we seek out food and eat. After an adequate meal we feel full and stop eating. Emptying a full bladder or bowel is associated with a transition from discomfort to comfort. Sexual consummation is linked with intense pleasure. Exercise makes our muscles ache, and, feeling tired, we rest. We feel drowsy after an appropriate period of wakefulness and find a comfortable place to sleep.

Ingestion of toxins may induce nausea, vomiting, and subsequent avoidance of the suspected food or water source. The Greek root of the old name for food poisoning (ptomaine poisoning) is ptôma, signifying a dead body. The very pronunciation of the word configures our lips for spitting out and rejecting unacceptable foods such as carrion. Thus, a particular taste may be so agreeable or so disagreeable that our gastronomic response is incorporated into language, as in mmm, or ptui.

Simple (reflex) and complex (purposive) adaptive behaviors are thus closely linked with affective experiences. Such responses are accurately described as "emotional" behavior, with emphasis on the movement connotation of "emotional." The term is now commonly used to emphasise a contrast with "reasonable" or "cognitive" behavior. Such a contrast reflects the extent to which technological advances, coupled with acceptance of the rights of others and the rule of law, have liberated humans from the constant task of ensuring daily survival. Many of the affective experiences associated with bodily homeostasis are now reduced: Our vision and hearing do not need to be constantly tuned to danger signals; we take food from the refrigerator. Although certain affective experiences (e.g., sexual experiences) and their behavioral accompaniments may be emphasized in a civilized society, in this context we have more opportunity to concentrate our thoughts on aspects of life unrelated to survival. With an artist's eye, we can appreciate the beauty and complexity of the world.

Whether experiences and purposes can be said to cause particular behaviors is a difficult question, one aspect of the mind-body problem, the paradox of consciousness. Philosophical accounts of the relationship between mental and physical events are discussed by Churchland (1988). Materialist theories (e.g. Dennett, 1991) equate experiences and purposes with physical brain processes, with the brain viewed as a sophisticated computer whose genetically inbuilt programmes are modifiable by life experiences. Chalmers (1996), in a spirited account, considers that the materialist view fails to take consciousness seriously enough. He argues for "naturalistic dualism," a variety of epiphenomenalism in which consciousness "supervenes" from physical states, or perhaps a variety of monism in which the physical and mental are two different aspects of what exists, just as matter and energy are different aspects of one thing. Thus, as Churchland discusses, explaining our actions in terms of experiences and purposes may be analogous to explaining the sunset in terms of the sun sinking below the horizon. We also accept the more physical explanation in terms of the rotation of the earth around the sun, and recognize its greater predictive power.

Whatever approach one adopts to the mind-body problem, it is important not to neglect the richness of our own awareness and experiences, and the purposiveness so evident in living systems. Living individuals struggle to survive and reproduce, be they unicellular organisms or multicellular humans.

Each individual struggles; the species survives. As physiologists, we understand homeostatic processes in the context of this struggle. We make sense of the reactions of experimental animals in accord with our own experiences, our own purposes, and our own consciousness. Neglecting this aspect imposes an unnecessary scientific handicap, even if such a strategy was once necessary to constrain the introspective excesses of armchair psychologists.

Nevertheless, in our physiological accounts, there is little to be gained by treating either conscious experiences or purposes as causes of behaviour. Cabanac (1971) emphasized the biological role of affective states by demonstrating that current physiological needs may determine whether a given stimulus evokes pleasant or unpleasant experiences. An approach such as Sherrington's, exemplified in his account of pain (1900:228-230), is probably as wise and as helpful as any. Sherrington proposed that repeated mechanical, thermal, and other forms of damage have, in the course of evolution, produced in the skin a specific sense whereby the individual detects injury—a sense that functions to "brand upon memory" a feeling derived from those past events that have been critical for the existence of the individual, and, by implication, of the species. Pain is thus "the psychical adjunct of an imperative protective reflex." When I tread on a thorn, my foot withdraws, but not because of the pain. My foot commences to withdraw before impulses could reach the forebrain and return to the spinal cord. The pain indicates the involvement of a higher representation center in the sense used by Hughlings Jackson. The pain-induced "brand upon memory" serves to alter my overall behavioral strategy so that next time I am in a similar situation I am careful not to tread on a thorn. I may even wear shoes.

The psychologist William McDougall (1931) emphasized the distinction between reflex actions and purposive behavior, with the latter thought to depend on cortical function. McDougall says:

If we saw a dog lying in the sunlight and then saw him get up and wander about, we might suppose that the heat of the sun's rays had stimulated him to reflex walking; but, if we saw him walk to a patch of shade and there lie down and resume his slumber, we should confidently infer that this was behavior, a purposive movement attaining its natural goal. (1931:54)

However, the distinction depends on the level of complexity from which particular events are viewed. From a physiological viewpoint it is better to regard the shadeseeing behavior as an integral part of the animal's temperature control system and to search for the relevant neural circuitry. In lizards, pyrogen-induced increases in body temperature are accomplished principally by a change in the animals' behavior. The pyrogen-treated animal, given an appropriate choice, increases its body temperature by choosing a warmer than usual environment (Vaughn et al., 1974), an action that illuminates the behavior of febrile humans who shiver and, complaining that they feel cold, cover themselves with even more bedclothes.

In humans with spinal cord transection, responses such as the withdrawal reflex occur in the absence of any conscious experience, excepting experiences mediated by sensory systems whose afferent pathways enter the nervous system above the level of the spinal transection. The paraplegic person can see his or her own paralyzed legs. The searching finger feels the leg, but, one might say, the leg

does not feel the finger. Other spinalized mammals retain variable degrees of neurological function in the portions of the body below the level of the lesion. Paraplegic monkeys may grasp a paralyzed leg and move it to a more acceptable position, but paraplegic mammals with less complicated neocortex appear, in Sherrington's words, "blithely unaware" of the catastrophe that has befallen them.

Nonmammalian vertebrates retain remarkably sophisticated functions below the level of a spinal lesion. McDougall's confidence in the link between neocortex and purposive behavior was shaken by the complex behavior of the spinalized frog. Such animals use the ipsilateral hind foot to remove a pledge of vinegar-soaked blotting paper applied to the flank. When the ipsilateral foot is forcibly restrained, the paper is removed by the contralateral foot.

McDougall considered such complex actions to be "purposive in a lowly sense." With reference to mammals, Sherrington had already noted that:

there is no wide interval between the reflex movement of the spinal dog whose foot attempts to scratch away an irritant applied to its back . . . and the reaction of the decerebrate dog that turns and growls and bites at the fingers holding his hind foot too roughly. (1947:267).

Similar apparently purposive reactions occur in anencephalic human infants and in adult humans with damage to the cerebral hemispheres.

As far as is known, the spinal cord and the brainstem are constituted of the same neural elements that constitute the neocortex and the rest of the forebrain. Yet somehow neural activity in the forebrain gives rise to the so-called higher functions—a sense of purpose, conscious awareness, cognition, and experience. Neural circuitry in dorsal regions of the rostral pons, midbrain, and thalamus are necessary for the occurrence of these functions (see Chapter 6). Somewhat surprisingly, the higher functions are preserved after selective anesthetization of either cerebral hemisphere, a remarkable phenomenon readily observed during unilateral intra-carotid injections of sodium amytal for assessing cerebral dominance. Consciousness is lost with simultaneous dysfunction of both cerebral hemispheres, even with preservation of midbrain and other brainstem function, as may occur after prolonged cardiac arrest or carbon monoxide poisoning.

McDougall noted that purposive behavior may be improved by repetition. No such improvement was thought to occur with reflex processes. Pavlov's demonstration of conditioned salivary secretion in the dog was a problem for McDougall. He temporized by interpreting the learned responses as instances of purposive behavior, justifying his stance by the assumption that the learning must be mediated by the cerebral cortex, the presumed seat of purposive behavior. However, we now know that the cerebral cortex is not essential for the acquisition of conditioned somatic and visceral responses. An electric shock causes a rat to "freeze" and exhibit particular cardiovascular changes. After the shock has been preceded by a tone on a number of occasions, the tone, by itself, will elicit similar freezing and cardiovascular change. McDougall might have explained this by supposing that the animal uses its neocortex to understand the significance of the tone, and, becoming afraid, it freezes. Yet the rat whose neocortex has been removed still freezes when the tone is sounded (LeDoux et al., 1990). There is a direct pathway from the medial geniculate to the amygdala, and

non-neocortical circuitry is sufficient for the acquisition and expression of the conditioned fear responses. Simple conditioned avoidance responses have been produced in decerebrate rats (Tomaz and Huston, 1986).

The occurrence of learned responses in decorticate or decerebrate animals precludes any purely "psychological" explanation of the behavior. An understanding of the complexities of learning in lower vertebrates and invertebrates (Hawkins and Kandel, 1984) might have averted unproductive debate between psychologists and physiologists and prepared us for the possibility that brainstem neural circuitry might mediate aspects of learning and memory:

Our mode of life has been achieved through eons of evolutionary change, during which the conservative and relatively stable organization of the brain stem has been supplemented and amplified by the addition of cortical apparatus with more labile patterns of action, resulting in greater freedom of adjustment to the exigencies of life. In all behavior there is a substrate of innate patterns of great antiquity, and in practical adjustments these primitive factors are manipulated and recombined in terms of the individual's personal experience. Memory and learning are pre-eminently cortical functions, but these cortical capacities have not been given to us by magic, and we want to know how they have been developed and the roots from which they have grown. (Herrick, 1948:122)

Eventually, all physiological and behavioral events, and their associated affective experiences, must be explained in terms of neural circuitry. This is not to deny the importance of purpose and experience. Explanations of these terms may be useful as temporary summaries, and such a framework provides overall meaning to our physiological studies. Whether a stimulus causes a simple or a complex response is partly a matter of definition, and it is not helpful to emphasize the distinction between simple reflexes and purposive behavior. Ultimately we require a neural circuitry account of all mammalian homeostatic actions, ranging in complexity from limb withdrawal in a spinal frog to the purposive actions of a chimpanzee using twigs to fish termites out of their nest. Physiological accounts of the volitional aspect of purposive actions are also necessary. Normally I breathe unconsciously, according to the periodicity set in my brainstem. Yet, by taking thought, I can easily make each breath part of my experience. I can take deep breaths or shallow breaths. I can interrupt my breathing, but not for too long. After 30 seconds or so I experience the urge to breathe. With time this urge dominates my whole experience, so that eventually I cannot resist the urge, and I "decide to breathe." The urge to breathe is another example of a psychical adjunct of an imperative protective reflex. In this instance the task for the neuroscientist is to discover how neocortical (presumably) circuitry inhibits the brainstem neurons generating the respiratory rhythm and how brainstem neuronal mechanisms overcome this inhibition.

## **Reflexes and Centers**

The complexity of the nervous system means that studying it during the course of natural activities is difficult. To some extent, modern techniques that directly image neuronal function have alleviated this

difficulty (see Chapter 2). In the early days of neuroscience it was necessary to proceed by selecting stimuli that elicited observable responses in the manner proposed by Descartes. This emphasized the link between stimulus and response. Such couplings were called reflexes, as in limb withdrawal to injury or in the knee-jerk response elicited by tapping the quadriceps tendon. Sometimes the reflexes have become ends in themselves, and their physiological significance has been neglected. An artificially isolated event, such as the knee jerk, should be incorporated into accounts of the natural regulation of behavior. Similarly, an abstraction such as the baroreceptor-heart rate reflex might be useful as an experimental tool, but it must be incorporated into the overall regulation of blood flow to the tissues. Our theoretical framework for understanding integrative physiology is still very primitive. A cat sits at the edge of a table, preparing to leap. The animal's body commences to fall, and, suddenly and just at the right time, it leaps to a perfect landing on the next table. Perhaps one day this dramatic change of state may be understood by the kind of physiological oscillation analysis of rhythmical swimming motions of the lamprey proposed by Grillner and colleagues (1995).

Once we accept the idea that particular brain regions are concerned with particular functions, it is necessary to develop terminology for referring to functional central nervous system (CNS) units important for regulating bodily homeostasis. The term center is convenient for referring to such units. Since knowledge of the central regulation of any function is still in an elementary state, most postulated CNS centers are largely uncharacterized in terms of neuroanatomy and transmitter neurochemistry. The danger is that the term center will take on more meaning than is appropriate and that the postulation of a particular center for a function will be taken as evidence that we understand how the brain regulates this function. The postulated existence of a "vasomotor" center in the medulla was followed by papers with titles such as "The effect of pneumonia on the vasomotor center." Such papers amounted to little more than a statement that certain cardiovascular events accompany certain clinical or physiological situations.

The tendency of a named center to assume a life of its own is possibly the worst aspect of the use of the term. Another is the assumption that a particular center must exist as a homogeneous cell group in the brain, discrete from nearby centers regulating different functions. Specifically connected neurons regulating a particular function may be regionally located, but they may be interspersed with neurons, also specifically connected, regulating different organs. Thus cardiovascular and respiratory "centers" exist in overlapping regions of the ventrolateral medulla. Criteria for defining a center regulating arousal and the sleep-wake cycle have been suggested by Steriade and McCarley (1990). They can be generalized:

1. A neural center should subserve one function, usually involving several end organs. Thus, activation of a vomiting center should produce appropriately coordinated gastrointestinal, respiratory, and cardiovascular changes.
2. Neurons constituting a center should be homogeneous in their input-output organization and in their chemical coding.
3. Stimulation of perikarya in a functional center should produce the function.

4. Inactivation of the perikarya in a center should substantially alter the expression of the function, with the proviso that this depends on the sophistication with which the function of the end organ is assessed.
5. Activity of neurons in the center should be correlated with the occurrence of the function, with appropriate time relationships.

It may turn out that the neurons controlling some functions are so widely distributed, or so closely interspersed with neurons regulating different functions, that it is impossible to identify any meaningful center. This is a matter for experiment. What is encouraging is how often particular homeostatic behaviors, and the appropriate functions of particular visceral end organs, do appear to depend on regionally located, relatively homogeneous, neuronal groups.

## **Visceral Neurons; Afferent and Efferent, Not the "Autonomic Nervous System"**

### **Langley's legacy**

Many accounts of the regulation of the milieu interieur concentrate on "the autonomic nervous system," a term introduced by Langley (1903) to describe the nerves controlling glandular tissues, cardiac muscle, and smooth muscle in viscera and blood vessels. After careful consideration, Langley excluded afferent neurons from the nerves defined as belonging to the autonomic nervous system. Most vascular and visceral afferents seemed to mediate pain, and Langley was inclined to include as autonomic afferents only those "which give rise to reflexes in autonomic tissues, and which are incapable of directly giving rise to sensation" (1903:26). He thought that autonomic afferents should give rise to centrally mediated reflex changes in autonomically innervated tissues and that such afferents should belong to a morphologically special subclass. Langley was especially discouraged by his failure to find afferent cell bodies in autonomic ganglia. Anatomists at the time expressed a general feeling that visceral afferents must be somatic because they pass through the dorsal spinal roots, *"but with whimsical inconsistency they do not apply such restrictive criteria to the autonomic fibers emerging through ventral spinal nerve roots"* (Mitchell, 1956:90).

The methylene blue procedure used for detecting unmyelinated fibers was suitable for examining tissues, but it was not so applicable to nerve bundles. Evidence suggested that visceral afferents were rather sparse, and Langley judged that the total population of visceral afferents would prove to be quite limited. In his time it was not known that at least 75% of fibers in the cervical vagus nerve are afferent and that in the subdiaphragmatic vagus over 90% of these afferents are unmyelinated (Evans and Murray, 1954; Agostoni et al., 1957; Hoffman and Schnitzlein, 1961). Langley believed that vagal afferents give rise to pain and must therefore be somatic. Visceral afferents were thus excluded from the structures defined as belonging to the autonomic nervous system; it was considered a purely motor system.

By thus defining the autonomic nervous system, Langley relegated visceral afferents to a neuro-anatomical limbo, neither autonomic nor somatic. This has proven most unfortunate. Presumably as a consequence of the intellectual framework thus created, the physiological role of visceral, particularly

vagal, afferents has often been overlooked. Thus a major reference work in rat neuroanatomy, the second edition of *The Rat Nervous System* (Paxinos, 1995), omits any detailed consideration of thoraco-abdominal vagal afferents and their CNS-mediated contribution to the regulation of the *milieu interieur*.

When searching for a term to describe the ganglionic nervous system Langley gave good reasons for discarding vegetative and involuntary. He chose autonomic, recognizing that the term:

does suggest a much greater degree of independence of the central nervous system than in fact exists, except perhaps in that part which is in the walls of the alimentary canal. But it is, I think, more important that new words should be used for new ideas than that the words should be accurately descriptive. (1921:6)

He conceived of the autonomic nervous system as functioning with "a certain degree of independent action, but exercised under control of a higher power" (1898). The role of the higher power (the CNS) is acknowledged, but the independent action of the autonomic nervous system is emphasized by the system part of the term. Such a word suggests an intrinsic operational unity and capacity to respond so as to achieve a particular end—an inbuilt purposiveness. Langley was not discouraged by his conclusion (1900:677) that "on the whole the evidence at present leads us to conclude that autonomic ganglia, after separation from the central nervous system, do not exercise any considerable tonic action on unstriated muscle." Even in the CNS, he noted, many nerve cells have either no automatic action or an apparent automatic action that in reality reflects the influence of afferents. This is not a convincing defence.

Little evidence has accrued to demonstrate that autonomic ganglia have inbuilt discharge patterns capable of sustaining physiological function. Activity in sympathetic nerves innervating vessels in human forearm and leg muscles is highly correlated (Sundlöf and Wallin, 1977), indicating that the pattern originates centrally, not peripherally. In humans with high spinal transection, a degree of basal tone eventually returns to vasomotor nerves, but neurally mediated physiologically appropriate regulation of blood flow probably does not occur. There is little spontaneous activity in postganglionic sympathetic vasomotor axons (Stjernberg et al., 1986). Postural hypotension remains a persistent problem, and the quadriplegic patient is subject to hypertensive crises (autonomic dysreflexia), precipitated by activation of sympathetic preganglionic vasomotor neurons by bladder afferents. Specific patterns of neural outflow to cardiovascular and visceral organs originate almost exclusively within the brain (Stjernberg and Wallin, 1983; Jänig and McLachlan, 1992a,b; Jänig, 1988). Thus, the application of the word system to autonomic neurons is misleading. We do not speak of a "spinal nervous system" even though the isolated spinal cord certainly does possess a degree of operational unity and integrated action.

If future research documents extensive integrative functions in peripheral visceral motoneurons, this knowledge can be incorporated into the overall picture of homeostatic control. The presence of integrated functions in the isolated gut, together with appreciation of the number and complexity of gut wall neurons, led Langley to introduce the concept of the "enteric nervous system." This

definition obviously has its wisdom. The enteric nervous system does have intrinsic integrative properties that justify its definition as a separate system (Furness and Costa, 1987; Goyal and Hirano, 1996). However it is still reasonable to wonder how the gut would actually function in vivo if it were completely isolated from the CNS. Gastrointestinal processes such as secretion of pancreatic digestive enzymes depend on vagovagal reflexes initiated by the action of cholecystikinin on vagal afferent nerve terminals, not via a direct pancreatic action of the hormone (Li and Owyang, 1994). The disturbance of gastroduodenal function that follows vagotomy is well recognized. The task of identifying which particular enteric neurons function as postganglionic parasympathetic neurons innervated by vagal efferents has been neglected until recently. The modern emphasis on brain-gut interaction is a healthy counterbalance to overemphasis of the functional unity of the enteric nervous system.

The very idea of "autonomic function," conceived as involuntary automatic function mediated by a special nervous system, has had unfortunate consequences. It has contributed to the virtual divorce between "autonomic" physiologists studying the cardiovascular system and their "nonautonomic" colleagues studying the respiratory system, even though the two systems share a common physiological purpose. It has emphasized the arbitrary division between "central" and "peripheral" physiologists studying bodily homeostasis, thereby diverting attention from the role of the CNS in the integration of visceral function with the behavior of the whole organism.

Langley considered using Gaskell's term visceral nervous system rather than autonomic nervous system but decided against this alternative because he balked at including nerve fibers innervating organs such as skin, blood vessels, and eyes in the definition of a visceral nervous system (Langley, 1898). Nevertheless the term visceral nervous system has periodically been reintroduced to describe both efferent and afferent innervation of viscera (Livingston, 1935; Sheehan, 1936). This is a sensible suggestion. However, as discussed above, the system part of the term is misleading. The term autonomic nervous system should be abandoned. It is wiser simply to refer to visceral neurons, both efferent and afferent. The definition of viscera should be as broad as necessary, including all bodily smooth muscle and secretory cells, regardless of their location (Schott, 1994). The terms sympathetic and parasympathetic should be used sparingly, as summary anatomical terms for the appropriate preganglionic or postganglionic (actually ganglionic) motoneurons and their axonal processes. Visceral neurons should be recognized for what they are—one means whereby the CNS communicates with peripheral organs.

### **Cannon's contribution**

Cannon also contributed to the concept of a unitary "autonomic nervous system." He viewed the parasympathetic nervous system as functioning in a manner analogous to the separate keys of the piano, specifically altering the function of individual organs in a variable pattern. Bodily emergencies involved the sympathetic system, which was seen as acting in a manner analogous to the loud and soft pedals on a piano (Cannon, 1932:258), affecting smooth muscle and glands throughout the body, as well as the adrenal medulla via a generalized, rather than specifically patterned discharge:

The preganglionic fibers of the sympathetic division of the autonomic nervous system are so related to the outlying neurones that the resulting innervation of smooth muscles and glands throughout the body is not particular but diffuse. At the same time with the diffuse emission of sympathetic impulses adrenin is poured into the blood. Since it is thereby generally distributed to all parts and has the same effects as the sympathetic impulses wherever it acts, the humoral and the neural agents cooperate in producing diffuse effects. In consequence of these arrangements the sympathetic system goes into action as a unit—there may be minor variations as, for example, the presence or absence of sweating, but in the main features integration is characteristic. (Cannon 1927:109)

However, CNS control of viscera is probably highly patterned, as is CNS control of somatic muscles, a conclusion gradually being supported by studies of sympathetic activity in unanesthetized humans (Vallbo et al., 1979; Wallin and Fagius, 1988; Wallin and Elam, 1994). As Wallin argues, the concept of "sympathetic tone," supposedly reflecting a stereotyped, global level of activity in sympathetic nerves, is no longer tenable. Activity in different sympathetic nerves depends on what the individual is doing or thinking at the time. The brain uses both sympathetic and parasympathetic nerves to set the pattern of blood flow to the different organs according to the particular situation and the particular behavior. Alerting reactions in the rabbit may be associated with selective cutaneous vasoconstriction, with little change in renal, mesenteric, or femoral blood flows or in arterial pressure (Yu and Blessing, 1997). Even when the individual is markedly aroused there is no mass action of "the sympathetic system," just as there is no mass action of "the somatic system." Mass activation of cardiovascular-visceral motor nerves probably occurs only pathologically, as in a grand mal epileptic seizure or during a "dysreflexic" episode in a paraplegic. Normally patterned neural activity to both somatic and cardiovascular-visceral and endocrine targets produces an effective response of the whole individual.

The demonstration of specifically patterned sympathetic and parasympathetic outflows is supported by physiological studies (Jänig, 1988; Jänig and McLachlan, 1992a,b) and by our increasing appreciation of the multiplicity and complexity of neurotransmitter agents present in the terminals of pre- and post-ganglionic visceral efferents, both sympathetic and parasympathetic (Gibbins, 1990; Morris and Gibbins, 1992).

### **Not "Central Autonomic Regions," Not "the Limbic System," and Not "the Reticular Formation"**

Many investigators have postulated the existence of CNS regions thought to constitute the "central representation" of the autonomic nervous system. Hess (1954) divided the hypothalamus into anterior parasympathetic and posterior sympathetic components. Others have suggested that the CNS may operate in a predominantly "sympathetic mode" or a predominantly "parasympathetic mode" in different individuals. This is not a physiological distinction. When a rabbit detects smoke or other noxious vapor, breathing stops, the heart dramatically slows, peripheral vessels constrict, and cranial vessels dilate. The integrated response, initiated by trigeminal afferents, protects the airways and

preserves oxygen for the brain and the heart. The question whether the response is "primarily sympathetic" or "primarily parasympathetic" has little physiological meaning. Even when theoretical prejudices are set aside, the designation of certain brain regions as autonomic is a strategy open to all the criticisms directed to the concept of the autonomic nervous system earlier in this chapter. Should brainstem neurons controlling respiration, or swallowing, be included in these autonomic areas? Rather than enter into such sterile arguments, it is preferable to follow the strategy outlined in the concluding section of this chapter. If a definition is required, then one could refer to brain nuclei particularly relevant to control of visceral function and regulation of bodily homeostatic processes. Central control of visceral function, and associated emotional events, is sometimes attributed to forebrain regions designated as the limbic system. One line of thought leading to the concept derived from Cannon (1927), who, opposing the James-Lange theory, proposed that emotional feelings reflect primary activity in the brain rather than being secondary to the perception of peripheral events, such as a rapidly beating heart bumping on the chest wall. Neural activity in the thalamus was thought to be of particular importance, reflecting the influence of Head's ideas concerning its role in the perception of pain (see Chapter 8). Further support was provided by the emotional behavior elicited by hypothalamic stimulation and the sham rage that occurs in decorticate animals. Cannon also noted the easy crying and laughing that occurs in patients with cortical and subcortical forebrain lesions. In support of Cannon's ideas, Papez (1937) proposed a principally subcortical anatomical pathway that might mediate emotional experiences.

MacLean (1949, 1958) noted the dramatic relief from emotional symptoms that frontal lobotomy sometimes achieved. Nevertheless, he considered that the prefrontal cortex was unlikely to form the substrate of emotion because this region of the brain underwent extensive evolutionary development. Since basic emotional expression is generally similar across many phylogenetic levels, MacLean thought that emotional feelings and reactions were more likely to be mediated by regions of the forebrain that have not changed greatly during evolution. The emotional experiences of patients with temporal lobe epilepsy, considered by MacLean to reflect amygdala activity, included many alimentary symptoms, as well unpleasant feelings related to the struggle for existence. MacLean (1969) therefore elaborated on the Papez theory of emotional mediation, further integrating the circuitry into the phylogenetically older cortex located in Broca's limbic lobe: "The limbic cortex and the structures with which it has primary connections may be regarded as comprising one of the major systems of the brain. In taking advantage of Broca's descriptive term limbic, it may be appropriately referred to as the limbic system."

The more rostral limbic system, MacLean considered, was interconnected with the hypothalamus and the brainstem so that it could receive strong inputs related to visceral function. Nevertheless, neural activity within the limbic system was considered to be relatively confined to the system. MacLean (1958) described this in one of his colorful analogies, explaining that electrical stimulation of the hippocampus produces afterdischarges that are "like stampeding bulls which do not stampede beyond the corral of the limbic system."

This concept of the relatively self-contained limbic system was extremely influential, becoming part of the framework of many theories in physiological psychology, neurology, and psychiatry. Apart

from its importance in emotional behavior, the limbic system came to be seen as one of the main central representations of the autonomic nervous system. Thus, in a footnote explicating the concept of the limbic lobe, Mitchell (1956:16) tells us that "all these limbic cortical areas are predominantly but not exclusively autonomic in their affinities, whereas the neocortex is predominantly but not exclusively somatic."

The concept of the limbic system has been plagued by its anatomical and physiological vagueness and by the lack of precision with which the term is used. Cannon's original theory of emotion emphasized the role of the thalamus, not the hypothalamus. Papez's circuit included the hippocampus but omitted the amygdala, now recognized as a key nucleus for integrating behavioral and visceral components of emotional responses. Little attention was paid to the manner in which the limbic system was connected with the brainstem. MacLean considered that the central grey and the paramedian reticular regions of the midbrain provided the link. In practice little emphasis was placed on the lower brainstem, in spite of the long-established knowledge that brainstem regions receive primary visceral afferents.

Cajal (1909), for example, fully understood that the nucleus tractus solitarius in the medulla oblongata is the brain region receiving primary afferents from taste receptors and from the stomach receptors responsible for initiating vomiting, information surely relevant to emotional experience and behavior. Information entering the brain at the level of the medulla oblongata, from peripheral chemoreceptors and other cardiorespiratory and visceral receptors, was likewise largely neglected in accounts of limbic-mediated emotional behavior. This was in spite of the accurate appreciation, at the time the concept of the limbic system was formed, of the importance of such inputs in arousal behaviors (Dell, 1957; Heymans and Neil, 1958). The capacity of animals devoid of forebrain down to the thalamus, and even of animals decerebrated at the collicular level (i.e., with most of the limbic system removed), to express "pseudo-rage" reactions was well documented by the early part of the twentieth century (Woodworth and Sherrington, 1904; Cannon, 1927; Bard, 1928). What, we may wonder, could be more emotional than the behavior of a thalamic cat when peripheral chemoreceptors are stimulated by lobeline introduced into one carotid sinus? In an animal so prepared, "arterial pressure began to increase, breathing augmented in amplitude, pupils dilated, nictitating membranes became retracted, and soon, phasic struggling and clawing movements, lashing of the tail and facial expression of rage became apparent" (Bizzi et al., 1961).

Yet, in the summary diagram of the limbic system in MacLean (1958), the lower brainstem is left blank. In MacLean's triune brain concept, the phylogeny of the three levels of cortex was likened to the uneven expansion of a toy balloon, with the brainstem relegated to "the stick holding the balloon." Thus, although the limbic system was based in the forebrain region postulated to be important for emotional and visceral function, the concept of the limbic system actually isolated the relevant forebrain regions from the lower brainstem, thereby paradoxically neglecting actual visceral inputs to what was considered to be the "visceral brain." We now appreciate (see Chapter 3) that the nucleus tractus solitarius has extensive direct monosynaptic bidirectional connections with both the hypothalamus and the amygdala and with the parabrachial nuclei and the periaqueductal gray, also of key importance in integrating behavioral and visceral components of daily life.

It has never been established that the so-called limbic system functions in any unified manner. In practice, the concept has mostly served to provide undeserved biological respectability for speculative theories of emotional and psychiatric functions. Brodal (1957, 1975, 1981) described the limbic system as "foggy," and as "substituting magical naming for understanding." Given his deep knowledge of neuroanatomy, Brodal's criticism should have been enough to put the concept to rest. Thankfully the term has largely been abandoned by those who wrote the relevant chapters in the second edition of *The Rat Nervous System* (Paxinos, 1995), and one hopes that the limbic system rapidly disappears from the intellectual stage, leaving the real players, the amygdala, the hypothalamus, and other basal forebrain regions, in their rightful roles (LeDoux, 1991).

The role of the brainstem in homeostatic regulation and behavior was neglected for another reason. The brainstem contains large areas in which neurons are scattered among interlacing networks of fiber bundles, with no obvious collections into easily recognized and defined nuclei. These regions were referred to as reticular formation by the early anatomists. Brodal (1957) assures us that these colleagues held no special theories concerning the specificity or otherwise of the neural connections formed by reticular neurons. In his wonderful book *The Brain of the Tiger Salamander* (1948), Herrick considered sensory, intermediate, and motor zones. The intermediate, region (the reticular formation) was seen as composed of interneurons for coordinating stereotyped responses and for integrating these with more complex behaviors. As argued in Chapter 3, there was nothing in Herrick's concept of the intermediate zone to suggest nonspecificity of neuronal connectivity. Herrick (1948:65) notes that with evolutionary development the number of intermediate-reticular neurons, and the complexity of their interactions, increased in parallel with the more complex responses of higher vertebrates and mammals: "The final result is that in the human brain the apparatus of intermediate-zone type has increased so much that it comprises more than half the weight of the brain, for both cerebral and cerebellar cortices are derivatives of this primordial matrix." By including the neocortices in his concept of the human reticular formation, Herrick emphasized his concept of the complexity and connectional specificity of the constituent neurons.

The paradigm of the reticular formation was changed when Moruzzi and Magoun introduced their concept of the "ascending reticular activating system." These investigators simply assumed that large regions of the brainstem consisted of nonspecifically interconnected neurons whose output functions as a kind of volume control for the level of arousal and consciousness. Scheibel and Scheibel bestowed anatomical respectability (see Chapter 3). The concept then became one of the most important theories of brainstem structure-function ever formulated. However, as is argued in a detailed consideration of the reticular formation in Chapters 3 and 6, and as is apparent throughout this book, the evidence now strongly indicates that neurons in the reticular formation make definable, functionally specific connections. There are no special, nonspecifically interrelated, brainstem reticular neurons. The terms reticular formation and reticular core, because of their unfortunate connotations, should be abandoned, as first suggested by Olszewski (1954) and considered by Brodal (1957). The terms could be replaced by brainstem interneurons, the denotation of this theoretically neutral term encouraging us to ask which particular neurons, in which particular region of the brainstem, are under consideration. Neurons in all brainstem regions, including those relevant

to arousal and consciousness, need to be anatomically and functionally characterized, just like other nerve cells in the brain. Even if brainstem interneurons discharge in synchronized coherent patterns, as has been proposed for other brain regions (Hebb, 1949; Steriade et al., 1991; Singer, 1993b), this does not mitigate against the specificity of their neuronal connectivity any more than the existence of a respiratory-related rhythmical discharge in hypoglossal motoneurons suggests nonspecificity of their anatomical connections.

## Conclusion

The neglect of visceral afferents by Langley, the triumph of Cannon's forebrain theory of the emotions, the limbic emphasis on the basal forebrain as mediator of these emotions, the presumed nonspecificity of the brainstem "reticular core"—each contributed to the depreciation of the role of the lower brainstem in the regulation of the *milieu interieur*. Homeostasis involves specifically patterned changes in the activity of all peripheral neurons, visceral and somatic, afferent and efferent, together with neurally mediated changes in the secretion of hormones. Regulation by Langley's "higher power" is constantly required, and only the whole brain has the complexity and inbuilt patterning for the necessary integration. We are better off without reticular, limbic, and autonomic systems. All three concepts are magical constructs reflecting our human tendency to use words as deputies for comprehension.

To study how the nervous system maintains our everyday integrity we should begin by characterizing CNS neurons in three classes: the class of neurons receiving direct inputs from visceral (broadly defined) afferents, the class of central output neurons innervating peripheral ganglionic neurons, and the class of central premotor neurons monosynaptically connected to these central output neurons. These known reference points can then be used to investigate, step by more complex step, the central loops linking these afferent and efferent viscerally connected CNS neurons. Such circuitry will underlie central command programs those genetically inbuilt and those acquired through experiences, especially the "narrow escape" experiences that powerfully affect our subsequent behavior. A complete account will integrate visceral events into all homeostatic aspects of the individual's daily life.

We must subdivide the organism in order to study it. However, our subdivisions should reflect functional and anatomical realities, and they should be temporary. As more becomes known, interrelationships will be apparent, and each subdivided portion can be reintegrated into the whole. Hughlings Jackson (1931:47) reminds us that "the highest nervous processes are potentially the whole organism." There is not one nervous system for Bichat's *vie de nutrition* and a separate system for the *vie de relation*. There is just one individual and just one nervous system.