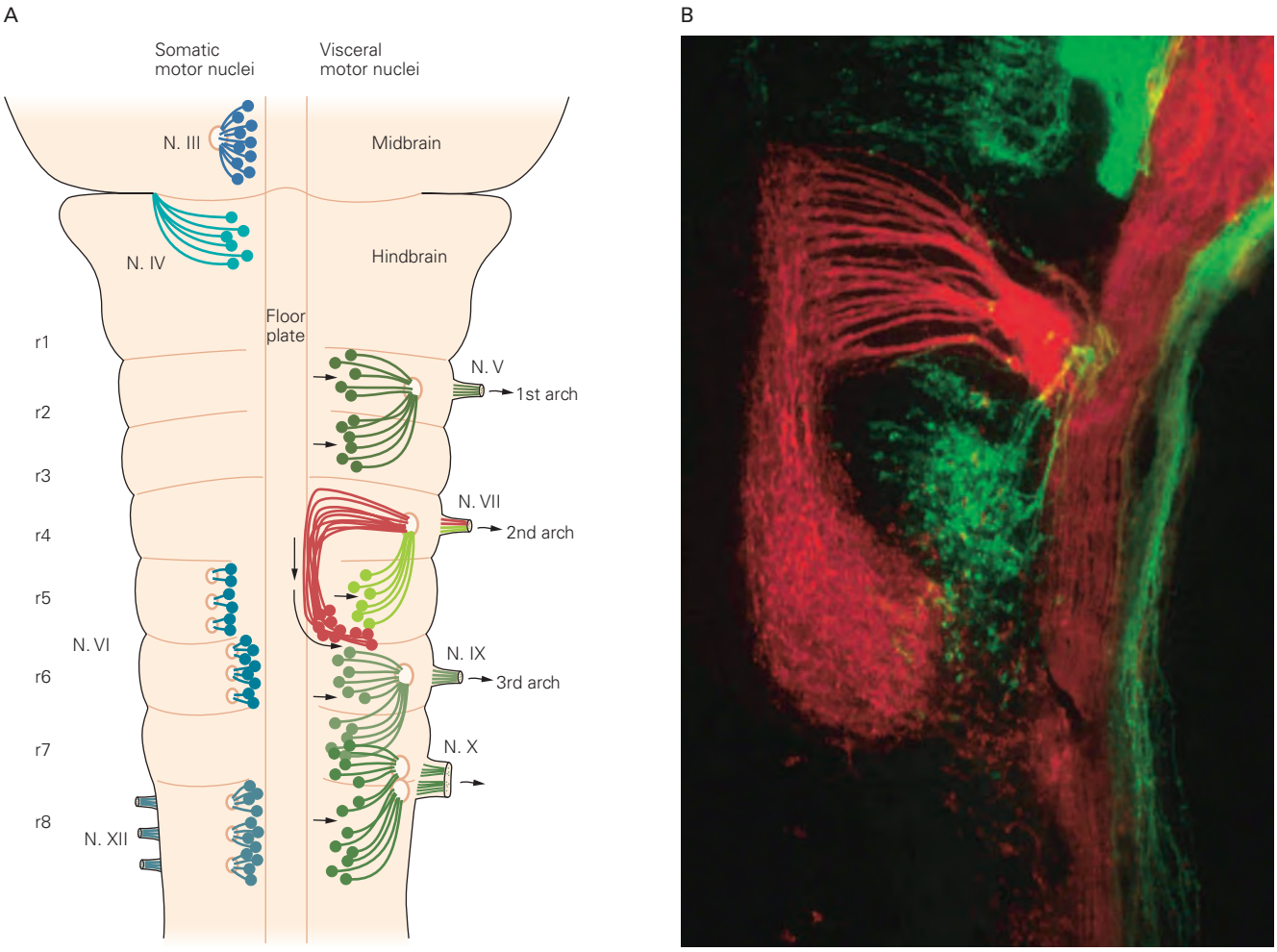

Figure 40–5 Embryonic cranial nerve nuclei are organized segmentally.

A. In the developing hindbrain (seen here from the ventral side), special and general visceral motor neurons (represented on the right side of the brain stem) form in each hindbrain segment (rhombomere) except rhombomere 1 (**r1**). Each special visceral motor nucleus comprises neurons in two rhombomeres: the trigeminal motor nucleus is formed by neurons in r2 and r3, the facial nucleus by neurons in r4 and r5, the glossopharyngeal nucleus by neurons in r6 and r7, and the motor nuclei of the vagus by neurons in r7 and r8. Axons of neurons in each of these nuclei course laterally within the brain, leaving the brain through exit points in the lateral neuroepithelium (of r2, r4, r6, and r7) and running together outside the brain to form the respective cranial motor nerves (V, VII, IX, X). The trigeminal (**V**) nerve innervates muscles in the 1st branchial arch, the facial (**VII**) nerve innervates muscles in the 2nd branchial arch, and the glossopharyngeal (**IX**) nerve innervates muscles in the 3rd branchial arch.

All of the visceral motor neurons (various shades of **green**, represented on the right side of the brain stem) develop initially next to the floor plate at the ventral midline; after extending their axons toward their respective exit points, the cell bodies then migrate laterally (**arrows**). Exceptions are the facial motor neurons formed in r4 (**red**); the cell bodies, after extending their axons toward the exit point, migrate caudally to the axial level of r6 before migrating laterally. General visceral (parasympathetic) motor neurons associated with nerve VII (**light green**) take a more conventional course (see panel **B**).

General somatic motor nuclei (**various shades of blue**, represented on the left side of the brain stem) are formed in r1 (trochlear nucleus), r5 and r6 (abducens nucleus), and r8 (hypoglossal nucleus). The cell bodies of these neurons remain close to their place of birth, next to the floor plate. The axons of abducens and hypoglossal neurons exit the brain directly ventrally, without coursing laterally. The axons of trochlear neurons (**light blue**) extend laterally and dorsally within the brain until, caudal to the inferior colliculus, they turn medially, decussate just behind the inferior colliculus, and exit near the midline of the opposite side.

B. The brain stem of a mouse embryo in which fluorescent dyes label different populations of cranial nerve VII motor neurons. A red-fluorescing dye fills the cell bodies of facial motor neurons via retrograde transport from the motor root of the facial nerve. These neurons develop initially in r4 and then migrate posteriorly, alongside the floor plate, to r6 (see **red** neurons in part **A**). A green-fluorescing dye fills the cell bodies of general visceral motor neurons in r5 (see **light green** neurons in part **A**) via retrograde transport from the root of the intermediate nerve (sensory and preganglionic general visceral motor axons). (Micrograph reproduced, with permission, from Dr. Ian McKay.)

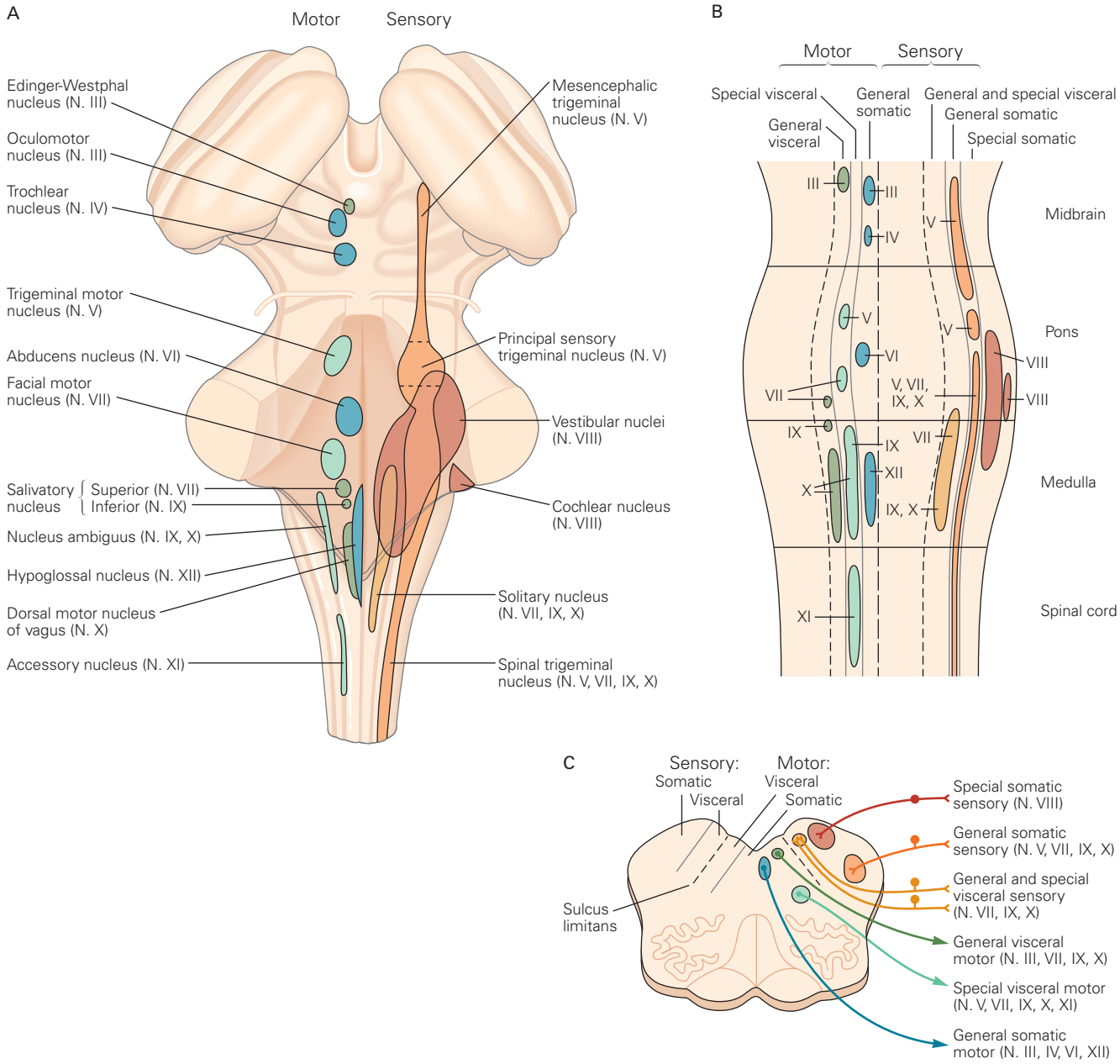

Figure 40–6 Adult cranial nerve nuclei are organized in six functional columns on the rostrocaudal axis of the brain stem.

A. This dorsal view of the human brain stem shows the location of the cranial nerve sensory nuclei (*right*) and motor nuclei (*left*).

B. A schematic view of the functional organization of the cranial nerve nuclei makes it clearer that they form motor and sensory columns.

C. The medial-lateral arrangement of the cranial nerve nuclei is shown in a cross section at the level of the medulla (compare with Figure 40–4D).

is represented ventrally and the oral region dorsally, with the tongue extending medially toward the taste region of the nucleus of the solitary tract, with which it shares some afferent information concerning food texture and temperature. Axons from the spinal trigeminal nucleus descend on the same side of the brain stem into the cervical spinal cord, where they cross the midline in the anterior commissure with spinothalamic axons and join the opposite spinothalamic tract. (For this reason, upper cervical spinal cord injury may cause facial numbness.) The trigeminothalamic axons then ascend back through the brain stem in close association with the spinothalamic tract, providing inputs to brain stem nuclei for reflex motor and autonomic responses in addition to carrying pain and temperature information to the thalamus.

The *principal sensory trigeminal nucleus* lies in the mid-pons just lateral to the trigeminal motor nucleus. It receives the axons of neurons in the trigeminal ganglion concerned with position sense and fine touch discrimination, the same types of sensory information carried from the rest of the body by the dorsal columns. The axons from this nucleus are bundled just medial to those from the dorsal column nuclei in the medial lemniscus, through which they ascend to the ventroposterior medial thalamus.

The *mesencephalic trigeminal nucleus*, located at the midbrain level in the lateral surface of the periaqueductal gray matter, relays mechanosensory information from the muscles of mastication and the periodontal ligaments. The large cells of this nucleus are not central neurons but primary sensory ganglion cells that derive from the neural crest and, unlike their relatives in the trigeminal ganglion, migrate into the brain during development. The central branches of the axons of these pseudo-unipolar cells contact motor neurons in the trigeminal motor nucleus, providing monosynaptic feedback to the jaw musculature, critical for rapid and precise control of chewing movements.

Special Somatic Sensory Column

The special somatic sensory column has inputs from the acoustic and vestibular nerves and develops from the intermediate region of the alar plate. The *cochlear nuclei* (N. VIII), which lie at the lateral margin of the brain stem at the pontomedullary junction, receive afferent fibers from the spiral ganglion of the cochlea. The output of the cochlear nuclei is relayed through the pons to the superior olivary and trapezoid nuclei and bilaterally on to the inferior colliculus (Chapter 28). The *vestibular nuclei* (N. VIII) are more complex. They include four distinct cell groups that relay information from the vestibular ganglion to various motor sites in the brain stem, cerebellum, and spinal cord concerned with maintaining balance and coordination of eye and head movements (Chapter 27).

Visceral Sensory Column

The visceral sensory column is concerned with special visceral information (taste) and general visceral information from the facial (VII), glossopharyngeal (IX), and vagus nerves (X). It is derived from the most medial tier of neurons in the alar plate. All of the afferent axons from these sources terminate in the *nucleus of the solitary tract*. The solitary tract is analogous to the spinal trigeminal tract or Lissauer's tract, bundling afferents from different cranial nerves as they course rostrocaudally along the length of the nucleus. As a result, sensory information from different regions of the viscera produces a unified map of the internal body in the nucleus.

Special visceral afferents from the anterior two-thirds of the tongue travel to the nucleus of the solitary tract through the chorda tympani branch of the facial nerve, whereas those from the posterior parts of the tongue and oral cavity arrive through the glossopharyngeal and vagus nerves. These afferents terminate in roughly somatotopic fashion in the anterior third of the nucleus of the solitary tract (or solitary nucleus). General visceral afferents are relayed through the glossopharyngeal and vagus nerves. Those from the rest of the gastrointestinal tract (down to the transverse colon) terminate in the middle portion of the solitary nucleus in topographic order, whereas those from the cardiovascular and respiratory systems terminate in the caudal and lateral portions.

The solitary nucleus projects directly to parasympathetic and sympathetic preganglionic motor neurons in the medulla and spinal cord that mediate various autonomic reflexes, as well as to parts of the reticular formation that coordinate autonomic and respiratory responses. Most ascending projections from the solitary nucleus that carry information from the viscera to the forebrain are relayed through the parabrachial nucleus in the pons, although some reach the forebrain directly. Together, the solitary and parabrachial nuclei supply visceral sensory information to the hypothalamus, basal forebrain, amygdala, thalamus, and cerebral cortex.

General Visceral Motor Column

All motor neurons initially develop adjacent to the floor plate, a longitudinal strip of non-neuronal cells

at the ventral midline of the neural tube (Chapter 45). Neurons fated to become the three types of brain stem motor neurons migrate dorsolaterally, settling in three distinct rostrocaudal columns. The neurons that form the general visceral motor column take up a position along the most lateral region of the basal plate, just medial to the sulcus limitans. During development, the parasympathetic motor neurons destined to join the superior salivatory nucleus (part of the facial nerve) and nucleus ambiguus (part of the vagus nerve) migrate ventrolaterally, leaving behind axons that ascend medially before turning laterally to exit the brain stem, in a course similar to the facial motor neurons.

The *Edinger-Westphal nucleus* (N. III) lies in the midline separating the somatic oculomotor neurons just below the floor of the cerebral aqueduct. It contains preganglionic neurons that control pupillary constriction and lens accommodation through the ciliary ganglion.

The *superior salivatory nucleus* (N. VII) lies just dorsal to the facial motor nucleus and comprises parasympathetic preganglionic neurons that innervate the sublingual and submandibular salivary glands and the lacrimal glands and intracranial circulation through the sphenopalatine and submandibular parasympathetic ganglia.

Parasympathetic preganglionic neurons associated with the gastrointestinal tract form a column at the level of the medulla just dorsal to the hypoglossal nucleus and ventral to the nucleus of the solitary tract. At the most rostral end of this column is the *inferior salivatory nucleus* (N. IX) comprising the preganglionic neurons that innervate the parotid gland through the otic ganglion. The rest of this column constitutes the *dorsal motor vagal nucleus* (N. X). Most of the preganglionic neurons in this nucleus innervate the gastrointestinal tract below the diaphragm; a few are cardiomotor neurons.

The *nucleus ambiguus* (N. X) runs the rostrocaudal length of the ventrolateral medulla and contains parasympathetic preganglionic neurons that innervate thoracic organs, including the esophagus, heart, and respiratory system, as well as special visceral motor neurons that innervate the striated muscle of the larynx and pharynx, and neurons that generate respiratory motor patterns (see later in chapter). The parasympathetic preganglionic neurons are organized in topographic fashion, with the esophagus represented most rostrally and dorsally.

Special Visceral Motor Column

The special visceral motor column includes motor nuclei that innervate muscles derived from the branchial (pharyngeal) arches. Because these arches are homologous to the gills in fish, the muscles are considered special visceral muscles, even though they are striated. During development, these cell groups migrate to an intermediate position in the basal plate and are eventually located ventrolaterally in the tegmentum.

The *trigeminal motor nucleus* (N. V) lies at midpontine levels and innervates the muscles of mastication. Nearby in separate clusters are located the *accessory trigeminal nuclei* that innervate the tensor tympani, tensor veli palatini, and mylohyoid muscles, and the anterior belly of the digastric muscle.

The *facial motor nucleus* (N. VII) lies caudal to the trigeminal motor nucleus at the level of the caudal pons and innervates the muscles of facial expression. During development, facial motor neurons migrate medially and rostrally around the medial margin of the abducens nucleus before turning laterally, ventrally, and caudally toward their definitive position at the pontomedullary junction (Figure 40–5A). This sinuous course that the axons leave behind forms the *internal genu of the facial nerve*. The adjacent *accessory facial motor nuclei* innervate the stylohyoid and stapedius muscles and the posterior belly of the digastric muscle.

The nucleus ambiguus contains branchial motor neurons with axons that run in the glossopharyngeal and vagus nerves. These neurons innervate the striated muscles of the larynx and pharynx. During development, these motor neurons migrate into the ventrolateral medulla, and as a consequence, their axons run dorsomedially toward the dorsal motor vagal nucleus, then turn sharply within the medulla to exit laterally, similar to the course of the facial motor axons.

General Somatic Motor Column

The neurons of the somatic motor column migrate the least during development, remaining close to the ventral midline. The *oculomotor nucleus* (N. III) lies at the midbrain level; it consists of five rostrocaudal columns of motor neurons innervating the medial, superior, and inferior rectus muscles, the inferior oblique muscle, and the levator of the eyelids. The motor neurons for the medial and inferior rectus and inferior oblique muscles are on the side of the brain stem from which the nerve exits, whereas those for the superior rectus are on the opposite side. The levator motor neurons are bilateral.

The *trochlear nucleus* (N. IV), which innervates the trochlear muscle, lies at the midbrain/rostral pontine level on the side of the brain stem opposite from

which the nerve exits. The *abducens nucleus* (N. VI), which innervates the lateral rectus muscle, is located at the midpontine level. The *hypoglossal nucleus* (N. XII) in the medulla consists of several columns of neurons, each of which innervates a single muscle of the tongue.

The Organization of the Brain Stem Differs From the Spinal Cord in Three Important Ways

One major difference between the organization of the brain stem and that of the spinal cord is that many long ascending and descending sensory tracts that run along the outside of the spinal cord are incorporated within the interior of the brain stem. Thus, the ascending sensory tracts (the medial lemniscus and spinothalamic tract) run through the reticular formation of the brain stem, as do the auditory, vestibular, and visceral sensory pathways.

A second major difference is that in the brain stem, the cerebellum and its associated pathways form additional structures that are superimposed on the basic plan of the spinal cord. Fibers of the cerebellar tracts and nuclei are bundled with those of the pyramidal and extrapyramidal motor systems to form a large ventral portion of the brain stem. Thus, from the midbrain to the medulla, the brain stem is divided into a dorsal portion, the tegmentum, which follows the basic segmental plan of the spinal cord, and a ventral portion, which contains the structures associated with the cerebellum and the descending motor pathways. At the level of the midbrain, the ventral (motor) portion includes the cerebral peduncles, substantia nigra, and red nuclei. The base of the pons includes the pontine nuclei, corticospinal tract, and middle cerebellar peduncle. In the medulla, the ventral motor structures include the pyramidal tracts and inferior olivary nuclei.

A third major difference is that, although the hindbrain is segmented into rhombomeres during development, there is no clear repeating pattern in the adult brain. In contrast, the spinal cord is not segmented during development, but the final pattern consists of repeating segments. The prominent ladder-like arrays of ventral root axons and dorsal root ganglia suggest that segmentation is imposed by a polarizing effect of the adjacent body segments, or somites into which they migrate—in each somite, the rostral part attracts axonal growth cones and neural crest cells, whereas the caudal part is repulsive. In the head, such patterning is lacking as the cranial mesoderm is not segmented into somites but rather develops under the influence of the rhombomeres.

Neuronal Ensembles in the Brain Stem Reticular Formation Coordinate Reflexes and Simple Behaviors Necessary for Homeostasis and Survival

In the 19th century, Charles Darwin pointed out in his book *The Expression of the Emotions in Man and Animals* that the muscles of facial expression are activated in similar patterns in all mammals during similar emotional situations (fear, anger, disgust, happiness). He hypothesized that the patterns of facial expression must be deeply embedded in the organization of the brain stem. We now recognize that a wide range of reflexes and simple, repetitive, coordinated behaviors, such as facial emotional expression, breathing, and eating, are controlled by neurons in the brain stem reticular formation called *pattern generators*, which produce stereotyped innate responses. Impairment of cranial nerve reflexes and motor patterns in patients with neurological disease can indicate the precise site of brain stem damage.

Cranial Nerve Reflexes Involve Mono- and Polysynaptic Brain Stem Relays

The responses of the pupils to light (*pupillary light reflexes*) are determined by the balance between sympathetic tone in the pupillodilator muscles and parasympathetic tone in the pupilloconstrictor muscles of the iris. Sympathetic tone is maintained by postganglionic neurons in the superior cervical ganglion, which in turn are innervated by preganglionic neurons in the first and second thoracic spinal segments. Parasympathetic tone is supplied by postganglionic ciliary ganglion cells under the control of preganglionic neurons in the Edinger-Westphal nucleus and adjacent areas of the midbrain.

Light impinging on the retina activates a special class of retinal ganglion cells that act as brightness detectors. These cells receive inputs from photopigment-containing rod and cone cells, but they also have their own photopigment, melanopsin, which allows them to respond to light even when the rods and cones have degenerated. These cells send their axons through the optic nerve, chiasm, and tract to the olivary pretectal nucleus, where they terminate on neurons whose axons project to preganglionic neurons in the Edinger-Westphal nucleus (Figure 40–7). Thus, injury to the dorsal midbrain in the region of the posterior commissure can prevent pupillary light responses (midposition, fixed pupils), whereas injury to the oculomotor nerve eliminates parasympathetic tone to that pupil (fixed and dilated pupil). The melanopsin-containing

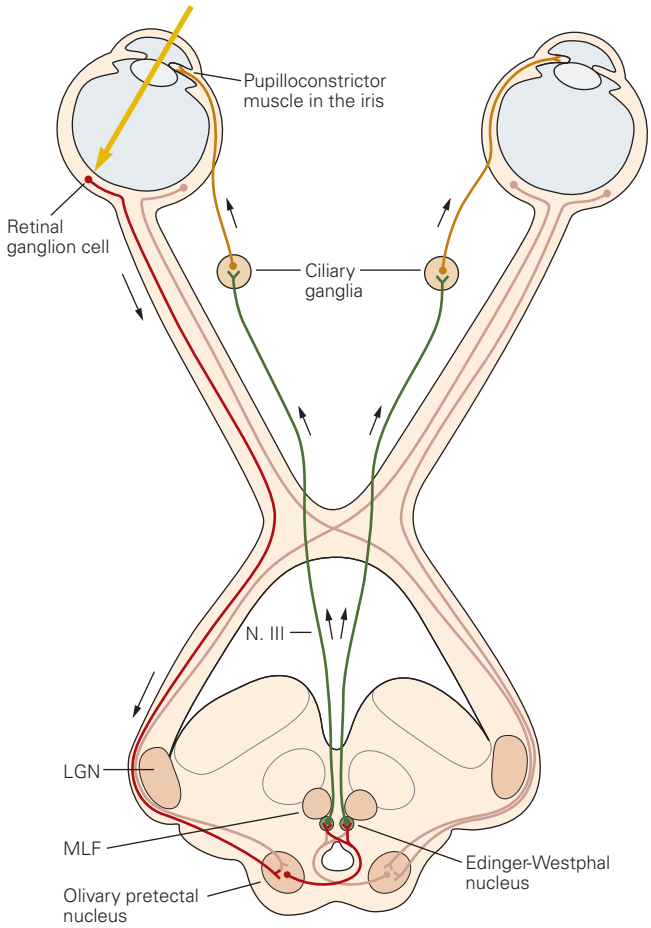

Figure 40–7 The pupillary response to light is mediated by parasympathetic innervation of the iris. Retinal ganglion cells that contain the photopigment melanopsin act as luminance detectors, sending their axons through the optic tract to the olivary pretectal nucleus, at the junction of the midbrain and the thalamus. Neurons in this nucleus project through the posterior commissure to parasympathetic preganglionic neurons in and around the Edinger-Westphal nucleus. The axons of the preganglionic cells exit with the oculomotor (III) nerve and contact ciliary ganglion cells, which control the pupilloconstrictor muscle in the iris. (Abbreviations: LGN, lateral geniculate nucleus; MLF, medial longitudinal fasciculus.)

retinal ganglion cells also project to the suprachiasmatic nucleus of the hypothalamus, where they entrain circadian rhythms to the day–night cycle (Chapter 44).

Vestibulo-ocular reflexes stabilize the image on the retina during head movement by rotating the eyeballs counter to the rotation of the head. These reflexes are activated by pathways from the vestibular ganglion and nerve to the medial, superior, and lateral vestibular nuclei, and from there to neurons in the reticular formation and ocular motor nuclei that coordinate eye movements. The reflex movements are seen most clearly in comatose patients, in whom turning the head will elicit counter-rotational movements of the eyes (so-called doll's eye movements). Damage to these pathways in the pons impairs these movements.

The *corneal reflex* involves closure of both eyelids as well as upward turning of the eyes (Bell phenomenon) when the cornea is gently stimulated (eg, with a wisp of cotton). The sensory axons from the first division of the trigeminal nerve terminate in the spinal trigeminal nucleus, which relays the sensory signals to pattern generator neurons in the reticular formation adjacent to the facial motor nucleus. The pattern generator neurons provide bilateral inputs to the motor neurons that protect the cornea from damage by causing the orbicularis oculi muscle to close the eyelid and the oculomotor nuclei to roll the eyes upward and back in the orbit. Because the output of the pattern generator is bilateral, damage along the sensory pathway prevents the reflex in both eyes, whereas damage to the facial nerve prevents closure on the same side only.

The *stapedial reflex* contracts the stapedius muscle in response to a loud sound, thus damping movement of the ossicles. The sensory pathway is through the cochlear nerve and nucleus to the reticular formation adjacent to the facial motor nucleus and from there to the stapedial motor neurons, which run in the facial nerve. As described earlier, in patients with injury to the facial nerve (eg, Bell palsy), the stapedial reflex is impaired, and the patient complains that sounds in that ear have a "booming" quality (hyperacusis).

A variety of gastrointestinal reflexes are controlled by multisynaptic brain stem relays. For example, the tasting of food causes neurons in the solitary nucleus that project to the reticular formation adjacent to the motor facial and dorsal motor vagal nuclei to stimulate the preganglionic salivary neurons. The contact of food in the mouth can also elicit gastric contractions and acid secretion, presumably through inputs from the solitary nucleus directly to parasympathetic preganglionic gastric neurons in the dorsal motor vagal nucleus. In patients who have had Bell palsy, the damaged VII nerve parasympathetic axons may regrow aberrantly so that salivary axons reach the lacrimal gland in error, causing tasty food to initiate reflex tearing (crocodile tears).

The *gag reflex* protects the airway in response to stimulation of the posterior oropharynx. The afferent sensory fibers in the glossopharyngeal and vagus nerves terminate in the spinal trigeminal nucleus, whose axons project to the reticular formation adjacent to the nucleus ambiguus. Branchial motor neurons in the nucleus ambiguus innervate the posterior pharyngeal muscles, resulting in elevation of the

palate, constriction of pharyngeal muscles (to expel the offending stimulus), and closure of the airway. Loss of the gag reflex on one side of the throat indicates injury to the medulla or to cranial nerve X on that side (cranial nerve IX has such a small territory of sensory and motor innervations in the pharynx that transection of this nerve does not cause a noticeable deficit).

Pattern Generators Coordinate More Complex Stereotypic Behaviors

As Darwin proposed, pools of pattern generator neurons in the reticular formation adjacent to the facial nucleus control facial emotional expression through stereotypic patterns of contraction of facial muscles simultaneously on the two sides of the face. Pattern generator neurons on each side of the brain stem project to the facial motor neurons on both sides of the brain, so that spontaneous facial expressions are virtually always symmetric. Even patients who have had major strokes in the cerebral hemispheres and cannot voluntarily move the contralateral orofacial muscles still tend to smile symmetrically when they hear a joke and can raise their eyebrows symmetrically, both of which are initiated by facial pattern generators.

Similarly, orofacial movements involved in eating are produced by pattern generator neurons in the reticular formation near the cranial motor nuclei that mediate the behaviors. Licking movements are organized in the reticular formation near the hypoglossal nucleus, chewing movements near the trigeminal motor nucleus, sucking movements near the facial and ambiguus nuclei, and swallowing near the nucleus ambiguus. Not surprisingly, neurons in these reticular areas are closely interconnected with each other and receive inputs from the part of the nucleus of the solitary tract concerned with taste and from the part of the spinal trigeminal nucleus concerned with tongue and oral sensation, as well as from neurons in the adjacent reticular formation that respond to more complex combinations of taste, texture, and temperature of food. As a result, even a decerebrate rat is able to make appropriate choices of which foods to swallow and which to reject.

Vomiting is another example of a coordinated response mediated by pattern generator neurons. Toxic substances in the blood stream can be detected by nerve cells in the area postrema, a small region adjacent to the nucleus of the solitary tract along the floor of the fourth ventricle. Unlike most of the brain, which is protected by a blood–brain barrier, the area postrema contains fenestrated capillaries that allow its neurons to sample the contents of the blood stream. These neurons, when they detect a toxin, activate a pool of neurons in the ventrolateral medulla that control a pattern of responses that clears the digestive tract of any poisonous substances. These responses include reversal of peristalsis in the stomach and esophagus, increased abdominal muscle contraction, and activation of the same motor patterns used in the gag reflex to clear the oropharynx of unwanted material.

A variety of responses organized by the brain stem require coordination of cranial motor patterns with autonomic and sometimes endocrine responses. A good example is the *baroreceptor reflex*, which ensures an adequate blood flow to the brain (Chapter 41). The nucleus of the solitary tract receives information about stretch of the aortic arch through the vagus (X) nerve and stretch of the carotid sinus through the glossopharyngeal (IX) nerve. This information is relayed to neurons in the ventrolateral medulla that produce a coordinated response that protects the brain against a fall in blood pressure.

Reduced stretch of the aortic arch and carotid sinus reduces drive to the parasympathetic preganglionic cardiac-vagal neurons in the nucleus ambiguus, resulting in reduced vagal tone and increased heart rate. Simultaneously, increased firing of neurons in the rostral ventrolateral medulla drives sympathetic preganglionic vasoconstrictor and cardioaccelerator neurons. This combination of increased cardiac output and increased vascular resistance elevates blood pressure. Meanwhile, other neurons in the ventrolateral medulla increase the firing of hypothalamic neurons that secrete vasopressin from their terminals in the posterior pituitary gland. Vasopressin also has a direct vasoconstrictor effect, and it maintains blood volume by reducing water excretion through the kidney.

Control of Breathing Provides an Example of How Pattern Generators Are Integrated Into More Complex Behaviors

One of the most important functions of the brain stem is control of breathing. The brain stem automatically generates breathing movements beginning in utero at 11 to 13 weeks of gestation in humans, and continues nonstop from birth until death. This behavior does not require any conscious effort, and in fact, it is rare for us to even think about the need to breathe. The primary purpose of breathing is to ventilate the lungs to control blood levels of oxygen, carbon dioxide, and hydrogen ions (pH). (These are often measured together clinically and referred to as "blood gases.") Breathing movements involve contraction of the diaphragm, activated by the phrenic nerve. The diaphragm is assisted

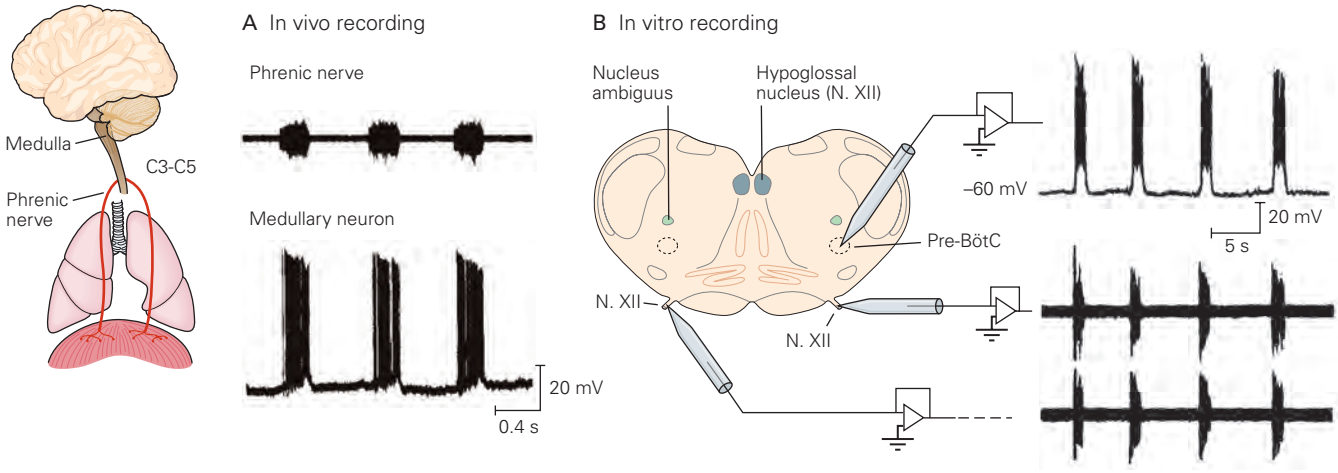

Figure 40–8 Rhythmic breathing is generated within the medulla.

A. Rhythmic activity in the phrenic motor nerve of a guinea pig causes contraction of the diaphragm. The firing of the phrenic nerve is phase-locked to bursts of firing by neurons in the medulla. The activity in a single medullary neuron, recorded intracellularly, is shown. (Reproduced, with permission, from Richerson and Getting 1987. Copyright © 1987. Published by Elsevier B.V.)

B. Similar rhythmic firing can be recorded in vitro from accessory respiratory nerves, such as the hypoglossal (**XII**) nerve. The minimal tissue necessary to support this rhythm is a slice about 0.5 mm thick at the level of the rostral medulla. Neurons in the pre-Bötzinger complex (**Pre-BötC**) near the nucleus ambiguus fire bursts that are phase-locked to the motor rhythm. (Reproduced, with permission, from Smith et al. 1991. Copyright © 1991 AAAS.)

when necessary by accessory muscles of respiration, including the intercostal muscles, pharyngeal muscles (to change airway diameter), some neck muscles (which help expand the chest), the tongue protruder muscles (to open the airway), and even some facial muscles (which flare the nares).

Respiratory activity can be generated by the medulla even when it is isolated from the rest of the nervous system. Many medullary neurons have patterns of firing that correlate with inspiration or expiration (Figure 40–8A). Some have more refined patterns, such as firing only during early inspiration or late inspiration. These respiratory neurons are concentrated in two regions, the dorsal and ventral respiratory groups.

The *dorsal respiratory group* is located bilaterally in and around the ventrolateral part of the nucleus of the solitary tract. Neurons in this group receive respiratory sensory input, including afferents from stretch receptors in the lungs and peripheral chemoreceptors, and participate in such reflex actions as limitation of lung inflation at high volume (the Hering-Breuer reflex) and the ventilatory response to low oxygen (*hypoxia*). The *ventral respiratory group*, a column of neurons in and around the nucleus ambiguus, coordinates respiratory motor output. Some of these neurons are motor neurons with axons that leave the brain through the vagus nerve and innervate accessory muscles of respiration or premotor neurons that innervate the phrenic motor nucleus, whereas others form a pattern generator, the *pre-Bötzinger complex*, that generates respiratory rhythm.

The intrinsic rhythmicity of the pre-Bötzinger complex is so resilient that, even in a transverse brain slice from the rostral medulla, neurons in the pre-Bötzinger complex are able independently to generate a respiratory rhythm that can be recorded in the rootlets of the hypoglossal (XII) nerve that emerge from the ventral surface of the slices (Figure 40–8B). Acute destruction of this cell group in an intact animal results in inability to maintain a normal respiratory rhythm.

The most important inputs to the respiratory pattern generator come from chemoreceptors that sense oxygen and carbon dioxide. Under normal conditions, ventilation is primarily regulated by the levels of CO_2 rather than O_2 (Figure 40–9A). However, breathing is also strongly stimulated if O_2 becomes sufficiently low, such as at high altitude or in people with lung disease. The peripheral chemoreceptors in the carotid and aortic bodies normally respond primarily to a decrease in blood oxygen, but during hypoxia, they also become more sensitive to elevated levels of CO_2 (*hypercapnia*). Afferent fibers from the carotid sinus nerve travel in the glossopharyngeal nerve and activate neurons in the dorsal respiratory group.

The response to hypercapnia is largely driven by *central chemoreceptors* in the brain stem that sense the

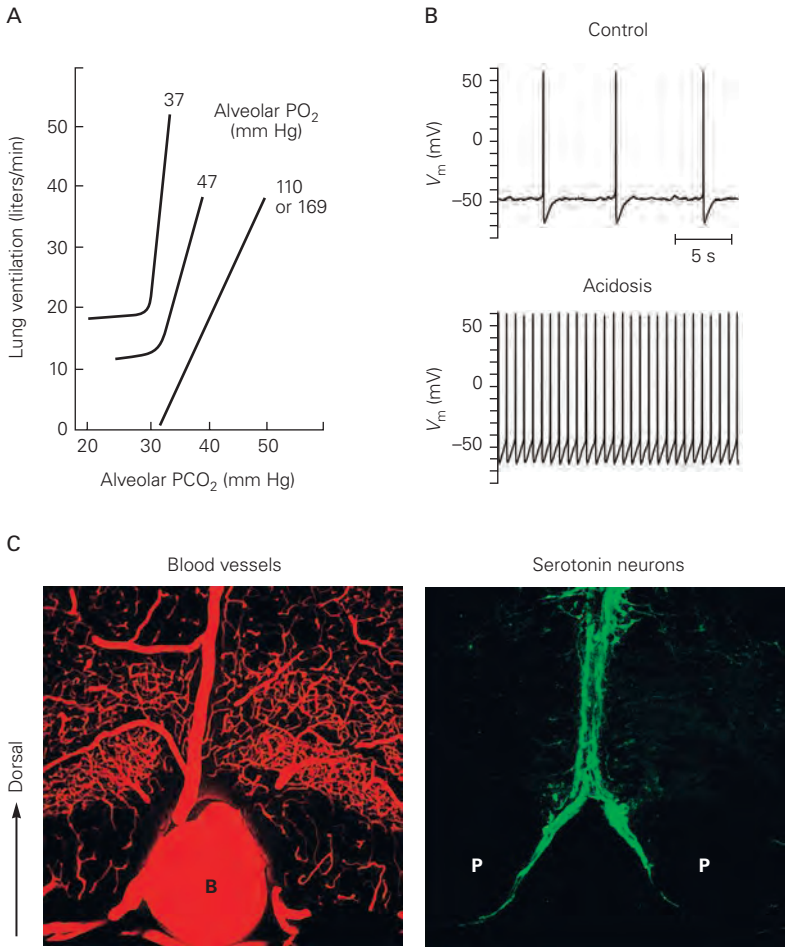

Figure 40–9 Respiratory motor output is regulated by carbon dioxide in the blood.

A. Lung ventilation (determined by the rate and depth of breathing) in humans is steeply dependent on the partial pressure of carbon dioxide (PCO_2) at normal levels of the partial pressure of oxygen (PO_2) (>100 mm Hg). When PO_2 drops to very low values (<50 mm Hg), breathing is stimulated directly and also becomes more sensitive to an increase in PCO_2 (seen here as an increase in the slope of the curves for alveolar PO_2 of 37 and 47 mm Hg). (Reproduced, with permission, from Nielsen and Smith 1952.)

B. Central chemoreceptors in the medulla control ventilatory motor output to maintain normal blood CO_2. The firing rate of serotonergic neurons within the raphe nuclei of the medulla increases when elevated PCO_2 causes a pH decrease. The records shown here are from in vitro recordings of a neuron in the raphe nuclei of a rat at two different levels of pH (7.4, control, and 7.2, acidosis). (Reproduced, with permission, from Wang et al. 2002.)

C. Serotonergic neurons are closely associated with large arteries in the ventral medulla where they can monitor local changes in PCO_2. Two images of the same transverse section of the rat medulla show blood vessels after injection of a red fluorescent dye into the arterial system (*left*) and green antibody staining for tryptophan hydroxylase, the enzyme that synthesizes serotonin (*right*). The basilar artery (**B**) is on the ventral surface of the medulla between the pyramidal tracts (**P**). (Reproduced, with permission, from Bradley et al. 2002. Copyright © 2002 Springer Nature.)

accompanying decrease in pH. The most sensitive area for this is along the ventral surface of the medulla lateral to the pyramidal tract. This region contains at least two sets of neurons that respond to elevated CO_2. Glutamatergic neurons in the retrotrapezoid nucleus in the rostral ventrolateral medulla, near the facial motor nucleus, are highly sensitive to CO_2 levels. Absence of these neurons, due to a mutation in the phox2b transcription factor required for their development, causes congenital central hypoventilation syndrome, in which there is failure to breathe adequately, particularly during sleep. In addition, serotonergic neurons in the rostral ventrolateral medulla, like retrotrapezoid neurons, lie along penetrating arteries and are sensitive to acidosis (Figure 40–9B,C). Genetic deletion of these neurons reduces the ventilatory response to hypercapnia, especially during sleep. Recent studies demonstrate that a serotonin 5-HT_{2A} agonist can restore arousal responses to CO_2, suggesting that the serotonergic neurons play a modulatory role, increasing the sensitivity of the CO_2 reflexes during hypercapnia, and that this may be especially important during sleep.

The motor pattern generated by the respiratory system is remarkably stable in healthy people, but a variety of diseases can alter these patterns. One of the most common and easily recognized patterns is Cheyne-Stokes respiration, which is characterized by repeated cycles of gradually increasing then decreasing ventilation, alternating with cessation of breathing (apnea). This periodic breathing is seen, for example, in congenital central hypoventilation syndrome, where the central neurons are not sufficiently sensitive to rising CO_2, particularly during sleep. By the time they begin to respond, CO_2 levels may already be quite high. This causes hyperventilation, which reduces CO_2 levels below the threshold where breathing is required. The result is a period of apnea, until the CO_2 levels again become quite high (Figure 40–10).

A similar pattern is seen in people who have cardiac or pulmonary disease that increases the time it takes for the change in alveolar CO_2 to register with the medulla. Cheyne-Stokes respiration often occurs in hospitalized patients with marginal cardiac or respiratory reserve when they fall asleep, thus reducing