



The Meninges

12

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The story of the meninges is simple but complex. The basic components that make these layers are present from the moment the neural tube closes. But the different neuromeric levels from which these tissues arise impart create in the dura genetically distinct zones that are clinically relevant for the production of cranial bone. At the same time, it is impossible to discuss the dura without including the cutaneous coverage of the calvarium. Each layer has a developmentally distinct blood supply and sensory innervation. These differences have significance for the understanding of craniosynostosis and other anomalies of skeletal development.

We shall begin our discussion by first *defining the layers* of meninges as they exist in the fully formed organism. Next, a *timeline of embryonic stages* is presented, representing major events in the formation of tissue sources (neural crest and craniofacial mesoderm) and key surrounding structures (pharyngeal arches and CNS landmarks). Description of the *components of the meninges* emphasizes the dura but with a coda regarding the pia-arachnoid. A *narrative* of meningeal development follows. Finally, the *spatial relationships of the scalp, fascia, and dura* in the context of neurovascular planes.

Note that cranial meningeal development differs substantially from that of the spinal cord. The latter system is more simplistic and we shall refer to it as needed. For further information regarding the spinal subject of the spinal meninges, the reader is referred to a recent review of the subject.

Before beginning, we should bear caveat in mind when thinking about meningeal layers: (1) meninges consist of different cell populations but are initially a single stratum, (2) meningeal layers form, not as a consequence of the different cell populations, but as the result of differing distances from signals arising from either the underlying brain or the overlying soft tissues.

Layers of Meningeal Strata

The strata of the meninges are divided classically into three developmental layers: (1) an external thick *pachymeninx* which comprises the substance of the dura mater, (2) a delicate internal *leptomeninginx*, comprising the arachnoid barrier layer and the fibers making up the subarachnoid space; and (3) the *pia mater* (although in the literature pia is frequently lumped in with leptomeninginx) [Figs. 12.1, 12.2, 12.3 and 12.4].

From a developmental standpoint, this old terminology can be simplified as follows. The original mesenchyme surrounding the neural tube is known as the *meninx primitiva*. Under signals from the underlying brain and overlying epithelium the meninx primitive develops in two layers: (1) endomeninx, which differentiates into the leptomeninges, pia and arachnoid; and (2) ectomeninx, a three-layer dura. Because dura is the primary source for calvarial bone, an old term for ectomeninx, *pachymeninx*, has been used to describe the so-called skeletogenous layer.

The mesenchymal composition of the membranes of the brain, skull, and spinal cord varies along the neuraxis. Leptomeninges are a simple matter. They cover the entire CNS and are an admixture of local paraxial mesoderm (blood vessel endothelial cells) and local neural crest (blood vessel pericytes and stroma). Dura is another matter. Supratentorial dura, including tentorium cerebelli, is again a mix with neural crest predominant but is strictly limited to forebrain. Midbrain, cerebellum, and hindbrain have no dura. Despite its name, tentorium cerebelli has no anatomic relationship with the leptomeninges of the cerebellum. Posterior fossa is lined by periosteum derived from paraxial mesoderm. It has no dura. At the orifice of the foramen magnum, dura reappears, descending to cover the leptomeninges of the spinal cord. Spinal dura does not form bone. The periosteal lining of the vertebrae is PAM originating from the somites.

Big picture idea: Periosteum represents the stem cell layer surrounding bone laid down by whatever mesenchymal source produces the bone in the first place.

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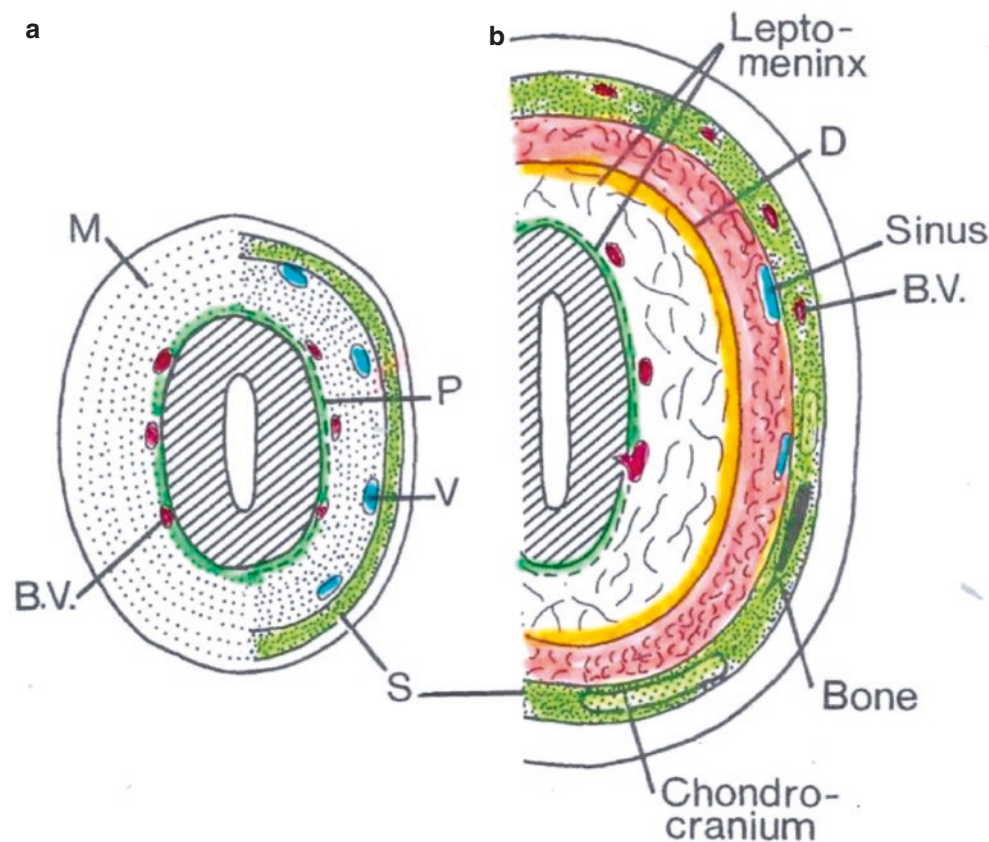


Fig. 12.1 Layers of the meninges. **a.** Mesenchyme (M) of paraxial mesoderm and (in the forebrain) neural crest surrounds the neural tube. It differentiates into layers depending upon the distance from the underlying neuroepithelium. Paraxial mesoderm is present from the very beginning. It accompanies the neural tube as soon as it rolls up during stages 8-9. It is admixed with neural crest in stages 9-10 and surrounds the neural tube. Blood vessels develop when the endothelial cells form tubes and are ensheathed by pericytes. Around the periphery, a layer of vascularized pia develops. Endothelial cells also migrate through the neuropil, seeking out the ventricular layer. They leave behind them a

trail of signals attracting pericytes to follow them “down into the hole,” thereby creating penetrating blood vessels between the surface and the periphery. A dense ectomeninx, skeletogenous layer (S), forms at the periphery. Deep to the ectomeninx, venous sinuses develop. **b.** Dural limiting layer D appears between the pia and the ectomeninx. Mesenchyme between pia and D becomes arachnoid. Bone or cartilage forms in the skeletogenous layer. [Reprinted from O’Rahilly R, Müller F. The meninges in human development. *J Neuropath Exp Neurol* 1986; 45(5):588–608. With permission from Oxford University Press.]

Dura mater consists of three layers. Let’s describe these structures, one-by-one, moving from external to internal: periosteum (endosteum), dura propria, and dural limiting membrane. These are referred to, collectively, as *dura*.

As one reflects the skull away from the periosteum one perceives the first layer: the **internal periosteum**, a delicate, nearly transparent endosteum. Lying subjacent to it are the meningeal arteries, lymphatics, and sensory nerves. The presence of the internal periosteal layer explains why surgical separation of the cranial bone from dura is so simple. It is virtually bloodless....but not quite. At surgery, small punctate bleeding points are seen over the surface of the periosteal layer marking the interruption of delicate vessels that extend outwards from meningeal vessels through the periosteum and into bone.

As we shall see, the meninges constitute a protective niche for stem cells. The internal periosteum represents a

stem cell layer “donated” to calvarial bone from the dura. On the other hand, the external periosteum is also “donated” to the bone, this time by the neural crest fascia surrounding muscles, either from Sm4 (mastication) or from Sm6 (muscles of animation). The two stem cell layers (intracranial and extracranial) are continuous with one another via foramina and sutures. In sum, membranous calvarial bones are bilateral structures synthesized by stem cells from biologically different sources.

Meningeal arteries and veins are readily seen coursing between the thin internal periosteum and the underlying dura. These consist of endothelial tubes from PAM surrounded by pericytes of neural crest origin (*vide infra*). Although meningeal vessels send small branches outward to the endosteum and more larger branches inward into the dura mater propria, they are not fused with either layer. Epidural veins drain into dural vessels.

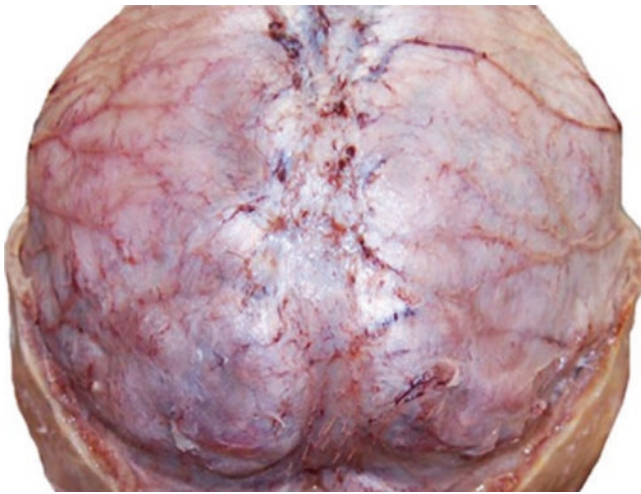


Fig. 12.2 Outer two layers of dura showing thin translucent internal periosteum covering over meningeal arteries running on the surface of dura propia. [Reprinted from Adeeb N, Mortazavi MM, Tubbs RS, Cohen-Gadol AA. The cranial dura mater: a review of its history, embryology, and anatomy. *Childs Nerv Syst* 2012; 28:827–837. With permission from Springer Nature.]

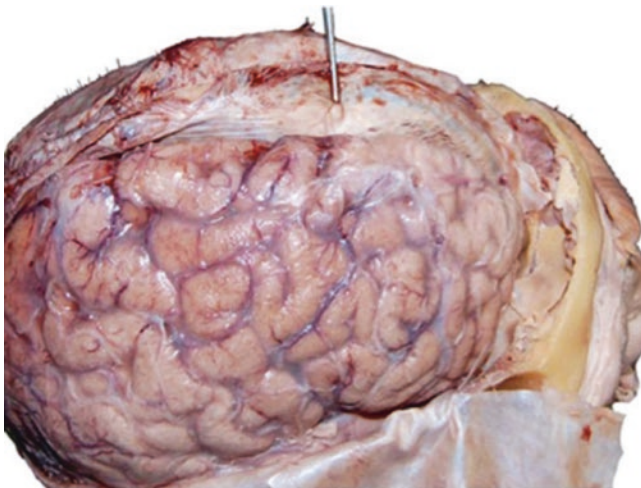


Fig. 12.3 Dura propia has dural limiting membrane fused to its under-surface. *Internal cerebral veins* are seen through the filmy *arachnoid limiting membrane*. Bridging veins between these vessels cross the *dural limiting membrane* to enter the subdural space. Here they can be traumatized to cause a subdural hematoma. [Reprinted from Adeeb N, Mortazavi MM, Tubbs RS, Cohen-Gadol AA. The cranial dura mater: a review of its history, embryology, and anatomy. *Childs Nerv Syst* 2012; 28:827–837. With permission from Springer Nature.]

The second layer is ***dura propia***. It is tough and thick. It is in continuity at foramen magnum with spinal cord dura. At sites of entry or exit of nerves and arteries, dura is continuous with epineuria, exemplified by optic nerve and adventitia. It contains veins subjacent to dura mater, and the subdural veins are encountered.

The mesenchyme of the cerebral dura is composed of neural crest and paraxial mesoderm from neuromeres (r1-



Fig. 12.4 Histology of meninges: *Dura mater propia* (intense dark pink) has distinct *dural limiting membrane* (faint pink) that is separated by a *subdural space* from *arachnoid limiting membrane* (dark pink) which is several cell layers thick. On left, vessel in the subarachnoid space penetrates brain substance. Arachnoid has no basal layer and does not follow the vessel. Pia mater ensheaths the vessel, defining the subarachnoid space into the brain and permitting circulation of the CSF. Pia is impermeable to fluid. In subarachnoid hemorrhage, red cells never have contact with the brain. [© 2020 The Regents of the University of Michigan. For information, questions or permission request please contact: Michael Hortsch, Ph.D. University of Michigan Medical School. Email: hortsch@umich.edu]

r3). Dura of the falx is more simplistic, being r1 at both ends of a central r2-r3 zone. Tentorium cerebelli is an exclusively r1 structure. Beneath the tentorium, dura as a covering for the remainder of the brain ceases to exist. Midbrain, cerebellum, and hindbrain are enveloped by meninges (pia and arachnoid), they have no dura mater. The lining of the cranial fossa below the tentorium is internal periosteum, not dura, and is composed of paraxial mesoderm. Finally, beginning at the level of foramen magnum, *spinal cord dura* is exclusively paraxial mesoderm beginning with neuromeric level c2 and continuing down the length of the neuraxis.

The third and final layer of dura we encounter is the ***dural limiting membrane***. It represents the inner layer of ectomeninx. This structure is important for three reasons. First, its appearance defines the differentiation of secondary meninx from primary matrix. Second, it is readily identifiable on light microscopy and it serves as a marker for the spatiotemporal development of dura. Third, its anatomic relationship with underlying arachnoid provides an explanation for surgical bleeding.

Dural limiting membrane is the external lamina of a structure approximately two to eight cell layers thick, termed the *subdural mesothelium* or (erroneously) *arachnoid membrane*. It is composed of the external dural limiting membrane and an internal *arachnoid barrier layer*. Under normal conditions these layers are collapsed together: there is no “subdural space.”

The leptomeninx begins with the *arachnoid barrier layer*, the outer boundary of endomeninx. Just deep into the interface layer one encounters a network of arachnoid cells interlaced with collagen fibers. The mesenchyme of these layers is likely to originate from neural crest admixed with PAM which furnishes the endothelial cells for the blood vessels that run within it. Arachnoid blends into the pia below it. There is no defining internal arachnoid layer.

Finally, the leptomeninx ends with a single-layer of *pia* abutting the surface of the brain. Pia mater is a homogenous neural crest derivative throughout the CNS, undoubtedly originating from the internal/deep migration of neural crest that immediately covers the neural tube. Pia is a source of pericytes that envelop the endothelial tubes formed in arachnoid. These blood vessels plunge into the neuropil. Pial cells are connected with desmosomes; they constitute a barrier between the subarachnoid space and the brain. In subarachnoid hemorrhage, red cells never make contact with neural tissue. Pia invests blood vessels entering into the substance of the brain. Once within the brain parenchymal, fenestrations in the pia coating permits circulation of nutrients.

Embryogenesis of Meningeal Circulation

Misunderstanding persists in so-called subdural bleeding. The dura-arachnoid boundary is easily disrupted, a fact is known to all neurosurgeons and neuropathologists; this creates a false plane. Although the dural limiting membrane and the arachnoid barrier layer can be distinguished histologically, throughout development these layers remain attached. Unlike the pleura and peritoneal cavities, a “*subdural space*” does not exist. This multicellular layer consists of stem fibroblasts (but no network of collagen fibers) and intracellular spaces. The term “dural border cell layer” or dural limiting membrane was defined by Nabeshima in 1975 and later incorporated by O’Rahilly and Müller [Fig. 12.5].

Early in development, the primitive meninx surrounding the neural tube contains a head plexus which is temporarily supplied by segmental branches from the dorsal aortae while the embryo manufactures a definitive cerebral circulation. During stages 9–10, the head plexus sends penetrating vessels into the brain. At stage 11, these connect with the nascent vessels from within the brain, a situation that makes the primitive meninx independent of external supply. That’s a good thing, considering all the changes in the transient nature of the aortic arch system. At stage 17, just as meninx primitive changes into a two-layer structure, and while endomeninx remains supplied from below, a separate system of meningeal arteries from the stapodial stem arrives at the scene “in the nick of time” to supply the ectomeninx from above.

Venous drainage also differentiates into separate systems. The original system lies within the leptomeninges while newly formed meningeal veins are superficial to dura. Initially, the pial and dural layers are connected by a primitive plexus system. As development proceeds, definitive cerebral veins form in the sulci and the plexus becomes “streamlined” by apoptosis. The cerebral veins of each hemisphere coalesce into 12–18 *bridging veins* that traverse the pia-dural border. Once in the substance of the dura, they run for variable distances and then enter the superior sagittal sinus [Figs. 12.6, 12.7, 12.8 and 12.9].

It should be emphasized that the dural sinuses do not mature until several months after birth and the early fetal venous circulation is quite plastic, a useful adaptation to the spatial demands of dramatic brain growth. The upshot of this biology is the creation of a blood-brain barrier in which, through a paring process, pio-dural anastomoses become dramatically reduced in number. These vessels are quite sturdy and are not good candidates for SDH without significant trauma.

In its final iteration, the ectomeninx is supplied by meningeal arteries and veins. Meningeal arteries supply the calvarium, penetrating arteries into the substance of the dura, and arteriovenous shunts. The penetrating arteries extend all the way through dura propria to reach within μm of the dural limiting layer where they form a dense vascular plexus. As depicted by Mack these vessels are the primary suspects for non-traumatic “subdural” bleeding [Fig. 12.10].

Only the Cerebrum Has Dura

All other parts of the brain are covered with pia and arachnoid, but not dura. Posterior fossa is lined with periosteum. Supratentorial dura and tentorium are neural crest derivatives. Infratentorial periosteum is paraxial mesoderm [Figs. 12.11, 12.12, 12.13 and 12.14].

Phylogeny of the Meninges

Meninges reflect the biologic sophistication of the underlying brain. Fishes have a single membrane known as the *primitive meninx*. In non-mammalian tetrapods this structure becomes bilaminar with an outer dura mater and a thick inner *secondary meninx*. In mammals, the secondary meninx further divides into the arachnoid and the pia. Recall the metabolic demands of the highly-convoluted cerebrum. Pial vessels are worked into the depth of these cortical folds. In 1909 work, Giuseppe Sterzi demonstrated that dura behaves differently in spinal cord versus in the skull. In the calvarium, dura is fused with the internal periosteum whereas, in the spinal cord, the two layers remain separate [Fig 12.15].

Fig. 12.5 Dural limiting membrane/dural border cell layer. **a.** DLM is composed of loosely adherent cells, no extracellular collagen, and enlarged extracellular spaces. **b.** Subdural hemorrhage represents accumulates in the dural border cell layer. [Reprinted from Mack J, Squier W, Eastman JT. Anatomy and development of the meninges: implications for subdural collections and CSF circulation. *Pediatr Radiol* 2009; 39:200–210. With permission from Springer Nature.]

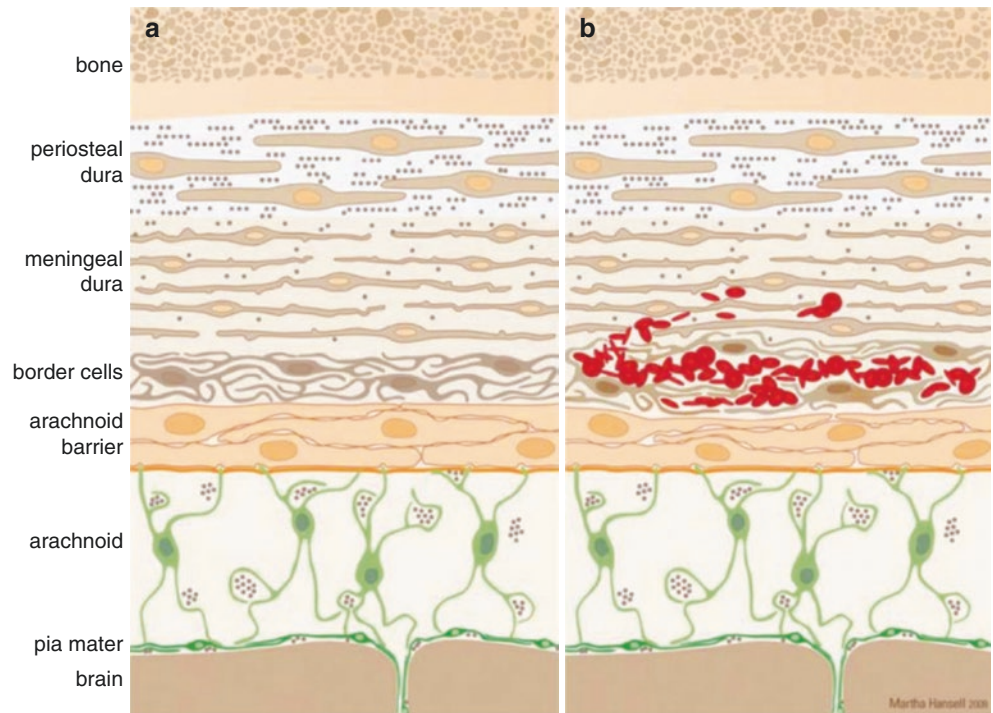


Fig. 12.6 Cerebral veins run within the leptomeninges. From these, 12–18 bridging veins connect through the arachnoid-dura interface, run for variable distances within the dura, and eventually drain into the superior sagittal sinus. [Reprinted from Wikipedia. Retrieved from: https://en.wikipedia.org/wiki/Superior_cerebral_veins#/media/File:Slide6Neo.JPG. With permission from Creative Commons License 3.0: <https://creativecommons.org/licenses/by-sa/3.0/deed.en.>]

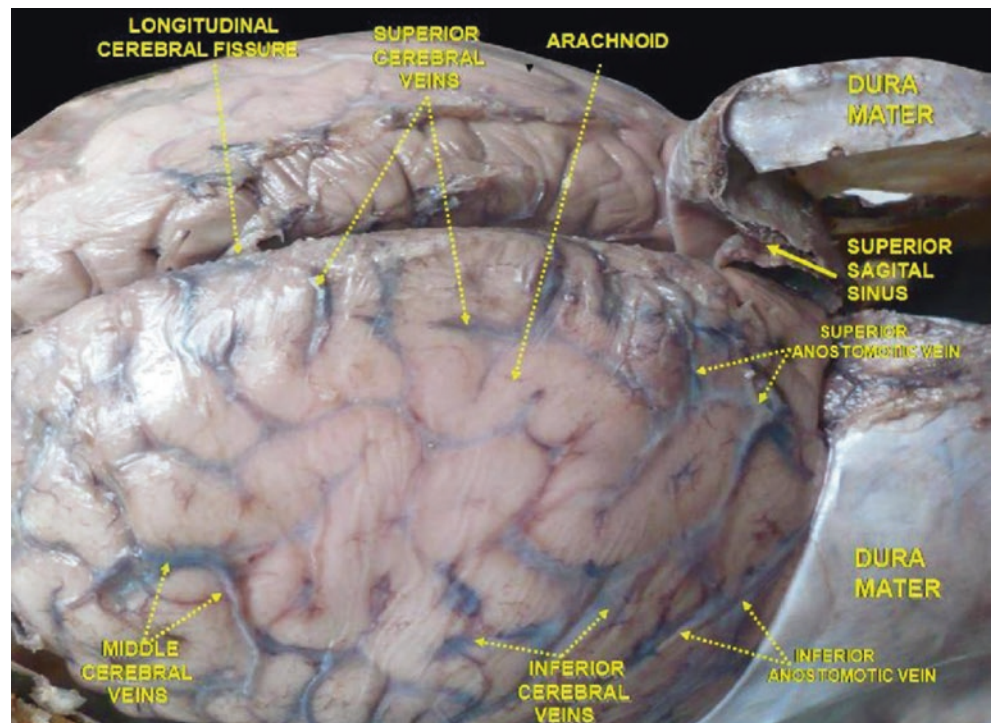


Fig. 12.7 Cerebral arteries and veins run in the arachnoid layer. Due to the pial barrier, subarachnoid hemorrhage does not penetrate the substance of the brain. Arachnoid granulations and dural bridging veins penetrate through the dura to communicate with the sinus. Histologic layers of dura are not shown here. [Reprinted from Cakmakci H. Essentials of trauma: head and spine. Pediatric Radiology 2009;39 Suppl 3:391–405. With permission from Springer Nature.]

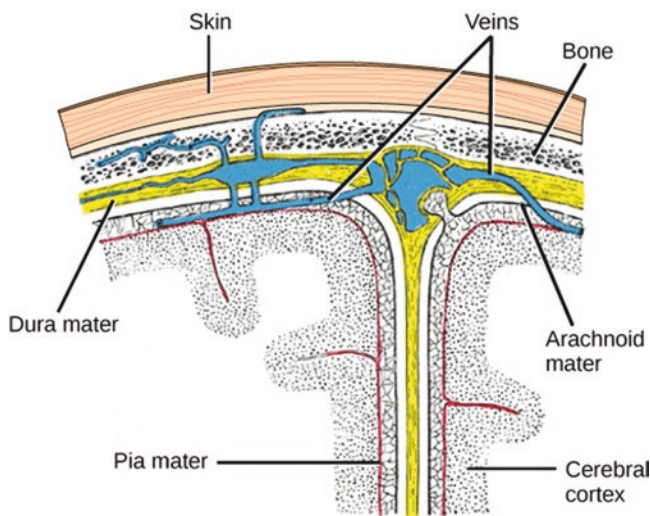
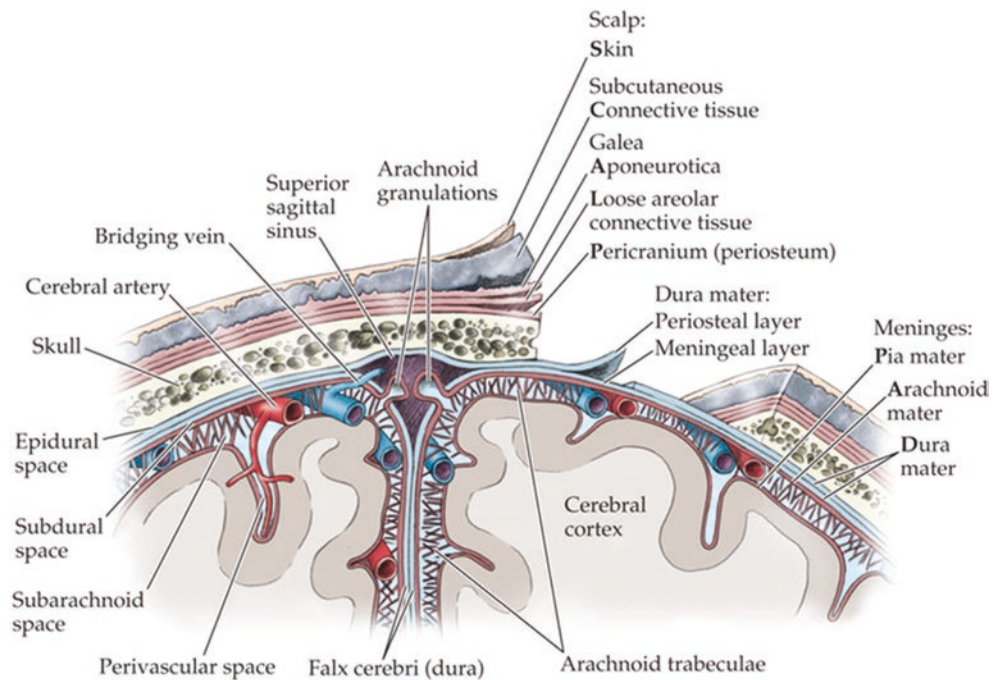


Fig. 12.8 Cerebral veins. Cerebral veins ascend through arachnoid into dura via 12–18 bridging veins. These run for variable distances and then empty into the sagittal sinus. Superficial meningeal veins drain the diploic space. These can emerge through the skull as diploic veins. [Reprinted from Wikimedia Commons. Retrieved from: https://commons.wikimedia.org/wiki/File:Figure_35_03_01.jpg. With permission from Creative Commons License 4.0: <https://creativecommons.org/licenses/by/4.0/deed.en>.]



Fig. 12.9 Diploic veins. Diploic veins drain the neural crest membranous bones of the calvarium. They notably avoid squamosal, as it is paraxial mesoderm. Diploic veins drain into the sagittal sinus and connect with meningeal veins running on the surface of dura, thereby establishing the relationship of calvarial bone, particularly the inner table, to dural stem cells. Emissary veins at scattered locations connect the intracalvarial diploic veins through the outer table to the periosteum. [Reprinted from Lewis, Warren H (ed). Gray’s Anatomy of the Human Body, 20th American Edition. Philadelphia, PA: Lea & Febiger, 1918.]

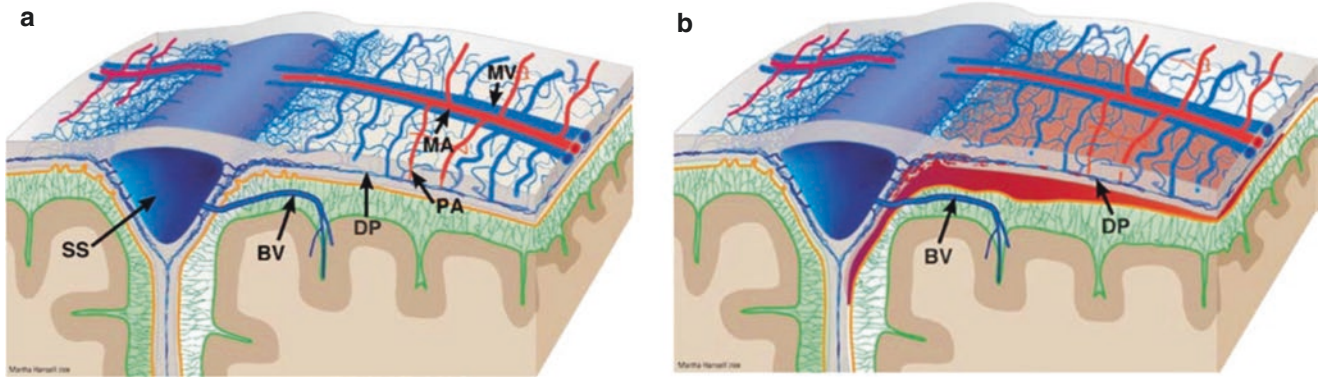


Fig. 12.10 a. Meningeal arteries and veins supply the ectomeninx, coursing between periosteum and dura propria (gray). Arachnoid proper is defined by the arachnoid limiting membrane (yellow). With the dural compartment is a dural plexus (DP) fed from above by penetrating branches from meningeal arteries. These run in the subdural compartment until reaching the sagittal sinus to which they connect. The DP adjacent to the sagittal sinus is distinct from the bridging veins (BV)

which run in the arachnoid layer. **b.** Bleeding occurs within the subdural compartment causing a downward displacement of the arachnoid barrier membrane (yellow). Blood never enters the subarachnoid space. [Reprinted from Mack J, Squier W, Eastman JT. Anatomy and development of the meninges: implications for subdural collections and CSF circulation. *Pediatr Radiol* 2009; 39:200–210. With permission from Springer Nature.]

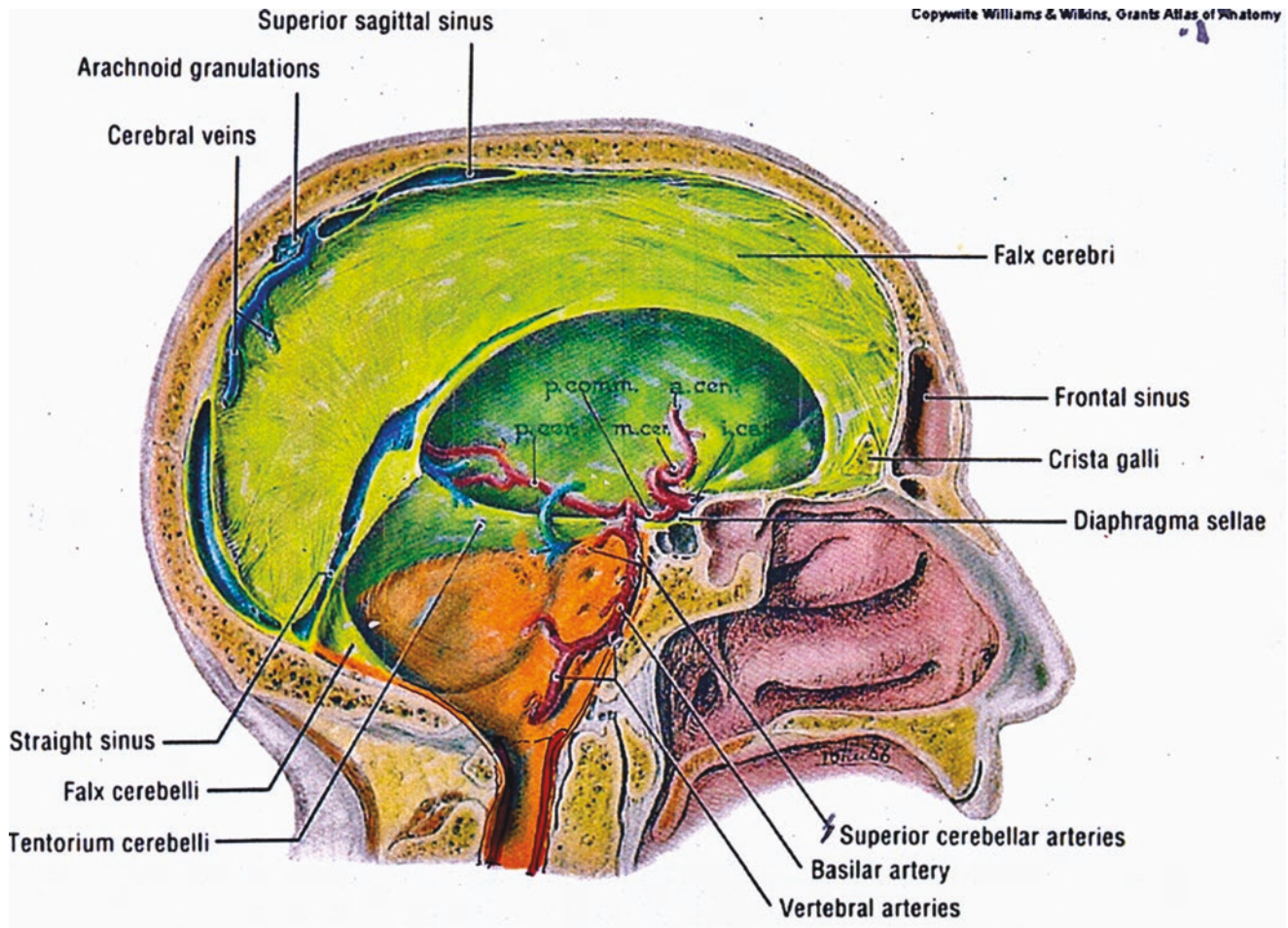


Fig. 12.11 Mesenchymal anatomy of intracranial membranes. Dura (green) is neural crest supplied by trigeminal nerves. Periosteum (orange) is mesoderm; it is not true dura. It continues all the way down the spinal canal, Mesodermal dura begins again at the foramen magnum

and is a separate layer (pink). It does not participate in osteosynthesis. [Reprinted from Boileau JC. Grant Atlas of Human Anatomy Philadelphia: Williams & Wilkins 1943.]

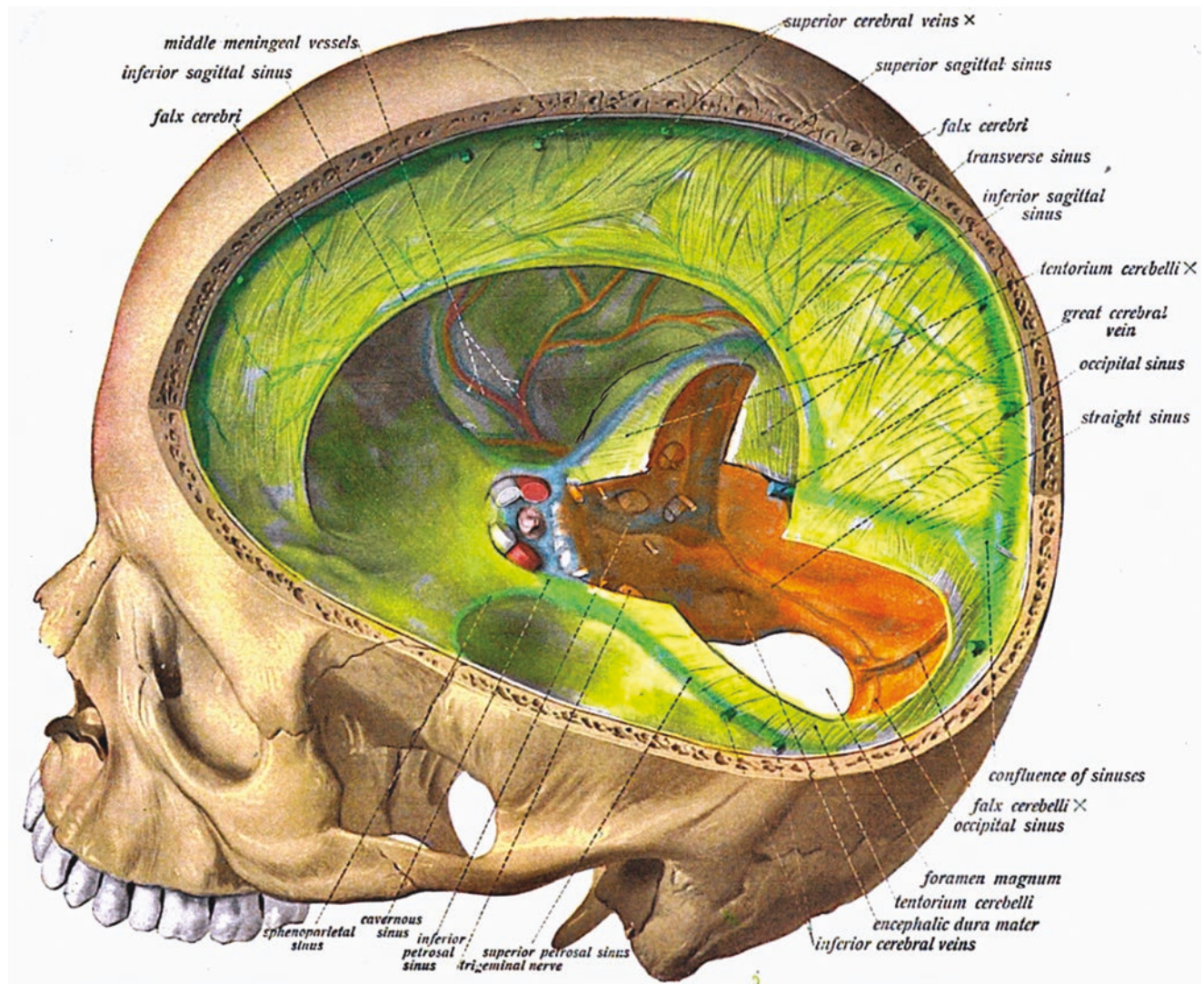


Fig. 12.12 Dura and tentorium (yellow) are classified as supratentorial. These are neural crest tissues. At sites of confluence with one another or with periosteum, venous sinuses are formed. Infratentorial periosteum (orange) is mesodermal and not bilaminar. It cannot contain

venous sinuses. Posterior fossa is defined as being medial to the sinuses. [Reprinted from Sobotta J. *Anatomic des Menschen*. Munich, Germany: Verlag JF Lehman, 1904.]

This important observation has a developmental explanation. The membranous bones of the supratentorial calvarium require a periosteum as a source of stem cells. The blood supply to this layer comes from meningeal arteries. Therefore, the layers are fused. In the infratentorial calvarium no dura exists. The blood supply to these chondral bones runs in the substance of the lining periosteum, (sic) dura, and

is *not* connected with CNS circulation. Dura reappears below the foramen magnum but is no longer required for vertebral synthesis – the layers remain separate.

Historical aspects of the meninges are summarized by O’Rahilly and Müller [1]. One can consult Sensenig’s original account available online through the University of New South Wales website, <http://embryology.med.unsw.edu.au>.

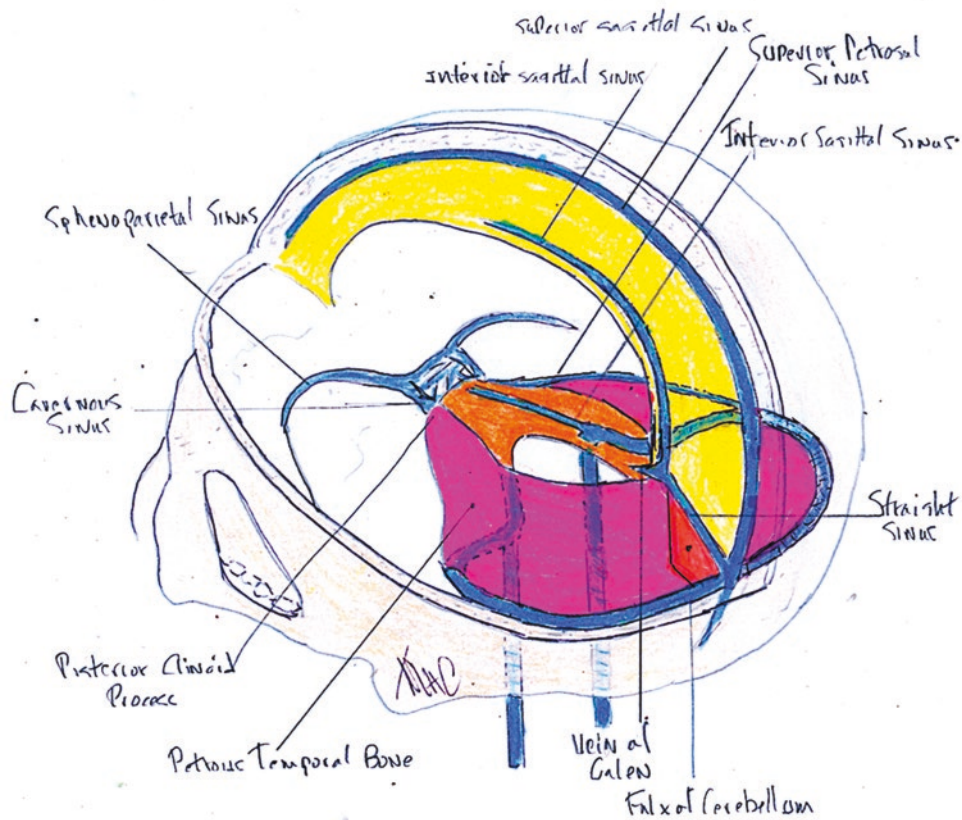
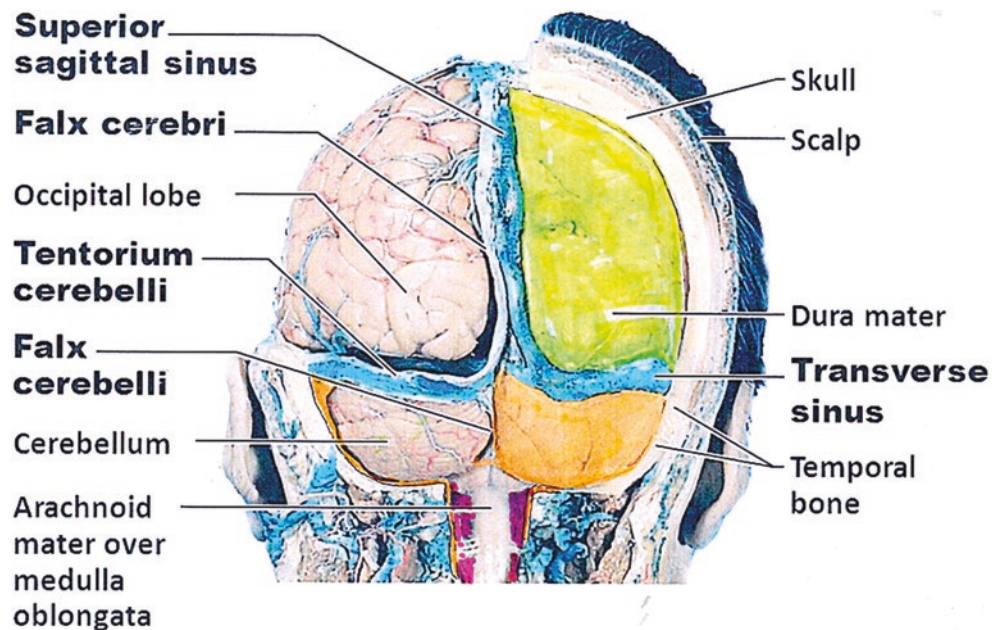


Fig. 12.13 Anatomy of the falx cerebri, tentorium cerebelli and falx cerebelli. These structures are defined by the venous sinuses that are enclosed by the bilaminar dura. *Falx cerebri* (yellow) runs from crista galli and internal frontal crest all the way back to internal occipital protuberance and the tentorium. *Tentorium cerebelli* (pink) has fixed margins from posterior clinoid process to petrous apex laterally and thence to the transverse sinus. Its free margin allows passage of midbrain. *Falx*

cerebelli (magenta) is a small reflection extending downward from midline of tentorium and along the inferior occipital crest. Chiari II malformations can occur in its absence. Posterior fossa periosteum (orange) extends medially from petrous apex, anteriorly along clivus, and posterolaterally below transverse sinus. [Courtesy of Michael Carstens, MD]

Fig. 12.14 Occipital dura (green) is r3 neural crest that covers posterior cerebral lobes. Posterior fossa periosteum (orange) is paraxial mesoderm and is juxtaposed to but does not cover the cerebellum. Interface between these tissues creates sinuses. Superior sagittal sinus results from the two laminae of r1 falx splitting apart and roofed over by r3 periosteum. Note the reappearance of spinal dura (pink) below foramen magnum. It has been opened to show arachnoid. [Reprinted from JC Boileau Grant Atlas of Human Anatomy Philadelphia: Williams & Wilkins 1943.]



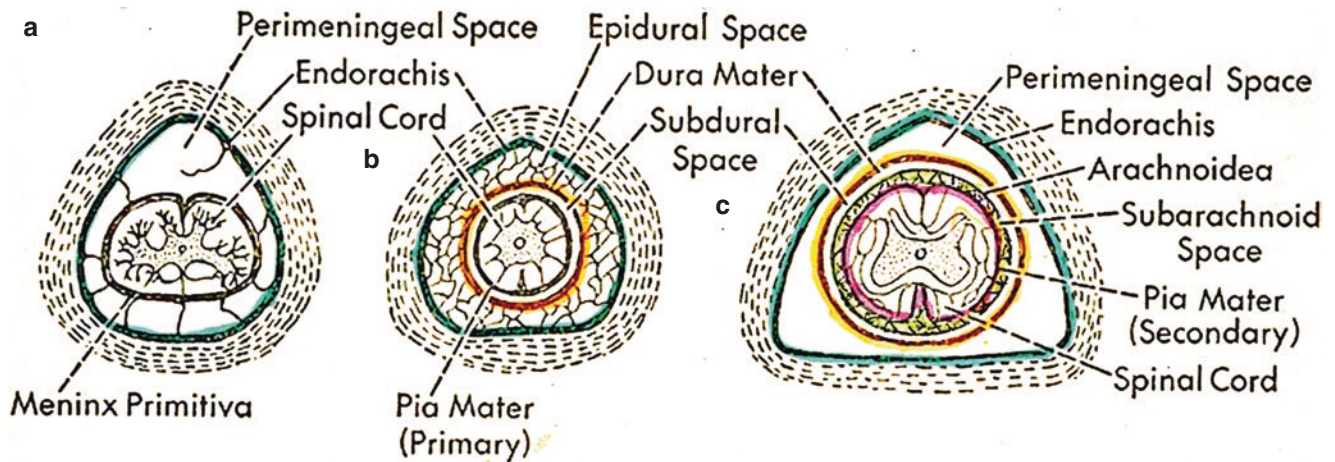


Fig. 12.15 Phylogeny of meninges. Fishes (a) have a single-layer primitive meninx. In non-mammal tetrapods (b) the primary meninx differentiates into internal lamina, the primary pia mater, and an external lamina, the dura mater. No arachnoid is present. In mammals (c) the

primary pia mater again differentiates into a secondary pia mater and arachnoid. The dura assumes a trilaminar histology, with a dural limiting membrane defining it from arachnoid. [Reprinted from Frazer JE. *Anatomy of the Human Skeleton*. Philadelphia: P Blakiston, 1904.]

Formation of Meninges by Developmental Stages

The purpose of the section is to review relevant events related to the production and transportation of the mesenchyme that surrounds the brain. The timeline at which various sectors of the meninges appear is defined. This material appears telegraphic and dense. Do not despair...it becomes quite useful when referring back to it from the text.

Stage 6 (13–14 days) Gastrulation starts

Primitive node and primitive streak extend from organizer forward to future level r0. At stage 6b, the dorsal aspect of PN produces prechordal mesoderm which flows forward from epiblast and hypoblast. This is the “herald event” of gastrulation in stage 7.

Stage 7 (15–17 days) CNS appears, gastrulation completed

PN at r0 produces prechordal notochord, then retreats backward, leaving additional notochord behind it. Gastrulation proceeds from r0 caudally. Notochord splits PCM as far forward as future prosomere hp2. *Otx-2* from r0 induces midbrain. Notochord (assisted by PCM) induces forebrain.

Stage 8 (18–19 days) *nervous system, segmentation, and supply*

General: This stage is short, lasting 48 h. The first indications of the future brain appear. Prechordal plate mesoderm (PCM) is situated directly in front of the future notochord. From the primitive streak, cells are populating the paraxial zone. By the end of stage 8, a total of 18 somitomeres have been synthesized, the first 7 of which are cranial.

CNS: The expansion of the paraxial mesoderm causes the elevation of neural folds. PAM remains tightly connected to

the folds so that, in subsequent stages, closure of the neural tube will drag mesoderm and non-neural ectoderm up and over the CNS to achieve complete coverage. Around the spinal cord, all components of dura (being 100% PAM) are thus present. At each neuromeric level, neural crest makes pia/arachnoid and PAM makes dura. Around the cerebrum, dural development requires an additional component, neural crest, which will appear at stage 9.

Stage 9 (20–21 days, 1–3 somites) *major divisions of the brain*

General: Embryo starts out as a disc. Mesencephalic flexure due to brain growth folds the future heart beneath the face and stretches anterior segment of dorsal aorta into the 1st aortic arch. As soon as the 19th somitomere is added on, the Sm8 transforms into somite 1.

CNS. Three major divisions of the brain are present but no vesicles are seen. The rolling up of the neural tube brings the brain in contact with the outlying mesoderm—this is the source of the endothelial cells for the *primitive head plexus*. Endothelial cells penetrate the embryonic neural tube and migrate through the neuropil on their way to the ventricles. As they do so, they lay down a pathway of molecular cues that will be subsequently followed by pericytes to complete nascent capillary tubes.

Mesoderm: Expansion of the forebrain in the midline displaces PCM laterally into the head mesoderm. The forebrain is coated with PAM from r1 to r3.

Neural crest: First indication of neural crest is seen in the midbrain (perhaps as early as stage 8). Neural folds of the spinal cord are beginning to develop. As they roll up like a burrito, they carry along with them associated paraxial mesoderm. The space between brain and PAM constitutes a pathway by which NC cells migrate downward.

Meninges: Physical contact between the walls of the neural tube and PAM ensures that primitive vascular channels, the head plexus, are immediately available to provide nutrition for the growing brain. The internal layer of neural crest—the future pia—surrounds the channels and provides a barrier between direct contact between mesoderm and neural tissue: the blood-brain barrier. Mesoderm: Three of four occipital somites present.

Stage 10 (22–23 days, 4–12 somites) *subdivision of forebrain, optic primordium*

General: 1st pharyngeal arch visible. 2nd aortic arch artery develops from unification of buds from dorsal aorta and from ventral cardiac outflow tract—all remaining aortic arches develop in the same way. The significance of the 1st arch for meninges is that it has already been populated by hypaxial invasion of neural crest from r2 to r3. This means that the primary epaxial migration of r1-r3 over the cerebrum has already been completed.

CNS: Diencephalon and secondary prosencephalon are now visible. Neural crest migration over the forebrain begins: Rostral hindbrain (r1-r3) NC flows around the sides of cerebrum and into the anterior cranial base. Midbrain (m1-m2) NC is directed to the eye, the future orbit, over the sidewalls of the forebrain. Neural tube fusion from the occipito-cervical junction backward rolls in the surrounding skin and buries the neural tube. This process cannot occur over the brain because no gastrulation takes place anterior to the tip of the notochord. For this reason, a *new source of epidermis* arises from the anterior forebrain neural folds.

Mesoderm: Prechordal plate mesenchyme is admixed with somitomeric paraxial mesoderm and neural crest. The significance of this for extraocular muscle development is debated (*vide infra*). Epaxial halves of somitomeric PAM remain in contact with CNS while hypaxial halves send out myoblasts for the future muscles of mastication into 1st arch...and into subsequent arches. *Epaxial PAM is responsible for creating the endothelial channel vessels supplying the primitive head plexus.*

Neural crest Migration takes place in two directions. *Segmental migration* involves NC movement within the same neromeric territory to (1) fill in pharyngeal arches and (2) interact with epipharyngeal placodes to create composite ganglia along the neural tube.

Meninges: Interaction between neural crest and primitive head plexus creates conditions necessary for the development of the *pia mater*. Pia mater is designed to form the blood-brain barrier; it will envelope all vessels penetrating into the brain parenchyma.

Stage 11 (24–25 days, 13–20 somites) *rostral neuropore closes, skin coverage complete*

General: 2nd pharyngeal arch visible. 3rd aortic arch artery develops.

CNS: Characterized by closure of the prosencephalic neural folds and the rostral neuropore. This process is *unidirectional*: upward (backward) from the optic chiasm (it was formerly thought to be bidirectional). The final location of the rostral neuropore will be the nasofrontal junction. Presence of definitive notochord established at the tip of the basisphenoid bone.

Mesoderm: Brain becomes enclosed within the mesoderm from superficial to neural crest. Blood vessels form *in situ* adjacent to the brain wall from the adjacent head mesoderm. *Penetrating blood vessels* develop when PAM endothelial cells migrate inward toward the ventricular layer. They lay down signals for pericytes which follow them into the neuropil and ensheath the endothelial tubes. Penetrating blood vessels are surrounded by pia.

Neural crest: Migration of neural crest over the forebrain takes place. Optic vesicle emerges from alar plate of prosomere hp2, to be surrounded by *optic neural crest* from m1 and m2. MNC interacts with neuroepithelium of the optic vesicle to form the sclera. Acting alone, MNC is the source of the fascia that will surround the extraocular muscles beginning at stage 12.

Meninges: First indication of meninges: *pia mater* represent local neural crest appearing at level of caudal hindbrain, that is, from rhombomeres r8–r11.

Stage 12 (26–27 days, 21–29 somites) *caudal neuropore closes*

General: 3rd pharyngeal arch visible, 4th aortic arch artery develops, 1st and 2nd arches fuse. Trigeminal and facial ganglia develop but are not yet subdivided. Neural crest from r4 to r5 has invaded the 2nd arch and becomes widely dispersed. From r4 backward, neural crest is available for leptomeninges but does *not* form dura. *Stapedial artery* forms as a remnant of the stump of the 2nd aortic arch artery, the axis of the 2nd pharyngeal arch.

CNS: longitudinal neural arteries replace the head plexus. They are constructed from PAM from levels r1-r11 like “beads on a string.”

Mesoderm: Paraxial mesoderm dedicated to the orbit condensing caudal to optic vesicle. Origin of extraocular muscles was originally thought to come from PCM but has now been mapped to somitomeres 1–3, and 5. More on PCM is below.

Neural crest: Cranial neural crest migration is now complete. Crest cells *per se* cannot be identified. Forebrain is covered with neural crest from rhombomeres r1-r3. Neural crest is now found in cranial nerve ganglia, admixed with head mesoderm.

Meninges: In the CNS, pia mater from local neural crest has further matured. *Pia mater is now visible at level of the midbrain.* Whereas MNC localizes to the orbit, neural crest from r1 to r3 now advances over the entire cerebrum, although it is not yet identifiable as a separate layer, it will

form a *second layer* of mesenchyme, the future pachymeninx. Pachymeninx is not a pure neural crest layer, it is admixed with mesoderm. Thus, it will have the capacity to form two separate layers of blood vessels: arteries will lie external to dura propria; veins will be located deep to it. Dura is not yet defined; the dural limiting membrane does not appear until stage 17.

Stage 13 (28–31 days, 30+ somites) *neural tube now closed, cerebellum develops from r1*

General: 4th pharyngeal arch is visible, 5th pharyngeal arch forms internal to the 4th arch, 5th aortic arch artery fails to develop. Fusion of the 2nd and 3rd arches takes place. Persistence of the 3rd aortic arch artery will form the common carotid, external carotid, and the proximal (extracranial) portion of the internal carotid artery. Scalp begins to form (first hairs of body are cranial).

CNS: Cellular sheath of notochord appears at occiput and extends to myelencephalon (medulla). It will extend caudal-to-cranial. Cranial nerve outgrowth begins. The stapedia system will be programmed by V and VII.

Mesoderm: lateral rectus appears in caudal zone.

Neural crest: internal migration surrounding the neural tube is now complete; it is segmental, each neuromere has its own distinct population. These cells populate individual peripheral nerves and autonomic nerves.

Meninges: Vessels appear between single-layer ependyma of the 4th ventricle and surface non-neural ectoderm.

Appearance of scalp hair indicates interaction between overlying ectoderm and underlying mesenchyme. Epicenter of hair formation, the *occipital whorl*, is at the boundary between hindbrain ectoderm and cervical somite ectoderm. This process indicates the induction of specialization of the outer layer of pachymeninx by its contact with overlying non-meningeal tissue.

Stage 14 (32 days) *cerebral hemispheres*

General: 6th aortic arch artery develops for pulmonary circulation. This marks the end of the pharyngeal arch period.

CNS: Cellular sheath of notochord reaches metencephalon (pons).

Mesoderm: superior oblique, then superior rectus appear in caudal-dorsal zone.

Meninges: Proliferation of vessels, especially at mid-brain. Vessels, surrounded by “protective” neural tissue, penetrate brain wall, always accompanied by pia. *Pia mater matures at level of telencephalon*. Cerebral hemispheres surrounded by mesenchyme (dorsal > ventral), indicating the directionality of pia mater.

Stage 15 (33–36 days) *longitudinal zoning of the diencephalon*

General: Amalgamated 1st and 2nd arch complex. Ventral fusion at the mandibular processes indicates midline closure of the floor of mouth and anterior neck.

CNS: Three divisions of trigeminal are present. These will innervate cerebral dura. Before exit, the skull forms StV1 in orbit and forms the StV3/StV3 “add-on” to the terminus of the external carotid, that is, the internal maxillo-mandibular artery. The cellular sheath of notochord advances forward to its terminus at the mesencephalic flexure (r0). This sheath constitutes the axis of the skull base. Note: this is a misconception of the FMROR model. Notochord actually extends forward to the terminus of hypothalamus (hp2); it induces the entire floorplate of the forebrain (cf Ch 5). Ossification subsequently proceeds caudal-cranial. Between day 28 and day 35 the primitive skull base, *desmocranium*, develops from basal condensation of neural crest (r1) and paraxial mesoderm (r1-r11) around the notochordal sheath.

Meninges: *Primary meninx formally recognized* – loose mesenchyme is seen around most of the brain—the floor is more developed than the roof. This reflects its vascularization because arterial supply matures basal-alar, that is, ventral-dorsal. The resulting from in situ formation of channels in contact with the brain that mature into vascular structures.

Stage 16 (8–11 mm, 37–40 days) *evagination of the neurohypophysis*

CNS: All cranial nerves are identifiable. Mesencephalic tract extends from trigeminal ganglion to isthmus. This mean StV1 has reached the orbit.

Mesoderm: medial rectus and then inferior oblique appear in rostral-ventral zone.

Meninges: Cellular sheath of the notochord is clearly involved with medial leptomeninges of tentorium cerebelli. Tentorium develops from midline-laterally).

Stage 17 (41–43 days) *olfactory bulbs, amygdaloid nuclei*

CNS: Interhemispheric fissure is filled with mesenchyme. This represents neural crest and mesoderm pulled inward by the tissue expansion of the cerebral hemispheres around a fixed central point. This will be the future *falx cerebri*. *Ossification* appears in sclerotomes 1–4; this process progresses cranially. The *stem of stapedia involutes* and extensive peripheral anastomoses take place. Extracranial stapedia via chorda tympani (StVII) joins ECA maxillary. IMMA promptly sends up StV3 recurrent branch into cranium to rendez-vous with intracranial stapedia system.

Meninges: *Dural limiting membrane* found first in cranial base areas...exactly where the mesenchymal condensations of the future chondrocranium are forming. “Holes” in the limiting membrane *pori dures* represent foramina for CN 3, 4, 5, and 12. Mesenchyme above the 4th ventricle is now loose (it has proliferated). *Skeletogenous layer* of future membranous calvarium now visible. Dural lining layer lateral to diencephalon is the extension of rostralateral tentorium. Note how extensively V1 is represented. This explains the “backward” pathway of *recurrent branch* of V1.

Stage 18 (44–47 days) *inferior cerebellar peduncles, corpus striatum, dentate nucleus*

General: Mesenchyme of the nasal septum indicates the flow of MNC into the midline. Production of premaxilla. Crista galli is not seen.

Meninges: Cavitation of the primary meninx creates a meshwork between the neural wall and the skeletogenous layer: this is the future arachnoid. Floor mesenchyme under 4th ventricle thicker than the roof (relates to increase in pia)

Stage 19 (48–50 days) *choroid plexus 4th ventricle, medial accessory olive*

CNS: Choroid plexus made up of leptomeninges.

Meninges: Changes in density between the leptomeninges, the primary meninx internal to the dural limiting layer is loose, and the pachymeninx is now dense. Dural sinus present. Medial tentorium was observed positioned between basilar artery and diencephalon (on coronal section).

Stage 20 (51 days) *choroid plexus lateral ventricles, optic, and habenular commissures, interpeduncular and septal nuclei*

General: Presphenoid, sella turcica, basisphenoid, and orbitosphenoid (all neural crest derivatives) are seen.

Meninges: Ventral-most hemispheric fissure contains the future falx to which is being added mesenchyme from the skeletogenous layer. The skeletogenous layer now contains very distinct parietal plate. Cartilage is distinctly seen in both basisphenoid and orbitosphenoid. Above the 4th ventricle the mesenchyme is dense but no dural limiting membrane is visible as yet above 4th ventricle.

Stage 21 (52–53 days) *cortical plate appears in the cerebral hemispheres*

General: Parietal plate and alisphenoid (neural crest). Chondrocranium shows: orbitosphenoid, basisphenoid, otic capsule.

Meninges: The primary meninx is more dense with a larger mesh pattern next to the cerebral wall and a smaller mesh beneath the skeletogenous layer. A dural limiting membrane is noted along the skull base, and at base of cerebral hemispheres but not over the sides. This fits the *caudal-cranial developmental pattern* of the vasculature. Roof of the 4th ventricle has large mesh except above the choroid plexus, where it is smaller. Medial tentorium reaches all the way to mammillary body, while lateral tentorium is distinct, both rostrally and caudally.

Stage 22 (52–55 days) *internal capsule and the olfactory bulbs*

Meninges: Dural limiting membrane now covers the roof of the hindbrain and reaches midbrain, but it does not completely cover the roof. The cerebello-medullary cistern is now defined by a limiting layer. The transverse and sigmoid sinuses are now present with the dura.

Stage 23 (56 days+) *embryonic period ends*

General: Chondrocranium replaces desmocranium, forming the primitive skull base in cartilage.

Meninges: Dural limiting membrane is now complete over hindbrain and midbrain. In forebrain it is present over the lateral fossae only. Subarachnoid tissue internal to the dural limiting layer now readily distinguished. Falx cerebri is well developed from skeletogenous layer at crista galli. Dural limiting layer also developing rostrally but tissue *between* hemispheres is still leptomeningeal (neural crest) only. Extent of dural limiting membrane correlates with chondrocranium and membranous skull. The transverse and sigmoid sinuses occupy the potential space between the skeletogenous and the pachymeninx. In the area of the otic capsule and posterior fossa, dural and skeletal components are difficult to differentiate. Perhaps this is because the petrous temporal bone is chondral, originating from r4 to r7 PAM. Most adult cisternae are now present. The medial projection of tentorium cerebelli, extending from sella turcica to mammillary body is thinning out. It creates a separation between 2 different subarachnoid zones: (a) telencephalon vs. diencephalon; and (b) cerebellum and rhombencephalon. The rostromedial tentorium joins the otic capsule.

Migration Patterns of Neural Crest

Neural crest development begins with that of the neural folds at stage 8 and persists in the brain until the end of the pharyngeal arch period, stage 14–15. Neural crest development in the spinal cord continues for much longer. In mammals, neural crest migration starts very early, just as soon as the neural folds round upward, at Carnegie stages 9, prior to closure of the neural tube. It occurs in two forms

- **Local migration** is perineural. The NC cells follow the surface of the neural tube as it rolls upward providing an immediate covering for CNS, much like wax dripping from a candle. This neural crest admixes with paraxial mesoderm to form the primitive perineural plexus. It is the source of endomeninx: in mammals, pia mater, and arachnoid.
- **Peripheral migration** follows different routes depending on its source.

Spinal Cord Neural Crest

Neural crest originating from the neural folds above the spinal cord begins at the cranial-cervical junction at stage 9. It continues neuromere-by-neuromere in a cranial-to-caudal sequence. The arrival of spinal NC at the target site depends upon its route. Migration within the same neuromeric level

means that cells travel a similar distance and arrive at approximately the same time. Polyneuromeric migrations take longer.

- *Superficial lateral migration* Neural crest cells flow outward just beneath the surface of non-neural ectoderm. This populates the entire skin with melanocytes.
- *Deep lateral migration* of neural crest flows in and around the somites. Once within the somites, neural crest provides internal organization; this is the source of neural crest fascia surrounding craniofacial muscles. Peripheral to the somites neural crest suffuses the out-lying lateral plate mesoderm.
- *Ventral migration* forms the sympathetic system and moves into the visceral/splanchnic lateral plate mesoderm provides the ganglia of the gut [Fig. 12.16].

Cranial Neural Crest

Cranial neural crest follows different pathways, which we have been previously described in terms of stages. Migrations are underway very early, from stage 9. The actual arrival of the cells at their destinations depends upon (1) the timing of their departure and (2) the relative length of the pathway. Since the physical appearance of derivatives such as bone or dura depends upon development of vascular support, deductions around neural crest populations were imprecise. The sequence was finally determined using the quail-chick chimera system and gene markers to determine trajectories and fates [Figs. 12.17 and 12.18].



Fig. 12.17 Stage 9 shows neuromeric origins of paraxial mesoderm and neural crest to form meninges. PAM (white) is produced by gastrulation from levels r0 backward. When the elevation of the neural folds from the plane of the embryo takes place in stage 8, hindbrain PAM from r0 to r3 forms two populations. The first population, being adherent to the neural folds, is immediately dragged over the forebrain where it makes the primitive head plexus. The second population remains *in*

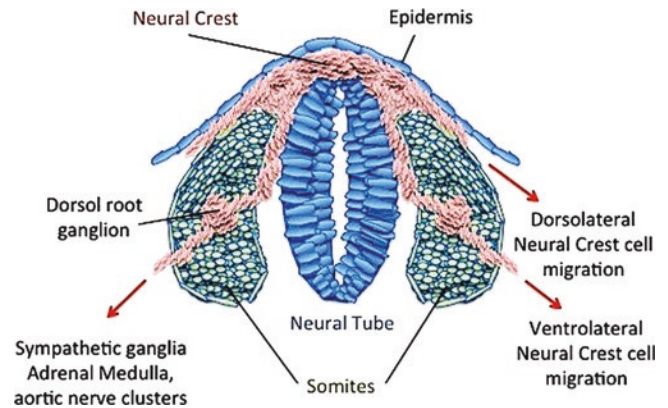


Fig. 12.16 Neural crest migration, spinal cord model. NC migrates immediately upon closure of each neuromeric segment of the neural tube. This model from the spinal cord fails to appreciate the triphasic arrival of mesenchymal populations over the cerebral wall. (1) Neural tube closure pulls up the adjacent PAM, much like pulling a hood over one's head. Since the forebrain arises from in front of level r0, it drags PAM from r0/r1, r2, and r3 over its walls to make blood vessels. This is initiated at stage 8 (2) Rhombomeric neural crest from r0 to r3 migrates forward and upward to be admixed with PAM only dermis, thus providing pericytes for the blood vessels. This happens at stage 9, that is, concomitantly or just after the arrival of PAM. This provides the dermis for all scalp skin except that in the distribution of nerve V1. This mesenchyme will be modified according to its distance from CNS signaling, from pia, to arachnoid, to dura/bone/periosteum, to dermis. [Reprinted from Ruggeri P, Farina AR, Cappabianca L, Di Ianni N, Ragone M, Merolle S, Gulino A, and Mackay AR. Neurotrophin and Neurotrophin Receptor Involvement in Human Neuroblastoma. In: Hiroyuki Shimada, (ed). Neuroblastoma" ISBN 978-953-51-1128-3, Published: May 29, 2013. With permission from Creative Commons License 3.0: <http://creativecommons.org/licenses/by/3.0>.]

situ, becoming reorganized as somitomeres 1-3 which produce all extraocular muscles except the lateral rectus. Neural crest (green and blue) migration to forebrain takes place at stages 9-10 and provides meninges. RNC precedes migration from MNC into the orbit. RNC is organized by the trigeminal sensory nerves, V1-V3. [Courtesy of Michael Carstens, MD]

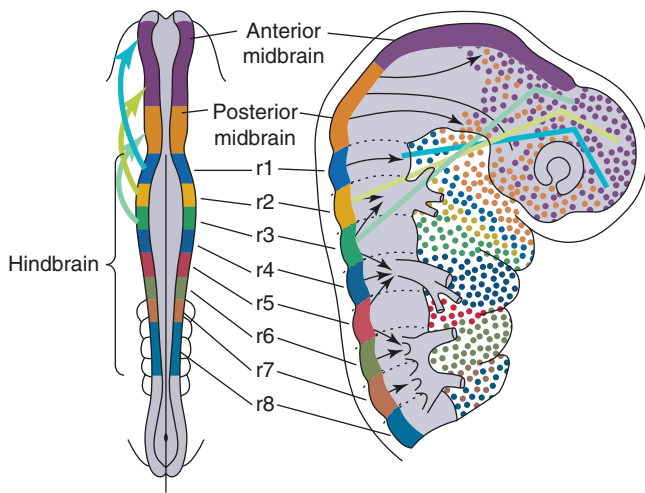


Fig. 12.18 Neural crest migration routes: r1 (blue) is distributed over basal forebrain, frontal lobe, and frontonasal mesenchyme; r2 (yellow) supplies frontolateral periorbital zone; r3 (green) supplies parietal/interparietal zone. Each the pharyngeal arch system, each arch is supplied by neural crest from two rhombomeres (even-odd). Order of migration: (1) rostral hindbrain r1-r3, followed by midbrain m1-m2 and rostral hindbrain r4-r7; (2) caudal hindbrain r8-r11; and (3) forebrain p1-p3. [Reprinted from Gilbert SF, Barresi MJF. *Developmental Biology*, 11th ed. Sunderland, MA: Sinauer; 2016. Copyright © 2016. Oxford Publishing Limited. Reproduced with permission of the Licensor through PLSclear.]

Cranial Neural Crest Migration, Local

- Hindbrain

Migration occurs just as in spinal cord. Hindbrain coverage is complete by stage 10 since the 4th occipital somites are present and pia is identified. Development of pia appears to progress seen to “develop” from caudal-to-cranial manner but this is deceptive, as it reflects the maturation pattern of the blood supply to the hindbrain.

- Midbrain and forebrain

At stage 8 genes produced from r0 induce midbrain; additional genes from r0 and midbrain induce the forebrain. Gastrulation is complete with prechordal populations of mesoderm in place. As the neural folds of the midbrain and forebrain rise up and project forward they *drag along with them an ensheathment* of two forms of mesenchyme essential for their survival: (1) neural crest populations from r0 to r3 provide the endomeninx and pericytes; and (2) local PAM from r1 to r3 contains endothelial cells. These tissue in combination provide barrier around the brain and the components for a primitive head plexus which will sustain the CNS until a definitive blood supply can be established. Primary coverage is complete by stage 10, marked by the subdivisions of prosencephalon: diencephalon and secondary prosencephalon.

Cranial Neural Crest Migration, Peripheral

- Hindbrain (r0-r3)

- *Hypaxial migration* stages 9–10

Neural crest from r2 to r5 enters the 1st and 2nd arches

- *Epaxial migration* stage 11–12

Neural crest from r0 to r3 follows the walls of the forebrain providing additional mesenchyme, the ectomeninx. Dura is first seen ventrally seen at the midbrain level at stage 12. These crest populations will be innervated by V1-V3 and will supply all dura of the cerebrum as well as the dorsal aspect of V1-supplied tentorium cerebelli. Note that this coverage takes place in a plane external to pia. The initial migration from rostral hindbrain is probably complete by stage 12. But continued NC migration pursues a more superficial course to form two functional planes: r1-r3 produces scalp dermis and r4-r5 creates an intervening later of fascia (the future SMAS).

- Midbrain (m1-m2)

- *Anterior migration* stages 11–12

Neural crest from m1 to m2 flows forward to populate the orbits

- Hindbrain (r4-r7)

- *Hypaxial migration* stages 11–13

Neural crest from r4 to r11 enters the 3rd, 4th, and 5th pharyngeal arches

- *Epaxial migration* stage 13+

Neural crest from r4 to r5 migrates massively over the entire head to form the superficial investing fascia (SIF) or superficial musculoaponeurotic fascia (SMAS) to accommodate the muscles of facial expression. Follows the previously-established pathway to cerebellum and coats the *ventral* aspect of tentorium cerebelli.

- Forebrain neural crest (p1-p3)

- *Anterior migration* stage 14+

Forward flow beneath neural folds of hp1 and hp2 establishes (1) dermis for high-priority full-thickness skin coverage for V1-innervated calvarial and frontonasal zones; and (2) interaction with adenohypophyseal, nasal, and optic placodes

Cerebrum has immediate epithelial coverage from NNE of the anterior forebrain folds; dermal populations can be assembled more leisurely

Forebrain Dermis Interacts with Previously Deposited MNC Structures

In any case, prior to formation of the frontal bone, we see r1 dura supporting p1-p3 dermis from diencephalon supporting hp1-hp2 epidermis from telecephalon. This topology means that MNC lies deep to the adenohypophyseal and nasal plac-

odes, forming an initially solid block of nasoethmoid mesenchyme. As the facial epithelia of the nasal processes invaginate backward into the MNC, they form cavities. The lining of the nasal cavities is non-neural epithelium from the anterior forebrain folds but the subvestibular or submucosal tissue is MNC. In response to this NNC-PNC template, the nasal capsule is converted into cartilages and membranous bones. Death of MNC in the midline ratchets the two nasal cavities toward the midline until their medial walls merge. The remaining MNC sandwiched in-between becomes the perpendicular plate of the ethmoid and the septum. Recall that in minimal cases of nasoethmoid apoptosis failure (hypertelorism) both septum and perpendicular plate can present as bifid or thickened.

It should be noted that the timing of visible appearance of certain zones of meninges as seen in human embryos is dependent on vascularization. The actual biologic migrations take place much earlier. The pathway for vascular development of the spinal cord is therefore *upward* from the ventral midline of the spinal cord. Both brain and scalp vessels appear ventrally and progressively ascend toward the vertex. Levels of scalp vasculature actually help to define stages 20–23.

Blood Supply of the Meninges

Blood Supply of Pia and Arachnoid

As discussed previously the neural tube is immediately surrounded by a primitive meninx, an admixture of “first responder” neural crest and PAM. These cells immediately produce vessels. Pia mater develops between the vessel layer and the cerebral wall. At stage 11, the vessels penetrate the brain substance seeking the ventricular layer. The vessel walls are coated with pia. In forebrain and midbrain, these vessels anastomose with the developing internal carotid system. In the hindbrain, they connect with developing longitudinal neural arteries which eventually recombine with cervical dorsal aortae to make the misnamed basilar-vertebral system. Recall that the vertebrals and former LNAs connect with each other just inside foramen magnum [Fig 12.19].

Arachnoid mater does not differentiate until stage 17, simultaneous with the beginnings of dural differentiation. The layers are kept quasi-separate by arachnoid limiting membrane and dural limiting membrane. Arachnoid is avascular, being supplied from below by the rich plexus of the pia. CSF circulate within arachnoid. Arachnoid villi penetrate into the plane between dural limiting membrane and the undersurface of dura propria. Within this subdural venous plane arachnoid granulations encounter venous sinuses thus permitting CSF from the subarachnoid space to drain into venous circulation.

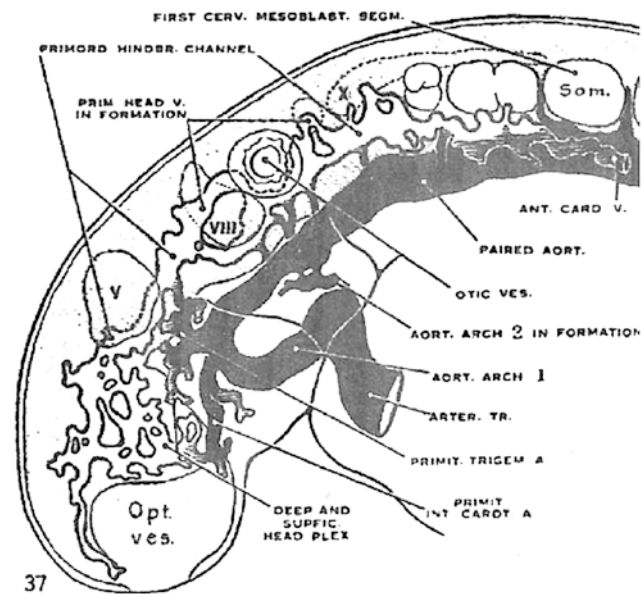


Fig. 12.19 Primitive head plexus at stage 10 The head plexus forms around the brain as soon as stage 8. By stage 9, it is connected with dorsal aortae by a series of segmental arteries, the first one, primitive trigeminal appearing at stage 9. At stage 10 the 2nd aortic arch artery is forming and multiple segmental arteries can be seen posterior to PrTg. The otic zone r4-r7 has three-four segmentals; occipital somites r8-r11 have four segmental arteries and 1st cervical segmental is identified. Beginnings of the internal carotid are seen. At stage 11 as the cerebral circulation forms, the plexus gives rise to penetrating centripetal vessels that connect with the centrifugal branches of the ICA system. Primitive head plexus remains at the surface of the brain to supply pia. In the hindbrain the plexus morphs into the longitudinal neural arteries. [Reprinted from Padgett DH. The development of the cranial arteries in the human embryo. *Contribution to embryology*. Carnegie Institution 1948; 32: 205–261. With permission from Johns Hopkins School of Medicine.]

The circulations to pia mater and dura appear to be separate but actually they are connected at six different levels [Fig 12.20].

Internal Carotid, Anterior Division

1. Primitive olfactory artery has two branches. Medial olfactory is the leading edge of anterior division ICA and is the forerunner of anterior cerebral. Lateral olfactory artery gives rise to lateral striate, anterior choroidal, and is the forerunner of middle cerebral artery.
 - The *olfactory branches* represent the original medial branch of the primitive olfactory artery. These supply the pia of basal frontal lobe.
2. Anterior cerebral artery is the second branch of anterior division, although contemporary texts list it as primary.
 - Pericallosal branches extend backward to the posterior cerebral circulation. They supply the pia of the frontal lobe.

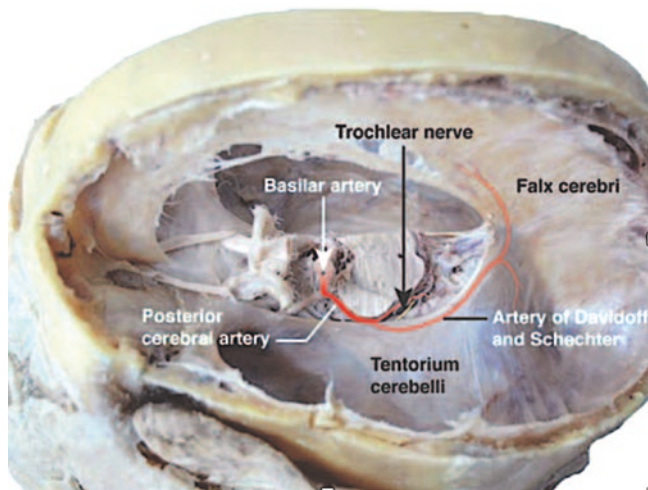


Fig. 12.20 Pia mater shares circulation with cerebral arteries. It is also supplied by direct pio-dural artery anastomoses. These are primitive olfactory (olfactory branches), anterior cerebral (pericallosal branches and anterior falcine artery), posterior cerebral artery (artery of Davidoff and Schechter), superior cerebellar artery (medial dural tentorial branch), anterior inferior cerebellar artery (subarcuate artery), posterior inferior cerebellar artery (posterior meningeal artery). The artery of Davidoff and Schechter is a normal variant, seen here supplying tentorium and falx cerebri. [Reprinted from Griessenauer CJ, Loukas M, Scott JA, Tubbs RS, Cohen-Gadol AA. The artery of Davidoff and Schechter: an anatomical case study with neurosurgical case correlates. *Br J Neurosurg* 2013; 27(6):815–181. With permission from Taylor & Francis.]

- Anterior falcine artery supplies medial pia corresponding to anterior falx, that is, frontal and parietal lobes.

Internal Carotid, Posterior Division

1. Posterior cerebral artery
 - *Artery of Davidoff and Schechter* supplies pia in region of falx and tentorium cerebelli, that is, posterior lobe

Longitudinal Neural Artery

1. Superior cerebellar artery
 - medial tentorial branch
2. Anterior inferior cerebellar artery
 - *subarcuate artery* supplies area of petromastoid
3. Posterior cerebellar artery
 - *posterior meningeal artery*

Blood Supply of the Dura and Periosteum

This subject is of great importance. Blood supply patterns are like paleontological clues giving information about the development of the meninges. We shall see that the dura and periosteum of the convexity over the cerebrum are relatively straightforward but the anatomy of dura covering the basal

forebrain and the periosteum of the posterior fossa is more complex. We shall begin with general comments regarding terminology. We then proceed to look at specific arteries of importance. Finally, the developmental significance will be assessed [Fig 12.21, 12.22].

A note on the figures. For a general orientation to the meningeal arteries and a caveat regarding circulation to the anterior cranial fossa reader is advised to review figure 21 by Wolf-Heidigger. Superb work by Rhoton's group classifies the dural supplies by region and source [Figs. 12.23, 12.24, 12.25, 12.26 and 12.27]. The color scheme is simple but misleading: ICA (green), ECA (blue), and (sic) vertebrasilar (red). *Stapedial system is not recognized.* Thus, areas in green ascribed to ICA should rightfully be only assigned to the territory of cavernous ICA. The remainder of V1 territory should really be another color. Similarly, with ECA. Here StV2 and StV3 stapedial arteries supply dura, whereas true ECA vessels (ascending pharyngeal and occipital) supply periosteum. Finally, the vertebrasilar system is an embryologic misnomer which is explained below. The anterior and posterior meningeal arteries supposedly from VBA are really branches of the C1 segmental artery interposed between the occiput and the axis. Relationships in the posterior fossa are further amplified by Figs. 12.28 and 12.29.

General Comments

Dura mater covers the cerebrum and separates the cerebellum from posterior lobes. It does not envelop cerebellum. Midbrain and hindbrain do not have dura; they are enclosed within leptomeninges only. Dura mater starts again at foramen magnum and envelops the entire spinal cord.

Supratentorial dura develops from two tissues: (1) neural crest arising from anterior hindbrain (r0-r1, r2, and r3); and paraxial mesoderm from the same levels. Migration from levels m2 to m1 occur later and is reserved for the globe. PAM furnishes the endothelial cells required to make blood vessels for the cerebrum and cerebellum while neural crest produces the pericytes. We shall see that the neurovascular map of supratentorial dura has functional significance: it defines distinct developmental fields of the overlying calvarial bone and enables us to map out the origin of these bone fields.

Although supratentorial dura and periosteum are products of r1-r3 neural crest these tissues are NOT the “true” pharyngeal derivatives. Recall that in the gnathostome revolution, the 1st arch is so radically modified that a new vascular supply, the stapedial system, must be invented. Therefore, as we shall see, its primary blood supply does NOT arise from the original external carotid system. Instead, the predominant vascular source for the dura is the stapedial artery system.

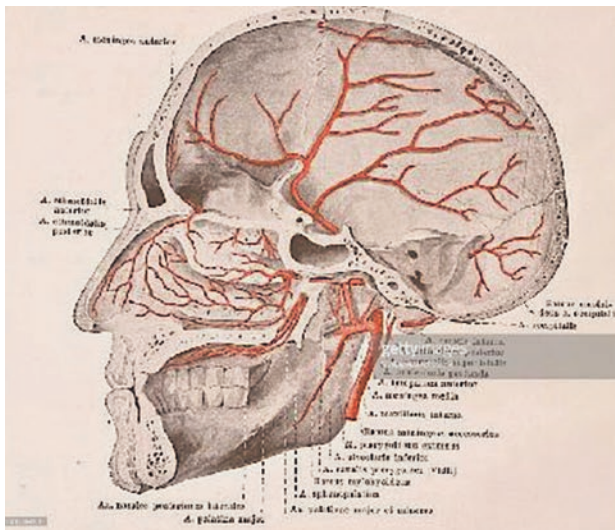
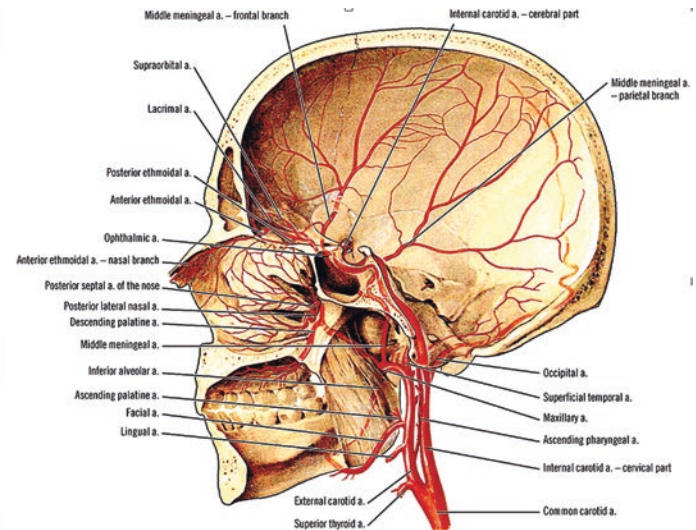


Fig. 12.21 Blood supply to the dura. Exceptional artwork depicts the anterior meningeal artery coming from StV2 but minimizes the contribution of StV prior to the orbit and anastomosis with ophthalmic. The ethmoids coming through the cribriform plate to the base of frontal lobe are shown. This is one of the few dissections showing the “recurrent



meningeal artery fully developed. Penetrating branches from occipital are shown but not ascending pharyngeal. [Reprinted from Spalteholz W. Hand Atlas of Human Anatomy, Volume 2. Philadelphia, PA: JB Lippincott, 1928]

Infratentorial “dura” is a *misnomer*. Cerebellum, mid-brain, and hindbrain have pia and arachnoid but not dura. Therefore, what has been historically referred to as dura in the posterior fossa is, in reality, *periosteum* with no biologic relationship to the neural structures it encloses. It is manufactured exclusively from paraxial mesoderm. From levels r4 backward, PAM acquires the ability to make pericytes so neural crest is no longer needed. Periosteum of the posterior fossa is derived from r4 to r7 mesoderm over the petromastoid complex and from r8 to r11 over the occipital complex. Levels r4-r7 relate biologically to 2nd and 3rd aortic arches therefore external carotid branch arteries occipital and ascending pharyngeal provide blood supply for this layer.

Extracranial dura mater encloses the spinal cord. It begins at foramen magnum. The mesenchymal source for spinal dura is paraxial mesoderm. Each somite beginning with C1 provides PAM to its respective neuromere. Blood supply to each zone of spinal dura is provided by paired epaxial branch from the aorta.

The Internal Carotid System, Cavernous Segment

Here we are going to concentrate on the cavernous segment of ICA and ignore the ophthalmic. In reality, the stapedial system (intracranial division), derived from the dorsal remnant of 2nd aortic arch artery, is the genetic source for meningeal supply along branches of StV1. The anastomotic

relationship between stapedial has been previously detailed [Cf Fig. 12.21].

The cavernous segment of internal carotid supplies dura from r1 mesenchyme at the base of the brain, particularly that of sella turcica and tentorium cerebelli, is supplied by a seemingly confusing number of arteries arising from the cavernous internal carotid. The vessel area is organized by directionality. Medial vessels perfuse (what else?) the hypophysis and clivus. Lateral vessels supply lateral tentorium. Posterior vessels supply medial tentorium and dorsal meningeal artery. For our purposes, we shall concentrate on those vessels perfusing tentorium and clivus. An extensive review is given by Rhoton’s groups [Figs. 12.22, 12.23, 12.24, 12.25, 12.26 and 12.27].

Big picture idea: The dura covering the basisphenoid and circle of Willis is r1 neural crest as is tentorium cerebelli sweeping backward from the posterior clinoid processes. These zones are continuous with the periosteum covering basioccipital which is of r8-r11 occipital somite derivation. Arteries serving these structures are programmed by V1 but are *not* part of the stapedial system.

Arteries of the Tentorium

These r1 tissues are supplied by two arteries of the *meningo-hypophyseal trunk*, the largest intracavernous branch of ICA. *Medial tentorial artery* (Bernasconi’s artery) travels along the free edge of tentorium all the way back to the straight sinus. *Lateral tentorial artery* travels along petrous ridge

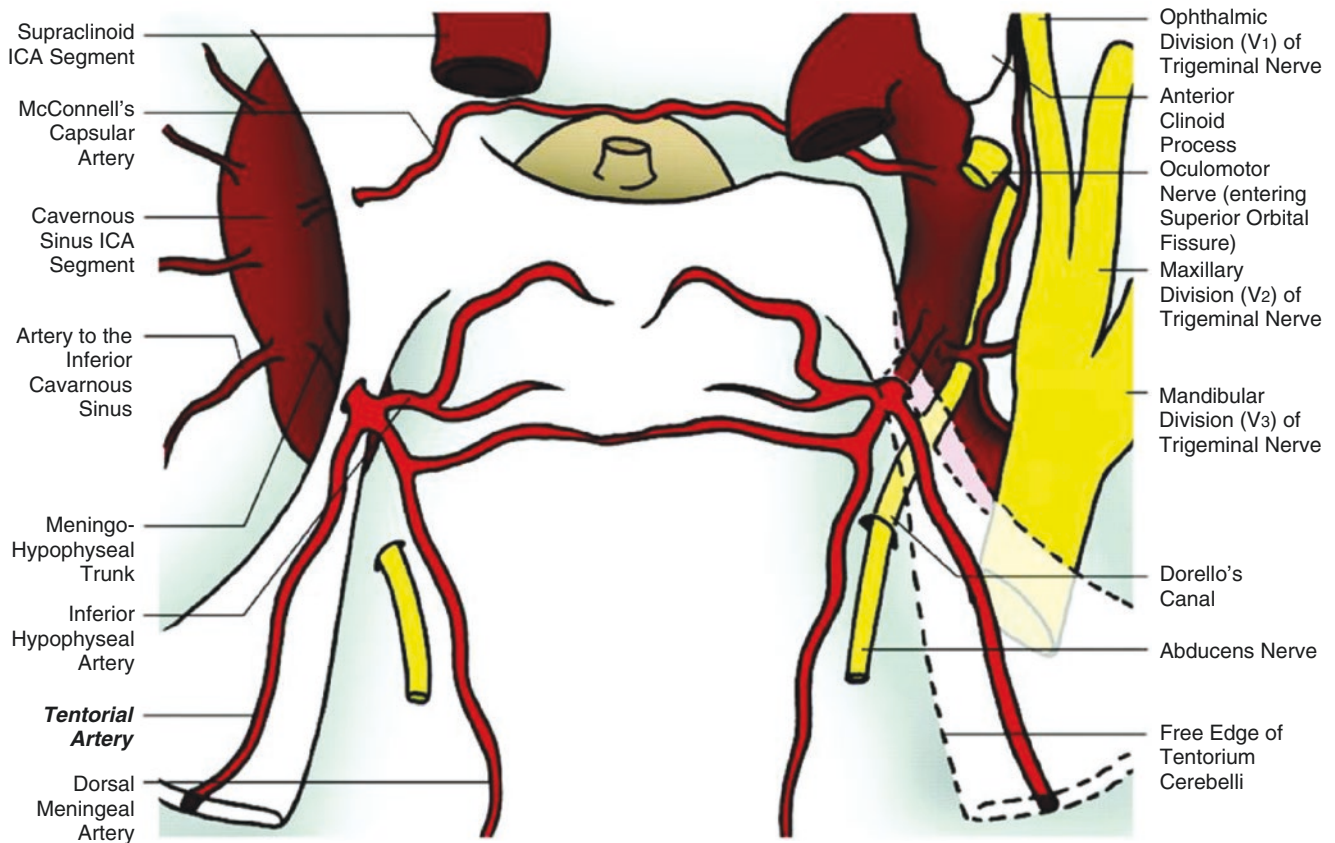


Fig. 12.22 Posterior/inferior hypophyseal artery is the embryologic remnant of the primitive maxillary artery, the very first branch of dorsal aortae. It originally was directed to the eye and served as the initial supply to the optic vesicle. Subsequently, it relocates. Here one observes anterior hypophyseal arteries directly from carotid sinus. IHA supplies the r1 tentorium and the clivus. This Arterial supply from the cavernous

ICA is of vital embryologic importance because it supports the r1 mesenchyme of tentorium. [Reprinted from Banerjee AD, Ezer H and Nanda A. The Artery of Bernasconi and Cassinari: A morphometric study for superselective catheterization. *Am J Neuroradiol* October 2011; 32(9):1751–1755. With permission from American Society of Neuroradiology.]

peripheral to its medial colleague. In the posterolateral skull, it anastomoses with StV3 petrosquamous branch. [Fig 12.22]

Arteries of the Clivus

Clivus has a matched set of arteries, both with eminently forgettable names.

Lateral clival artery, AKA dorsal meningeal artery, It is a remnant of the primitive trigeminal artery. It also arises from meningo-hypophyseal trunk, which supplies dorsum sellae and divides. The medial branch goes to clivus. A lateral branch follows superior petrosal sinus along petrous ridge. Thus it remains outside the territory of tentorium. Posteriorly, it makes anastomotic loop with lateral tentorial artery.

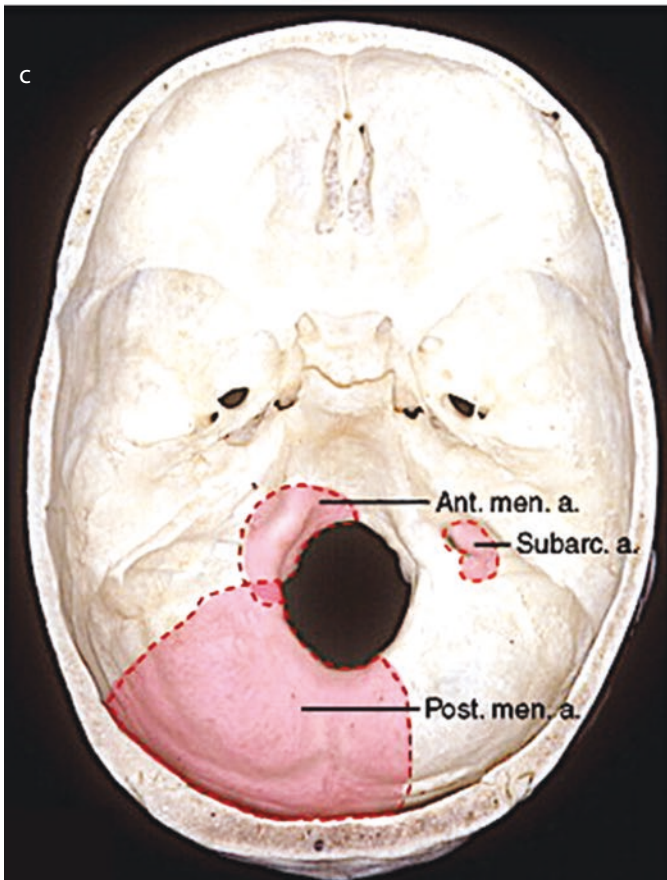
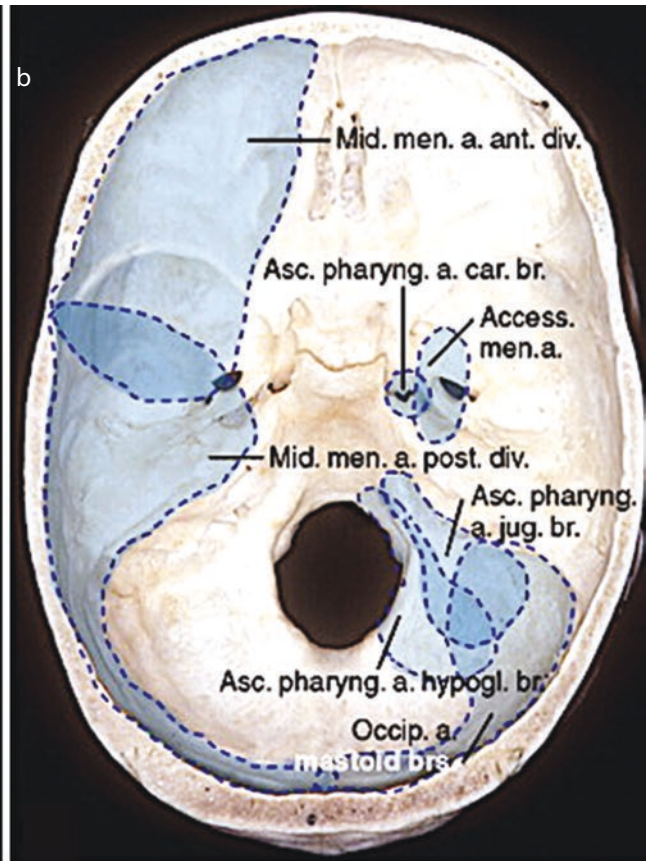
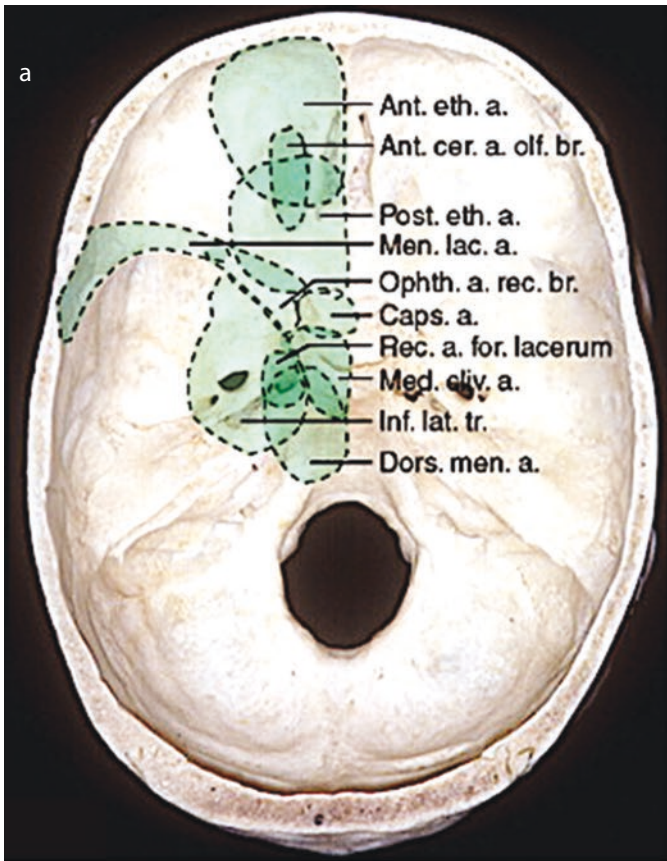
Medial clival artery, AKA inferior hypophyseal artery, is a remnant of primitive maxillary artery. Yes, it supplies posterior lobe of pituitary but it then proceeds to run down the clivus for good measure.

Note that the clival arteries *descend* down the slope of basioccipital whereas, just lateral to it, flanking branches

from r6 to r7 *ascend* to terminate at the petrous apex. This vascular watershed zone is an example of boundaries around neuromeric bone fields. Basioccipital r8-r11 is flanked by r6-r7 petrous.

Embryonic precursors

Prior to stage 9, ICA does not exist. Instead, the embryonic CNS is supplied by a primitive plexus and the body is supplied by dorsal aortae. At stage 9, with mesencephalic flexion driven by forebrain growth, the embryonic heart is tucked ventrally at level r0-r1. The connecting segments between dorsal aortae and the heart are stretched downwards and backward like parentheses to form the 1st aortic arches. From the site of flexure, forward growth produces primitive internal carotid which faces three main challenges: (1) establish a connection between dorsal aortae and the neural plexus, longitudinal hindbrain channels; (2) provide an immediate and temporary blood supply for the developing eye; and (3) continue forward to supply the brain.



(continued)

Solution 1 is the *primitive trigeminal artery* which the heart to body supplies (dorsal aortae) and hindbrain (primitive plexus). Solution 2 is the primitive maxillary artery which is directed toward the optic vesicle as it erupts from the basal forebrain. Solution 3 is the forward axis of internal carotid. Our attention here is to primitive maxillary which is in genetic register with r0, the very tip of the notochord. As described in Chap 7 and this chapter when alternative vessels supply the eye, primitive maxillary artery is no longer needed. It returns to its original niche at Rathke's pouch, becoming inferior hypophyseal artery.

At this location, IHA is positioned at the interface between the r1 neural crest basisphenoid and the r8 segment of basioccipital. It therefore performs two distinct functions. It follows recurrent branch of StV1 to supply the posteriorly directed r1 mesenchyme of tentorium via *lateral and medial tentorial arteries*. It sends a mesial branch down the clivus to support r8-r11 occipital somitic basioccipital.

Why is this so important? First off, r1 neural crest migration along the cranial base is bidirectional. It tracks forward to form dura and periosteum of the anterior cranial fossa. It tracks backward between posterior cerebral lobe and cerebellum. These two parts of CNS have distinct blood supplies. ICA perfuses forebrain and midbrain while hindbrain *including cerebellum* is supported by the longitudinal neural system (future basilar). So which system is responsible for tentorium? IHA, being relocated at the exact interface between the systems at circle of Willis and cavernous sinus, wins the prize.

The second reason why IHA is important is that the occipital somites lose their designated segmental supply during vascular reorganization of the hindbrain. IHA takes over for basioccipital, while exoccipital and supraoccipital are rescued by occipital, ascending pharyngeal, and 1st cervical.

The Stapedial System: A Derivative of the External Carotid System

This subject is covered in the previous vascular chapters, with special contributions by MK Diamond and an extensive review by Rhoton; the reader is referred to these sources for further details. For our purposes, we shall consider the organization of the individual branches and their areas of supply from a selective embryological perspective.

Big picture idea: Trigeminal nerves V1-V3 are the exclusive supply for the entire supratentorial dura, a neural crest product of r1-r3.

Big picture idea: sensory nerves of the trigeminal system accompany and program the individual arteries of the stapedial system. The neuroangiosomes that result delineate the migratory pathways of neural crest to the face and dura.

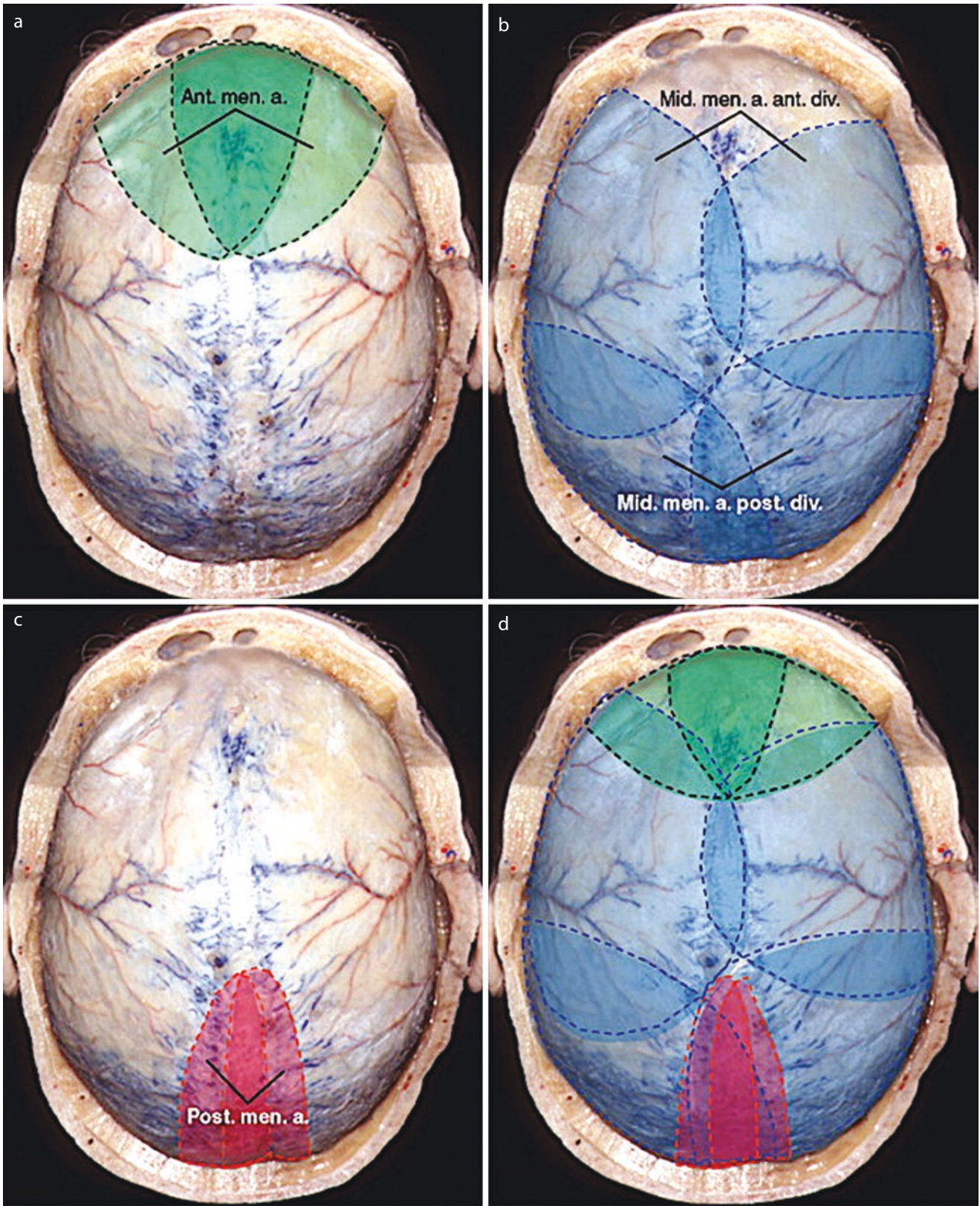
Trigeminal Anatomy, Reviewed

During stage 14 the cranial nerves develop rapidly. They (especially trigeminal and facial) determine the trajectories of the stapedial system. The innervation pattern is all-important for programming the branches of the stapedial system. *Of particular importance is the anatomic pathway for trigeminal supply to the dura.* After leaving the trigeminal ganglion V1 and V2 travel forward in the lateral wall of the cavernous sinus while V3 descends directly out of the skull. Note: ***the most proximal sensory branch of each part of trigeminal is dedicated to the innervation of the dura.***

The following facts about trigeminal are relevant to understand how these nerves conduct the blood supply to the orbit:

- (1) V1, upon exiting the cavernous sinus and just prior to entering the orbit, gives rise to the ***anterior meningeal***

Fig. 12.23 Blood supply of the individual meningeal arteries: internal carotid (green), external carotid system (blue), and vertebrobasilar (red). **a**, Internal carotid system, here includes two forms of 1 programming: (1) V1 stapedial as ophthalmic artery branches; (2) V2 non-stapedial from the cavernous segment. The dura covering the medial part of the anterior fossa floor is supplied by StV1 and olfactory branches of the anterior cerebral artery. The cavernous internal carotid sector, through its inferolateral trunk and dorsal meningeal artery, supplies the parasellar dura part of the anterior wall of the posterior fossa and the sellar dura via paired capsular, inferior hypophyseal, medial clival, and dorsal meningeal arteries. **b**, External carotid (V2 and V3 stapedial as middle meningeal artery) supplies the dura covering the lateral skull base. The territories of StV1 anterior and posterior branches extend toward the supra- and infratentorial convexity dura and medially over the r1 falx and tentorium. The accessory meningeal and the ascending pharyngeal artery branches contribute supply periosteum between the internal carotid and middle meningeal territories on the middle and posterior fossae. The jugular and hypoglossal branches of the *ascending pharyngeal* arteries supply the inferior portion of the posterior surface of the petrous bone, lateral cerebellar dura, the midclivus, and anterolateral foramen magnum. The mastoid branch of the *occipital artery* constitutes the main supply to the lateral part of the cerebellar fossae. **c** Vertebrobasilar system. The anterior and posterior meningeal branches of the vertebral artery (1st cervical segmental) supply the foramen magnum periosteum. The posterior meningeal artery provides the major supply to the paramedial and medial portions of the dura covering the cerebellar convexity. The subarcuate artery, a branch of the anterior inferior cerebellar artery, supplies the periosteum of the posterior surface of the petrous bone and adjacent part of the internal acoustic meatus, as well as the bone in the region of the superior semicircular canal. **d** Overview. A., artery; Access., accessory; Ant., anterior; Asc., ascending; Br., branch; Brs., branches; Caps., capsular; Car., carotid; Cer., cerebral; Cliv., clival; Div., division; Dors., dorsal; Eth., ethmoidal; For., foramen; Hypogl., hypoglossal; Inf., inferior; Jug., jugular; Lac., lacrimal; Lat., lateral; Med., medial; Men., meningeal; Mid., middle; Occip., occipital; Olf., olfactory; Ophth., ophthalmic; Pharyng., pharyngeal; Pet., petrosal; Post., posterior; Rec., recurrent; Subarc., subarcuate; Tr., trunk. [Reprinted from Martins C, Yasuda A, Campero A, Ulm AJ, Tanriover N, Rhoton A. Microsurgical anatomy of the dural arteries. *Neurosurgery* 2005; 56 (ONS Suppl 2):211–251. With permission from Oxford University Press.]



(continued)

nerve supplying the dura of the anterior cranial fossa. **Just behind the greater wing of sphenoid V1 bifurcated to produce (1) a lateral meningeal branch and (2) a medial orbital branch.** The meningeal branch proceeds directly forward into the orbit lateral to superior orbital fissure. Development of alisphenoid around the nerve creates a meningo-orbital foramen. One in the orbit, this branch is directed upward through what will become an un-named the foramen in orbital plate. The orbital branch turns medial and then enters the superior orbital fissure. Once in the orbit, V1 again supplies the dura via a separate *dural branch of anterior ethmoid nerve* that re-enters the cranial cavity via the cribriform fossa. A third *recurrent meningeal branch* of V1 supplies the tentorium. As we shall see, this fact is crucial for understanding development.

- (2) V2, before exiting the skull via foramen rotundum gives off the *middle meningeal nerve* to the postorbital dura of anterolateral frontal lobe behind alisphenoid. Recall that V1 and V2 are running close to each other through the lateral wall of the cavernous sinus. Upon exiting, they part company behind the backwall of the orbit. V2 continues downward and lateral into the floor and lateral wall of the temporal fossa while V1 plows straight ahead to the orbits, it then bifurcates, as described above. Retrograde horseradish peroxidase label studies show tracer from the lacrimal gland back to both V1 and V2 parts of the trigeminal ganglion [2]. The V2 component reaches the gland via extracranial zygomatic nerve from the pterygopalatine fossa. In sum: intracranial V2 supplies the lateral wall of temporal fossa including, conducting StV2 arterial supply to the dura and the inner aspect of the calvaria plate of alisphenoid. **At no time does intracranial V2 enter the orbit.**
- (3) V3, after exiting the skull via foramen ovale, V3 is distributed to lower jaw and oral cavity, but prior to doing so, the nerve is required to send its first branch to the dura. To accomplish this, V3 of the *recurrent meningeal nerve* supplying the temporo-parietal-occipital lobes. The nerve accompanies the StV3 middle meningeal

artery upward through foramen spinosum to reach its target.

Historical note: Friedrich Arnold [3] described a recurrent branch of V1, *nervus tentorii*, having an extensive distribution to tentorium cerebelli, parieto-occipital dura of the basal posterior lobe, posterior 1/3 of falx, and superior sagittal sinus [3]. Arising in r1, the recurrent meningeal nerve of Arnold is in register with the anlage of the cerebellum which arises from that neuromere. It is given off from the superior surface of V1 inside lateral wall of cavernous sinus and tracks backward in parallel with cranial nerve IV. Note that the midsection of the remainder of falx is supplied by V1 while the anterior 1/3 is innervated by anterior ethmoid nerve, arising more distally in the orbit and then tracking backward through the cribriform plate. The distribution of Arnold's nerve explains which pain from this region can be referred forward to the eye and forehead.

Stapedial Stem Divides Within the Tympanic Cavity

The stem of stapedial is the remnant of the primitive *hyoid artery* to the 2nd pharyngeal arch. When the second aortic arch to PA2 disintegrates at stage 12 it leaves behind a dorsal remnant, the hyoid artery, dangling from the dorsal aorta. With the growth of the embryo, the hyoid is repositioned backward toward the otic capsule where it eventually is identified as the sole extracranial branch of ICA.

At stage 14, the definitive circulation of the internal carotid is established. The hyoid artery remains extracranial but it gives off the stapedial stem which immediately tracks upward into the tympanic cavity where stapes form around it (henceforth the name). Directly beyond stapes, the artery bifurcates. The upper division runs directly forward to the trigeminal ganglion where it picks up V1 and V2 just as the nerves exit the cavernous sinus. The lower division follows chorda tympani out from the tympanic cavity into the face via the pterotympanic fissure. It then picks up V3 sensory nerve just below foramen ovale. All subsequent branches of the stapedial system follow the trajectories of V1, V2, or V3.

Fig. 12.24 Superior view of the convexity. Blood supply of the individual meningeal arteries: internal carotid (green), external carotid system (blue), and verteobasilar (red). **a** Internal carotid system. The anterior ethmoidal artery (StV1) has also been called the anterior meningeal artery when its territory extends to the dura of the frontal convexity. It gives origin to the anterior falcine artery, also called the artery of the falx cerebri, which supplies the anterior portion of the falx cerebri and adjacent dura covering the frontal pole. **b** External carotid system. The convexity dura is supplied predominantly by branches of the middle meningeal arteries (StV2 and StV3), which supply the dura of frontal, temporal, and parietal convexity and the adjacent walls of the transverse and sigmoid sinus. **c** Verteobasilar system. The C1 posterior meningeal artery may reach the dura of the posterior convexity in the area above the torcula. **d** Overview. The dura over the frontal convexity is supplied by the anterior meningeal branch of the anterior ethmoidal artery and branches of the anterior division of the middle meningeal artery that also reaches the dura in the anterior parietal region. The parieto-occipital and petrosquamosal branches of the posterior division of the middle meningeal artery supply the dura over the posterior convexity. A., artery; Access., accessory; A., artery; Ant., anterior; Div., division; Men., meningeal; Mid., middle; Post., posterior. [Reprinted from Martins C, Yasuda A, Campero A, Ulm AJ, Tanriover N, Rhoton A. Microsurgical anatomy of the dural arteries. *Neurosurgery* 2005; 56 (ONS Suppl 2):211–251. With permission from Oxford University Press.]

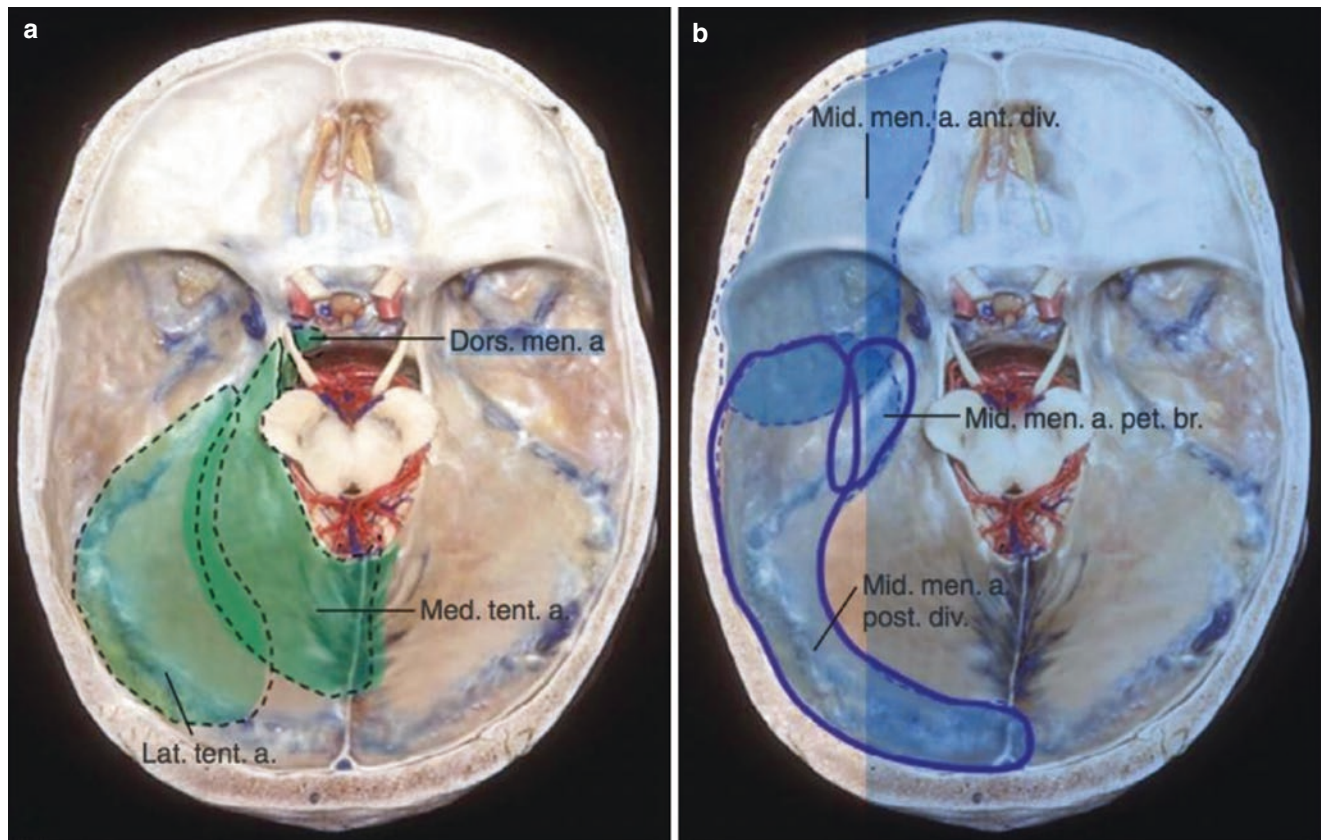


Fig. 12.25 Superior view of the tentorium. Tentorial branches from the cavernous segment of ICA (green), external carotid (blue), and the vertebralbasilar system (red). A, Cavernous ICA (StV1). From medial to lateral, the dorsal meningeal, the medial and lateral tentorial arteries supply the tentorium at its petrosal attachment. B, External carotid system. The branches of the posterior division (StV3) of the middle meningeal artery contribute to the supply of the anterolateral tentorium and extend superiorly to supply the falcotentorial junction and falx. The posterior StV3 branch of the middle meningeal artery gives rise to the *petrosquamosal branch* at the junction of the skull base and convexity

and supplies the insertion of the tentorium along the petrous ridge and groove for the transverse sinus; the dura of the torcula; and the junction of the sigmoid, transverse and superior petrosal sinuses. A., artery; Ant., anterior; Br., branch; Div., division; Dors., dorsal; Lat., lateral; Med., medial; Men., meningeal; Mid., middle; P.C.A., posterior cerebral artery; Post., posterior; Tent., tentorial. [Reprinted from Martins C, Yasuda A, Campero A, Ulm AJ, Tanriover N, Rhoton A. Microsurgical anatomy of the dural arteries. *Neurosurgery* 2005; 56 (ONS Suppl 2):211–251. With permission from Oxford University Press.]

Upper division stapedia: forward to the orbit and upward to the V1 and V2 dura.

The stem artery follows greater petrosal nerve forward to the trigeminal ganglion. Here, it picks up cranial nerves V1 and V2 as they run forward in the lateral wall of cavernous sinus. Immediately upon leaving the sinus both V1 and V2 give off *dural branches* prior to exiting the skull. Upper-division stapedia artery bifurcates to provide vascular support for all branches of V1 and V2. These arteries supply their respective areas of dura in the anterior and posterior cranial fossae. Orbital branch of V1 passes through superior orbital fissure. Meningeal branch of V1 gains access lateral to the fissure.

StV1 becomes identifiable at stage 18, enters the orbit during stage 19, and forms an anastomosis with the primitive ophthalmic at stage 20. The “annexation” of stapedia takes place due to the involution of the stapedia stem. Thus, the

final product, “ophthalmic artery,” is a hybrid system. Primitive ophthalmic, being derived from ICA, supplies CNS tissue exclusively, that is, the optic nerve and globe. All remaining tissues of the orbit innervated by V1 are supplied by branches from the derivatives of the original stapedia system.

V1 stapedia artery follows a similar time course by stage 19 enters the orbit as *two distinct vessels*. StV1 meningeal branch follows the nerve into lateral orbit via a separate *meningo-orbital foramen* in the greater wing of sphenoid. Sometimes this foramen merely a lateral extension of the superior orbital fissure.. StV1 orbital branch goes through the fissure heading directly for the stem of ophthalmic artery. When lacrimal artery forms, both arteries connect to it but the flow changes that occur when orbital branch connects with ophthalmic make it dominant. The lateral STV1 usually involutes but sometimes it persists as the recurrent menin-

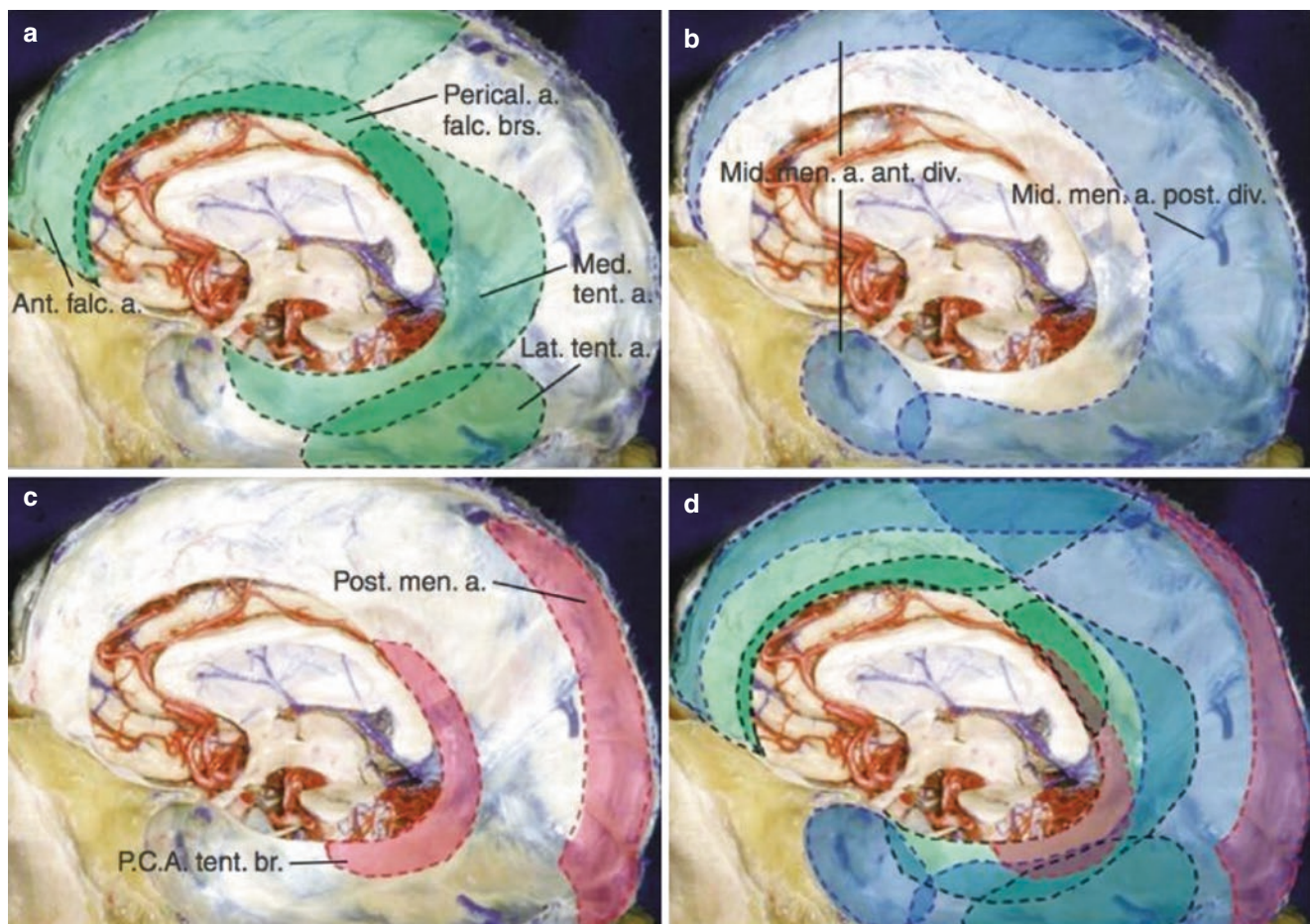


Fig. 12.26 Lateral view showing the supply of the tentorium and falx: dural branches from the internal carotid arterial system (green), the external carotid system (blue), and the vertebrobasilar system (red). **a** Internal carotid system. The *anterior falcine artery*, the distal continuation of the StV1 anterior ethmoidal artery, enters the falx at the cribriform plate and supplies the anterior portion of the falx cerebri and adjacent dura covering the frontal pole. The free border of the falx and the walls of the inferior sagittal sinus receive branches from the anterior cerebral *pericallosal arteries* anteriorly and the posterior cerebral *medial tentorial artery* posteriorly. **b** External carotid system. The anterior and posterior divisions of the middle meningeal artery (StV2 and StV3) supply the walls of the superior sagittal sinus and give rise to

descending branches that are the *main supply to the falx and the falcotentorial junction*. **c** Vertebrobasilar system. The posterior meningeal arteries (C1 segmental) reach the falcotentorial junction and posterior third of the falx cerebri. **d** Overview. A., artery; Ant., anterior; Br., branch; Brs., branches; Div., division; Falc., falcine; Lat., lateral; Med., medial; Men., meningeal; Mid., middle; P.C.A., posterior cerebral artery; Perical., pericallosal; Post., posterior; Tent., tentorial. [Reprinted from Martins C, Yasuda A, Campero A, Ulm AJ, Tanriover N, Rhoton A. Microsurgical anatomy of the dural arteries. *Neurosurgery* 2005; 56 (ONS Suppl 2):211–251. With permission from Oxford University Press.]

geal artery (RMA). The dual anastomosis to lacrimal explains when, in some cases, no connection with ophthalmic transpires. In this case, the entire system of non-ocular orbital arteries is supplied by the StV1, connecting backward to the middle meningeal system. In any case, two dual branches of StV1 explains why the clefts can occur in the lateral-most zone of the orbit (Tessier zone 9).

At stage 20 upper division stapedia becomes a target for a 3rd artery arising programmed by V3. This anastomosis takes place proximal to the ganglion, that is, before StV1 and StV2 have bifurcated. Extracranial stapedia (see below) passes up from below via the foramen spinosum as the mid-

dle meningeal nerve and artery. When this anastomosis takes place, the previous connection with stapedia stem involutes. StV2 now becomes the *anterior branch of the middle meningeal artery*. StV3 subsequently defines the *posterior branch of middle meningeal artery*.

Nota bene: RMA immediately connects with lacrimal. The connection generally involutes but sometimes the entire orbital stapedia system can be filled from lateral StV1 via a patent RMA. In the orbital floor zygomatic nerve and artery track laterally, giving off zygomaticofacial nerve and artery to the jugal bone field. Zygomatic nerve continues up to lacrimal gland where, as zygomatico-temporal nerve, it joins

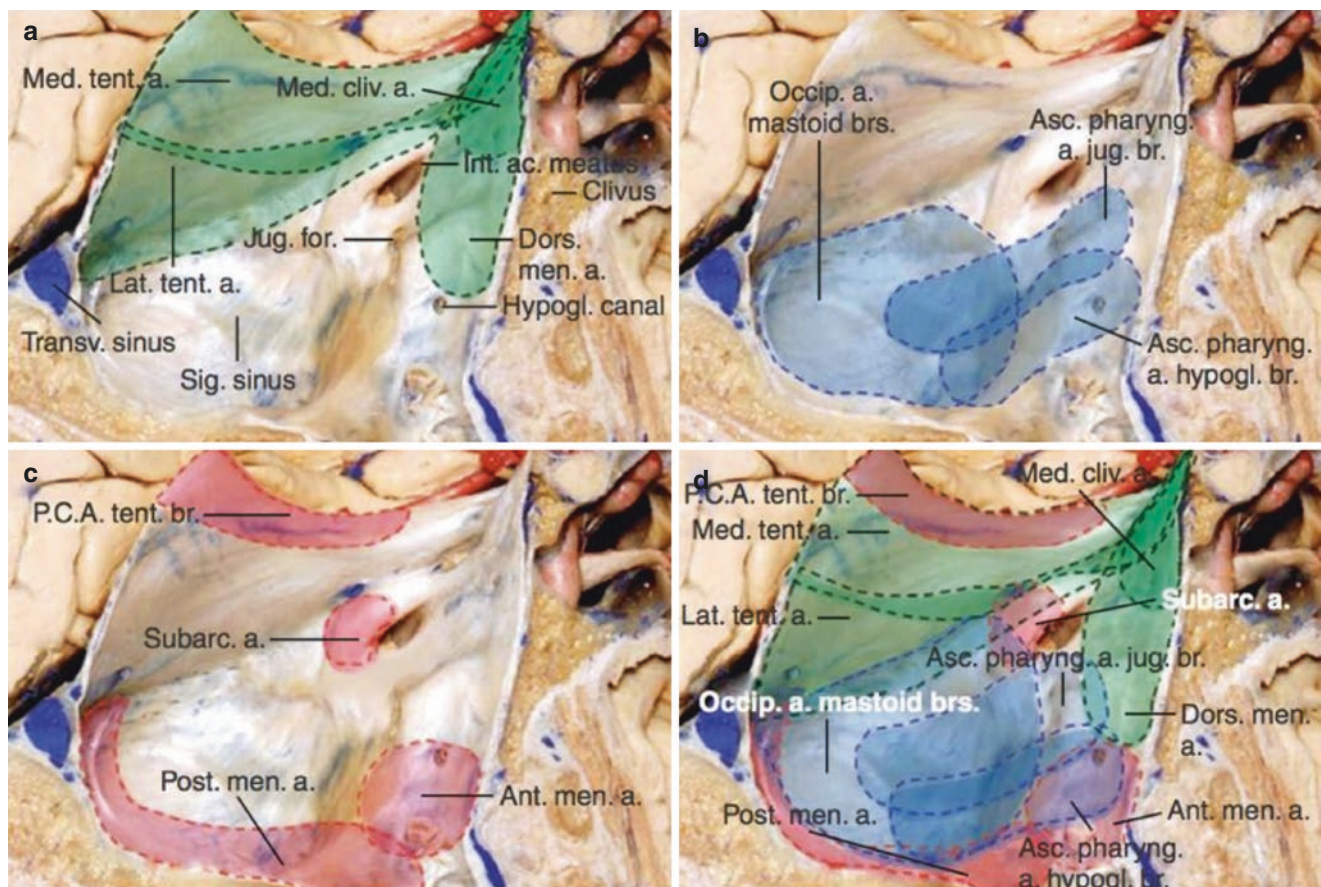


Fig. 12.27 Posterior fossa and tentorial dura. The view is directed from medially into the left half of a posterior fossa in which the cerebellum was removed. The clivus is on the right and the transverse sinus on the left. Blood supply of the individual meningeal arteries: internal carotid (green), external carotid system (blue), and verteobasilar (red). **a** Internal carotid system, StV1 cavernous segment. The *medial tentorial artery* supplies the medial third of the tentorium and the *dorsal meningeal* and the *lateral tentorial artery* contribute to the arcade that supply the attachment of the tentorium to the petrous ridge. The medial clival and dorsal meningeal arteries supply the dorsum sellae and upper clivus. The medial edge of the tentorium is also supplied through a branch of the posterior cerebral artery (incorrectly classified as verteobasilar). PCA, tentorial branch should be colored green. **b** External carotid system. The hypoglossal and jugular branches of the r6-r7 ascending pharyngeal artery supply the periosteum of petrous zone and S3-S4 supraorbital. Branches of the r4-r5 occipital artery supply the periosteum of the lateral part of the cerebellar fossa and the internal surface of the mastoid bone. The mastoid branch of the occipital artery constitutes the main supply of the lateral part of the cerebellar fossae and has a role on the supply of the lateral tentorial attachment. **c** Verteobasilar system. The *subarcuate artery*, a branch of the anterior

inferior cerebellar artery, supplies the posterior surface of the petrous bone above the internal acoustic meatus and surrounding the subarcuate fossa. The anterior and posterior meningeal branches of C1 segmental artery supply the foramen magnum periosteum and dura descending below foramen magnum. The posterior meningeal artery supplies the medial and intermediate portions of the cerebellar fossae periosteum. The verteobasilar system is given credit for supplying the medial edge of the tentorium on the false assumption that through posterior cerebral artery is not an ICA derivative (which it is). This PCA zone should be colored green. **d** Overview. Branches derived from all three arterial systems supply the dura covering the posterior surface of the petrous bone and clivus. A., artery; Ac., acoustic; Asc., ascending; Ant., anterior; Br., branch; Brs., branches; Cliv., clival; Dors., dorsal; For., foramen; Hypogl., hypoglossal; Int., internal; Jug., jugular; Lat., lateral; Med., medial; Men., meningeal; Occip., occipital; P.C.A., posterior cerebral artery; Pharyng., pharyngeal; Post., posterior; Sig., sigmoid; Subarc., subarcuate; Tent., tentorial; Transv., transverse. [Reprinted from Martins C, Yasuda A, Campero A, Ulm AJ, Tanriover N, Rhoton A. Microsurgical anatomy of the dural arteries. *Neurosurgery* 2005; 56 (ONS Suppl 2):211-251. With permission from Oxford University Press.]

lacrimal nerve to provide PANS supply to the gland. From there, ZTN swings posteriorly to supply to exit the orbit and supply the postorbital field of the zygomatic complex. In doing so, it takes along with it an artery *having its stem from lacrimal*. Thus, zygomaticotemporal artery originates from infraorbital but can also receive flow from lacrimal artery. It is possible that ZTA represents a remnant of the embryonic RCA. Despite their differing sources of blood supply, both ZFA and ZTA are StV2 neuroangiosomes.

Lower division stapedia: forward to the jaws and upward to the V3 dura

As soon as chorda tympani departs from the tympanic cavity, it makes a beeline for the sensory root of V3, where it seeks out lingual nerve by which to convey itself to the tongue. Lower division stapedia tracks along with the nerve. At the same time, the poorly-named maxillary branch from external carotid tracks forward toward V3. At stages 18–19, anastomosis takes place between lower division stapedia and ECA creates the hybrid *maxillomandibular artery* (MMA).

These anastomoses cause increase distal flow with dramatic anatomic consequences. (1) MMA now becomes a composite structure. (2) Proximal extracranial stapedia shrinks down but persists as anterior tympanic. (3) Intracranial StV2 unites with the “newcomer” intracranial StV3 to form the definitive intracranial dural artery system. (4) StV1 attaches to primitive ophthalmic and the proximal segment extending back to trigeminal ganglion involutes.

MMA has two functions and three distinct zones. Branches associated with the stapedia system supply those structures reassigned from the 1st arch: jaws, the suspensory bones of the maxilla, and the dura. Branches associated with the external carotid supply all original structures of the 1st arch, such as the muscles of mastication, fat, and glands. The zones of MMA are as follows. The *proximal (mandibular) zone* gives off stapedia derivatives that re-enter the skull to supply the tympanic cavity and the dura of the middle and posterior cranial fossa. It also sends StV3 inferior alveolar to supply the mandible. The sole ECA branch of the proximal zone supplies mylohyoid. The branches of the *middle (infratemporal) zone* are distributed exclusively to muscles of mastication. *Distal (pterygopalatine) zone* gives off StV2 branches in the pterygopalatine fossa that are subsequently distributed to the maxilla and its suspensory bones.

Big picture idea: anastomoses to the stapedia system are responsible for its demise

Reunification and disappearance of the stapedia system (Please see Figures from Chaps. 6 to 7)

Toward the end of the embryonic period, the anatomy of the stapedia system is drastically altered, making it virtually unrecognizable. Three anastomoses are responsible for these changes.

- (1) At stage 20, within the orbit, StV1 is annexed by ophthalmic. Its proximal segment dies back to the bifurcation with StV2.
- (2) Also at stages 18–19, inferior division stapedia joins external carotid just lateral to V3. This anastomosis creates the hybrid *maxillomandibular artery* (MMA).
- (3) From MMA, middle meningeal artery follows sensory V3 middle meningeal nerve upward to supply the dura. At stage 20 middle meningeal annexes StV2. It does not annex StV1 proximal to the orbit because this segment has already undergone involution. Thus, intracranial middle meningeal becomes a hybrid system: its anterior branch arises from StV2 and its posterior branch arises from StV3.

The common denominator of these anastomoses is the exposure of the distal vessel for higher flow; the proximal segment therefore involutes. StV1 artery dies backward from the superior orbital fissure to the bifurcation of the superior division. **StV1 meningeal artery, the RMA**, dies backward from meningo-orbital foramen to its intersection with StV3. Note that RMA in the orbit leaves behind the source of zygomatico-temporal artery to zone 8. Superior division of stapedia is eliminated completely back to stapes. Inferior division of stapedia distal to stapes persists as the *anterior tympanic artery*. Proximal to stapes the stapedia stem persists as the *caroticotympanic artery*.

Fate of the Intracranial Stapedia System

V1 stapedia first gives off a dura branch to the anterior cranial fossa. Then, having traversed the superior orbital fissure it divides into three branches, each of which supplies structures both within the orbit and outside of the orbit.

- *Supratrochlear* (frontal) and its branches supply zones 13-12 composed of the ethmoid complex, the nasal envelope, and the medial forehead between the eyebrows.
- *Supraorbital* supplies zones 11-10 consisting of the orbital roof, the upper eyelid and lateral forehead defined by the eyebrows.
- *Lacrimal* supplies zone 9 which includes alisphenoid, the lacrimal gland and then lateral corner of the upper eyelid.

V2 stapedia supplies the dura of antero-lateral temporal fossa and the lateral orbit.

Fate of the Extracranial Stapedia System

In the pterygopalatine fossa maxillomandibular artery gives off branches to the maxillary complex and palate, all of which are V2 nerves. The arteries supplying the two fields of zygoma, jugal and postorbital (see below) represent Tessier zones 7 and 8. Greater sphenoid wing originally arose as the

epipterygoid bone, part of the ancient *palatoquadrate cartilage* from which maxilla evolved. The original function of epipterygoid was to serve as intermediate support between palate and maxilla. As such, the blood supply for AS logically relates to the structures hence its supply from the extracranial *zygomatic artery*. Additional support for alisphenoid comes from temporalis muscle via *anterior deep temporal branch* of the external carotid component of maxillomandibular artery. In sum, Tessier zone 9 is complex, supplied by the confluence of three distinct systems.

To complete our picture, V3 stapedial supplies two functionally-related zones: the mandible and the anterior tympanic cavity, including malleus and incus. Inferior alveolar supplies three dental units and the ramus whereas anterior tympanic is directed back to the temporal complex. This reflects the complex paleohistory of the mandibular bone complex in which its proximal components such as quadrate were brought backwards into the skull as structures of hearing.

Stapedial Branches to the Dura

Ophthalmic (V1) Branches of ophthalmic all represent the V1 stapedial added on to the primitive ophthalmic from internal carotid.

Anterior ethmoid : post-frontal dura, anterior falx

Posterior ethmoidal: medial 1/3 anterior fossa

Recurrent deep: cavernous sinus

Recurrent, superficial: lesser sphenoid wing, anteromedial middle fossa

Lacrimal: superior orbital fissure, sphenoid wings

Middle meningeal (V1, V2, and V3) The proximal 1/3 of maxilla-mandibular artery, gives rise to middle meningeal artery and accessory meningeal artery. These supply, collectively, nearly the entirety of dura over the cerebral convexities, the cerebellum and a significant sector of basal dura. They are accompanied by branches of V2-V3.

Middle meningeal artery

Petrosal branch (V1): trigeminal ganglion, geniculate ganglion

Anterior branch (V2: goes all the way forward to the back wall of the orbit

Posterior branch (V3): posterolateral middle fossa

Accessory meningeal artery

External: eustachian tube, external auditory meatus

Internal: medial middle fossa, CN III, IV, V, VI, VII

Intracranial Internal Carotid Provides Minor Branches to the Dura

Anterior cerebral artery provides minor branches to the medial 1/3 floor of anterior fossa. Posterior cerebral, in like manner supplies posterior falx and adjacent tentorium. It is of interest that neural crest cells from specific neuromeres have been mapped to the arterial walls of the internal carotid system.

External Carotid System

The branches of ECA give rise two dural arteries. The occipital a. is a derivative of 2nd aortic arch artery. Ascending pharyngeal is a derivative of 3rd aortic arch artery. Both must access the skull via foramina and they supply the posterior cranial fossa [Figs. 12.28, 12.29, 12.30 and 12.31].

Confusion arises regarding maxillary artery, as its middle meningeal branch is commonly considered to supply the dura. In reality, the stapedial system, derived from the dorsal remnant of 2nd aortic arch artery, is the genetic source for this supply. Its anastomotic relationship with IMMA have been previously detailed.

The *infratentorial periosteum (misconstrued as dura)* covers the bones of the posterior fossa below the transverse sinus. These correspond to the petromastoid complex and the occipital bone complex (supraoccipital, exoccipital, and basioccipital), both discussed at length previously. These mesodermal bones arise from r4 to r11 and ossify in cartilage. The zones are dependent on the external carotid system.

Aortic arch arteries: precursors of the external carotid system

Human embryos possess five pharyngeal arches (PAs) with which craniofacial structures are assembled. Running through the core of each arch is a vascular axis, *aortic arch artery (AA)*, that spans from the cardiac outflow tract tucked below the pharynx upward to paired dorsal aortae. The first four pharyngeal arches are important. PA5 is diminutive, producing the arytenoids, cricoid, and associated muscles. For this reason, the 5th aortic arch artery involutes almost immediately, making PA5 dependent upon the blood supply of PA4 for its survival. *There is no 6th pharyngeal arch.* Instead, the fate of the 6th and final aortic arch artery is to form pulmonary circulation.

Note: Textbook illustrations of the aortic arches are misleading. We can easily understand how they work by means of a little *embryonic origami*. Fact: the 1st aortic arch artery does *not* ‘sprout forth’ from the cardiac outflow tract. At stage 8, the embryo is still a flat trilaminar disc. The embry-

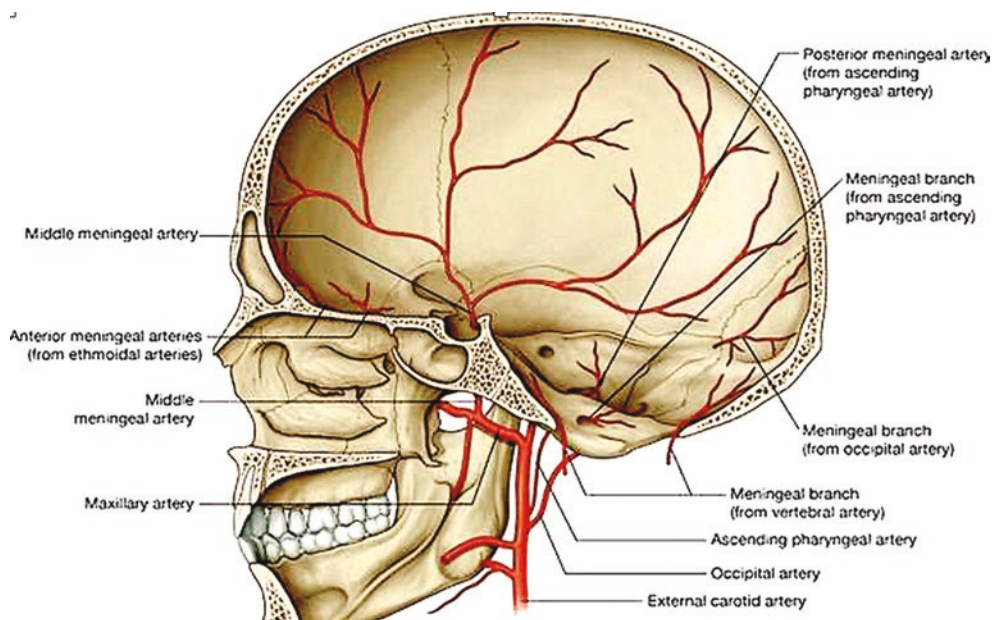


Fig. 12.28 Posterior fossa periosteum is supplied by two arterial systems. The occipital artery r4-r5 is developmentally related to 2nd aortic arch artery. It enters the skull via jugular foramen and condylar foramen. For this reason, it supplies S1–S2 that form the upper zone of supraoccipital bone. The ascending pharyngeal artery r6–r7 is developmentally related to 3rd aortic arch artery. Its neuromeningeal division

enters the skull at three sites: foramen magnum to supply the clivus, hypoglossal foramen to supply foramen magnum, and jugular foramen to supply S3–S4 that form lower zone of supraoccipital. [Reprinted from Drake R, Vogel AW, Mitchell AWM. *Gray's Anatomy for Students*, 3rd edition. Philadelphia, PA: Churchill-Livingstone. 2015. With permission from Elsevier.]

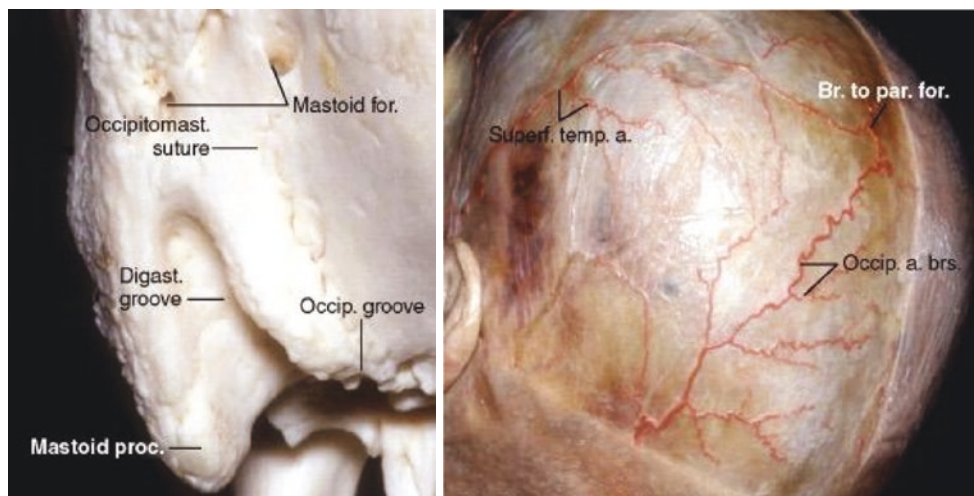


Fig. 12.29 Left: 2nd segment of occipital artery sends meningeal branch through the *mastoid foramen*, a probable boundary between r4-r5 and r6-r7 fields of mastoid. Right: 3rd segment ascends over occipitalis and perforates *parietal foramen* to supply dura of interpari-

etal/parietal boundary. [Reprinted from Martins C, Yasuda A, Campero A, Ulm AJ, Tanriover N, Rhoton A. Microsurgical anatomy of the dural arteries. *Neurosurgery* 2005; 56 (ONS Suppl 2):211–251. With permission from Oxford University Press.]

Fig. 12.30 Ascending pharyngeal system r6-r7 has two trunks: pharyngeal and neuromeningeal. From the latter, clival branch ascends of basioccipital, and it is directed to the S1-S2 zone. Neuromeningeal enters the skull via hypoglossal foramen and jugular foramen. [Reprinted from Haccin-Bey L, Daniels DL, Ulmer JL, Mark LP, Smith MM, Strootmann JM, Brown D, Meyer GA, WackLyn PA. The ascending pharyngeal artery: branches, anastomoses, and clinical significance. *Am J Neuroradiol* 2002; 23:1246–1256. With permission from American Society of Neuroradiology.]

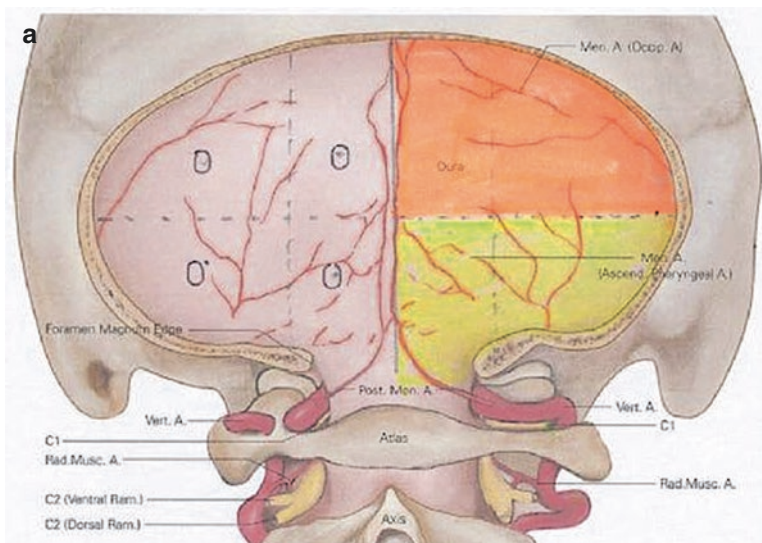
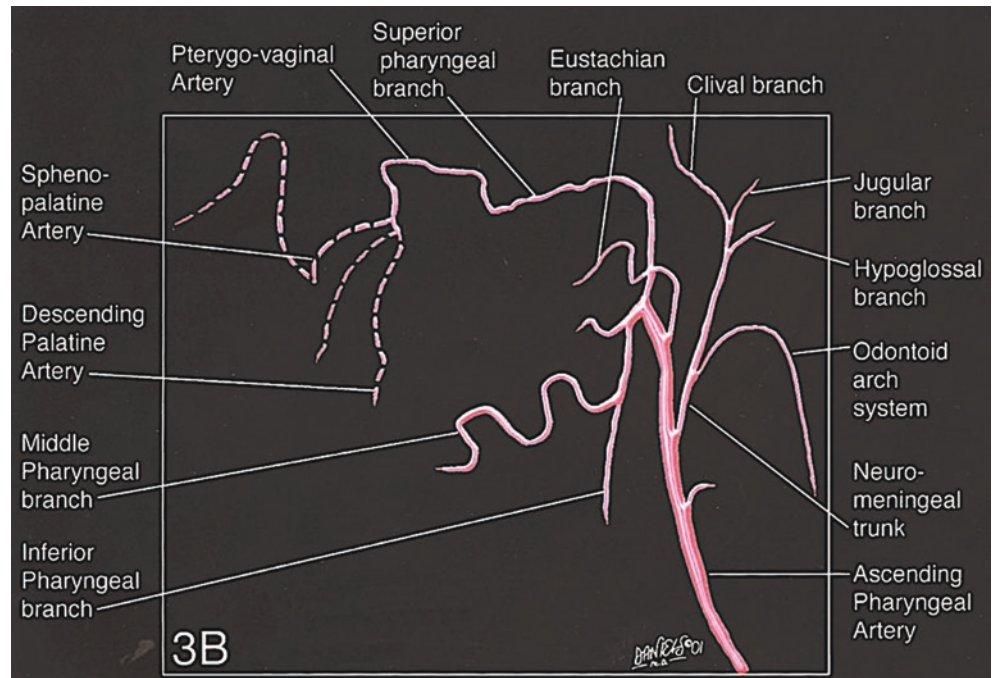


Fig. 12.31 Posterior meningeal arteries from 1st cervical intersegmental track up the midline to the torcula (not seen). Four quadrants were created which refer to the bone fields of Srivastava. A: [Reprinted from Zhao J, Feng X, Ren J, Manjila S, Bambakidis NC. Dural arteriovenous fistulas at the craniocervical junction: a systematic review. *Journal of NeuroInterventional Surgery* 2016;8:648–653. With permission from BMJ Publishing Group Ltd.] B: [Reprinted from Srivastava HC. Development of ossification centres in the squamous portion of the occipital bone in man. *J Anat* 1977; 124(3):643–647. With permission from John Wiley & Sons.]

Journal of NeuroInterventional Surgery 2016;8:648–653. With permission from BMJ Publishing Group Ltd.] B: [Reprinted from Srivastava HC. Development of ossification centres in the squamous portion of the occipital bone in man. *J Anat* 1977; 124(3):643–647. With permission from John Wiley & Sons.]

onic heart field is located in front of the future brain and is connected to the two dorsal aortae that run passively backward along the length of the embryo. At stage 9 explosive growth of the forebrain forces the embryonic head to flex downward almost 150°. The hinge point, located at the mid-brain, is called the *mesencephalic flexure*. The heart is now positioned under the neuraxis; specifically, directly below posterior pharynx.

Because the dorsal aortae are attached to the ventricles of the heart, in the process of folding they become stretched

downward and backward, forming bilateral arcs connecting the heart below with the embryo above. They have now termed the *1st aortic arch arteries*. The remaining five aortic arch arteries develop one per stage. Each arch represents the union of two distinct stems. From above, the dorsal aortae send out ventrally-directed stems while, from below, the out-flow tract produces paired dorsally-directed stems. The two sets of stems unite to produce the aortic arch artery. Failure of this anastomotic process explains: (1) the failure of AA5; and (2) the breakdown and reorganization of the system.

The six aortic arches appear in craniocaudal sequence in stages 9–14. The pharyngeal arch becomes visible one stage later. After their formation in stages 10–11, the 1st and 2nd pharyngeal arches merge together in stages 12–13, thus creating the tissue masses that will complete the construction of the face. In the process, their aortic arch arteries disintegrate, leaving behind arterial remnants dangling from the dorsal aortae. *Hyoid artery*, the dorsal remnant of AA2, will become the source of the stapodial system.

By the end of the pharyngeal arch period (stage 14), AA3 is transformed into the common carotid; it gives off the external carotid artery and then continues onward as the extracranial internal carotid. AA4 produces paired subclavians and, on the left side, the aortic arch. The two dorsal aortae into which AA4 inserts have merged into a single descending aorta. As a result of embryonic growth and spatial rearrangement of the pharyngeal arches the hyoid artery becomes the *first branch of the extracranial internal carotid artery* just below the otic capsule. Hyoid artery will morph into the stem of stapodial system.

The final configuration of the external carotid branches is as follows:

- AA1 – 1st arch: maxillary, lingual
- AA2 – 2nd arch: facial, superficial temporal, posterior auricular, occipital
- AA3 – 3rd arch: ascending pharyngeal
- AA4 – 4th arch: superior thyroid

Occipital Artery

This derivative of AA2 supplies structures in register with r4-r5 and supports the territories of r8-r9. It follows motor branches to facial muscles and DIF, sends penetrating branches down from SIF to underlying dura of posterior fossa. In some instances, once the bone forms, *emissary arteries* are an embryologic hold-hover of this process [cf Figs. 12.28 and 12.29].

Occipital artery has three segments: ascending cervical (described), horizontal occipital, and vertical occipital. Branches supplying posterior fossa originate from the 2nd and 3rd segments. The stem is given off from the posterior aspect of ECA at the mandibular angle. The first segment courses upward, being crossed by cranial nerve XII, running deep to digastric until it reaches mastoid process. Here it can travel either deep or superficial to longissimus capitis muscle.

Second segment *mastoid branch* enters via mastoid foramen at superior nuchal line and appears intracranially below transverse sinus, the embryologic boundary between the supraoccipital complex and interparietal complex. It takes three directions (1) It travels posteromedial to supply the lateral superior quadrant of supraoccipital. (2) It descends inferior to jugular foramen and anastomosis with ascending

pharyngeal. (3) It ascends to supply the periosteum over temporal bone at the cerebello-pontine angle.

The third segment supplies the soft tissues covering the posterior cranium. It enters the skull at parietal foramen 3–5 cm cephalad to the lambda; *parietal branch* supplies dura of the interparietal bone fields.

Ascending Pharyngeal Artery

This derivative of AA3 supplies structures in genetic register with r6-r7 and supports the territories of r10-r11. Its anterior pharyngeal division supplies soft palate, pharynx, and the tonsillar fossa. A *carotid branch* from this division supplies the periosteum of the carotid canal.

The posterior neuromeningeal division of APA must gain access to the skull via foramina. *Hypoglossal branch* follows cranial nerve XII as it exits the skull. Via the hypoglossal (anterior condylar) canal it is distributed in ring-like fashion to foramen magnum and clivus, following the mesenchyme of S4. The *jugular branch* follows cranial nerves IX, X, and XI as they exit through jugular foramen whereupon it divides. Medial branch supplies inferior petrosal sinus and hugs the territory of medial clival artery from cavernous carotid (inferior hypophyseal). It also supplies the petrous prootic field [cf Fig. 12.30].

Dorsal Aortae Segmental Arteries/the Vertebral System

1st Cervical Segmental Artery:

Two poorly named arteries are of great interest to us: anterior meningeal artery and posterior meningeal artery of extracranial vertebral are hopelessly obscure but important to understand the posterior cranial fossa. Here we shall be a bit more exacting for the sake of clarity. Both of these vessels arise from the first cervical segmental arteries, the final cross-link between the longitudinal neural arteries and the dorsal aortae prior to their demise and reconstruction [Fig. 12.31].

1. *Anterior meningeal branch of 1st cervical* supplies odontoid process, dura of the atlanto-occipital space, and anterolateral border of foramen magnum and occipital condyles. It anastomoses with ascending pharyngeal outside hypoglossal foramen.
2. *Posterior meningeal branch of 1st cervical* supplies dura of posterior atlanto-occipital space, falx cerebelli, paramedial cerebellar fossa, dura up to the transverse sinus. It ascends up the falx cerebelli, making successive anastomoses with ascending pharyngeal and occipital, thus defining the supraoccipital bone fields into four quadrants. Above the torcula, it terminates by anastomosing with two branches of StV3: petrosquamosal and parieto-occipital.

The first cervical arteries differ from those of C2 and C3 because they arise from the transverse bend of the vertebrals between atlas and the skull base. [The vertebrals subsequently ascend into the skull meet up of the longitudinal neural arteries.] In reality, 1st cervical is the original artery supplying derivatives of S5. It was designed to run *beneath* the proatlas (the original 1st cervical vertebra) but when proatlas was incorporated into the skull these arteries found themselves shipwrecked *above* the atlas. What do they supply and why?

All the derivatives of S5 are associated with the skull base. Proatlas forms the tip of the dens, a ligament from dens to basioccipital, and the posterior rim of foramen magnum and contributes (along with exoccipitals) to the occipital condyles. As S5 muscles are more numerous posteriorly, the posterior branches of c1 arteries are considerably larger than the anterior ones.

Caveat Embryologic confusion arises when these arteries are ascribed to “level C2-C3” as in the neurosurgical literature. The neuromeric levels of the occipito-cervical junction are described in detail in Chap. 10.

Longitudinal Neural/Basilar System

Cerebellum, as an r1 derivative, cannot be supplied by the internal carotid system. Recall that, immediately after giving off the posterior cerebral arteries, paired posterior communicating arteries anastomose LNAs. These come together in the form of the letter “Y” to fuse and form basilar. The mid-line extent of basilar is from r1 to r7, at which point the original LNAs persist although they are re-named vertebrals. The actual vascular boundary between the two systems is at level r11-c1 where the 1st cervical segmentals constitute the last connection between the old dorsal aortae and the LNAs prior to revision into the vertebral system.

Anterior Inferior Cerebellar Artery

This artery gives rise to subarcuate artery, which can also arise from the labyrinthine artery. Subarcuate anastomoses with r4-r5 stylomastoid artery and r4-r5 mastoid branch of occipital artery. This helps define the petrous bone anterior to internal auditory canal as pro-otic.

Analysis of Arterial Supply

Infratentorial “dura” (sic) periosteum is synthesized from PAM originating from rhombomeres r4-r11. Its blood supply comes from meningeal branches of the two branches of external carotid plus the meningeal arteries from c1. Occipital artery represents r4-r5 and supplies epaxial paraxial meso-

derm. It logical to expect that this artery will cover the r4-r5 prootic bone. Its branches extend posteriorly to the dura covering supraccipital bone. Ascending pharyngeal represents r6-r7 and defines epaxial paraxial mesoderm dedicated to the basioccipital, exoccipital, and the relatively small intracranial zone of opisthotic.

Why is there no apparent artery dedicated to mesenchyme from rhombomeres r8 to r11, that is, the occipital somites S1-S4? Why jump from the external carotid system all the way to the vertebrals? The answer lies in the embryologic formation of the vertebral system. Recall from Chaps. 6 and 7 that the occipital somites are originally supplied by segmental branches of paired dorsal aortae, a pattern continued all the way down the neuraxis. At stages 15–16, the system undergoes a radical transformation. Subclavians develop and give off vertical vessels that run up the neck interconnecting all the transverse segmentals. The great vessels of the heart morph into a single descending aorta and the paired dorsal aortae disappear. The vertical vessels become the vertebrals. At stage 17 the process is complete. At the level of r11-c1, the first cervical branch connects the vertebral with the old longitudinal neural arteries. And by stage 18 the external carotid system is fully developed with identifiable ascending occipital and pharyngeal arteries.

Faced with this “vascular drought” occipital somites get their blood supply in various and sundry ways. Tongue muscles move into pharyngeal arch territory and are supplied from external carotid. Sternocleidomastoid and trapezius are polysomitic muscles supplied by branches arising off the subclavian. But what of the bone derivatives of S1-S4?

These somites accept a “charity donation” from the external carotid system in a highly specific manner. Recall that, in neuromeric terms, occipital artery (r4-r5) is positioned anteriorly to ascending pharyngeal artery (r6-r7). S1 and S1 therefore “adopt” the more rostral of these two vascular axes, the occipital artery, whereas S3 and S4 depend upon the more caudal axis of ascending pharyngeal artery. Recall as well that each of the four occipital somites contributes to the occipital bone complex. Huang’s mapping shows that S1-S4 are laid down as concentric rings, with S1 being most peripheral and S4 at foramen magnum. For this reason, we find occipital supplying the periphery of supraoccipital and ascending pharyngeal surround the lower half of the bone.

Paleontologic note: When we examine the blood supply of the dura underlying the supraoccipital bone (see Fig. 12.31 with the bone removed) the striking pattern divides the dura into four (perhaps eight) quadrants. These correspond exactly to the subdivisions of the supraoccipital bone, each one of which bears a specific extensor muscle. Note: The zone between the superior transverse suture (superior nuchal line) and the mendosal suture (highest nuchal line) is chondral bone bearing the insertion of the

only two muscles with primary insertion at the occiput: trapezius and sternocleidomastoid.

Innervation of the Meninges/Periosteum

Nota bene Pia-arachnoid layers do not have somatic sensory innervation. These tissues likely behave in register with the neuromeric segment of the brain which they supply.

Supratentorial Innervation

The supratentorial dura is a very simple affair. Its mesenchyme (with one exception) is exclusively neural crest from rhombomere r1-r3. The lower zone of parietal dura includes paraxial mesoderm from r2 and r3. Recall that these form the poorly-appreciated “parietal cartilage” which appears in the lower zone of the temporoparietal region early in the formation of the cranial base. They could well be confined to squamosal bone. Blood supply is exclusive via the stapedia system [Figs. 12.32, 12.33, 12.34, 12.35, 12.36 and 12.37].

The cerebellar tentorium is worthy of comment as it represents the boundary zone between two different mesenchymes, two different circulations, two different innervations, and two different kinds of bone formation. Tentorium is like a trampoline that supports occipital lobes above the cerebellar hemispheres. Its anterior border is an open oval beginning at the posterior clinoid process which admits the cerebral peduncles to communicate from hind-brain to forebrain. It extends peripherally and backward along the petrous ridge, enclosing superior petrosal sinus which it follows backward to transverse sinus which it also encloses.

Sinuses form at the boundary of adjacent fields. Tentorium (r1) provides the upper/external lamina and infratentorial dura (r4-r7) gives the lower/internal lamina. The two layers track along either side of the sinus and then fuse together, forming a triangle enclosing the sinus.

Tentorium houses within itself the *straight sinus*. This implies that tentorium has *two layers*. Why? Although the entire structure of cerebellar tentorium is r1 neural crest, its two laminae result from different programming signals from posterior lobes of cerebrum above and from cerebellum below.

Anatomic implication. The cerebellum is completely wrapped in meninx arising from r1. Initially, it sticks up straight in the air like a mushroom, its sole innervation being V1. However, with brain development, it will fold backward until it comes to rest against the otic capsule and the developing braincase. As it does so, it pulls its meningeal coverings along with it. Fusion of the layers occurs as levels r4-r7 resulting in a horseshoe-shaped configuration, the tentorium cerebelli.

Infratentorial Innervation

The infratentorial periosteum (IP) differs in terms of anatomic distribution, mesenchymal origin, innervation, blood supply, and the bone structures that are associated with it. As stated, it lines the posterior fossa all the way from the posterior clinoid processes to the petrous ridge, that is, superior petrosal sinus, and sweeps backward to the transverse sinus. On the other side of this line, infratentorial periosteum fuses with the r1 tentorium cerebelli. This dura is constructed from paraxial mesoderm supplied by r4-r11. It covers bones derived from r4 to r7 petromastoid and r8-r11 occipital bone complex. Why in the world should this periosteum receive innervation from cervical nerves? First, let's look first at the what of this anatomy and second, why it makes developmental sense.

Infratentorial periosteum is supplied by sensory fibers from C2 to C3 (mostly C2) plus SANS neurons from the superior cervical ganglion (SCG). The nerves have three territories of distribution in the posterior fossa, depending upon their mode of access to the skull, via the foramen magnum, the hypoglossal canal, or the jugular foramen. Nerves entering foramen magnum un-accompanied are anterior rami which track along the post-central artery and ascend on a direct course up the basioccipital almost to the posterior clinoid processes. Nerves entering the skull via hypoglossal canal or jugular foramen are also anterior rami but their course is indirect. They first pass through the upper pole of superior cervical ganglion where they pick up sympathetic nerve fibers and proceed to track along cranial nerves XII and X until gaining entry to the skull; they then follow arteries.

Zone 1 nerves ascend the clivus from foramen magnum to the posterior clinoids. In so doing, they are accompanied (and programmed) by clival branch of ascending pharyngeal. The nerves defined the basioccipital bone fields.

Zone 2 nerves accompanying hypoglossal nerve fan out from the foramen. They innervate exoccipital and foramen magnum, which is framed by the exoccipital bone fields.

Zones 3 nerves accompanying vagus nerve via jugular part company with X at the foramen. They follow sigmoid sinus backward and upward and to transverse sinus and then track medially to innervate the supraoccipital bone fields.

Why This Innervation Pattern Makes Sense

When we analyze the somatic sensory distribution of r4-r7 we find hypaxial branches extensively represented in the oropharynx. Expaxial representation is limited to the tympanic cavity. Levels r8-r11 have hypaxial representation in the larynx and hypopharynx but no epaxial branches. Neuroanatomic studies confirm the complete absence of sensory fibers to dura from levels r4 to r11. These nuclei simply do not exist in the brainstem. Tissue cannot exist without sensory repre-

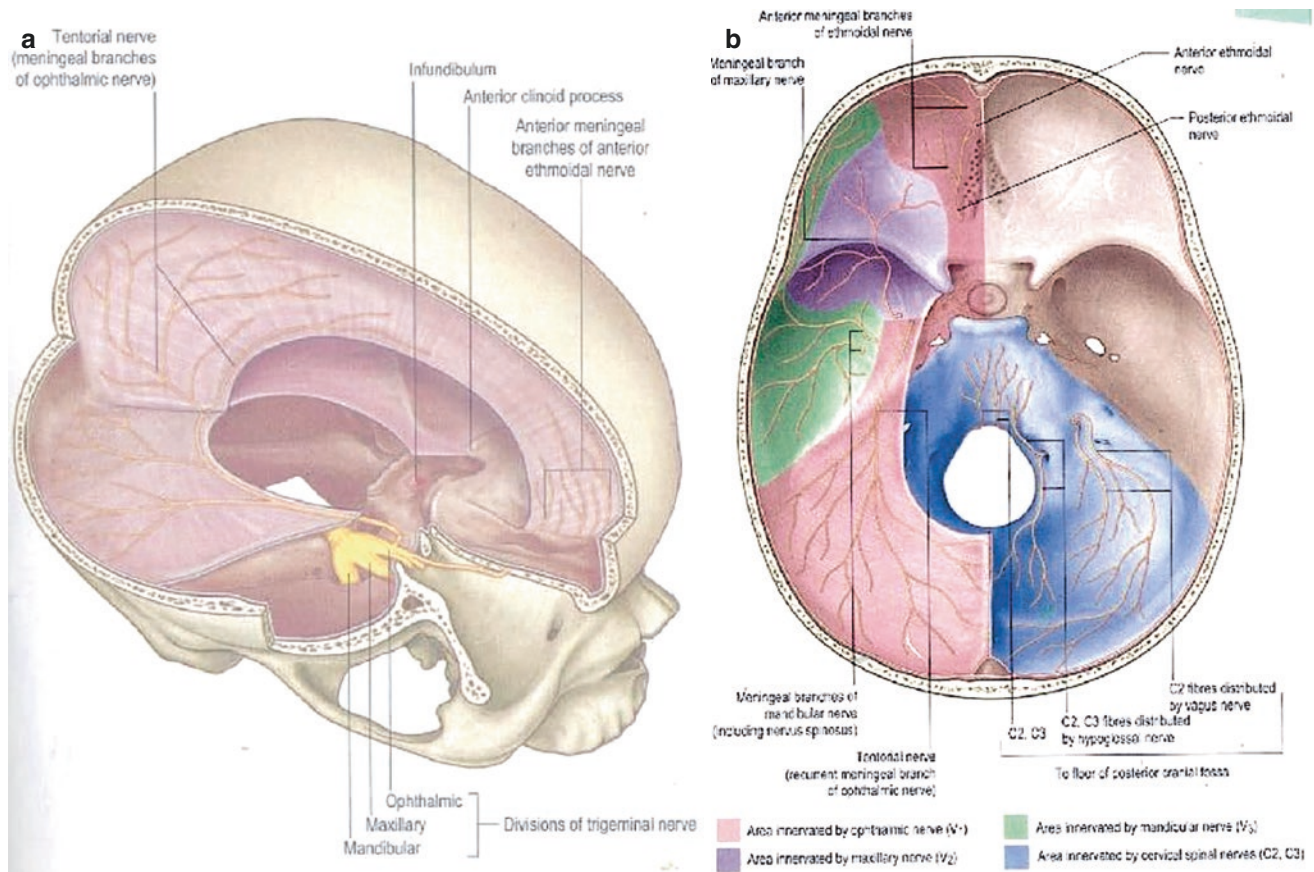


Fig. 12.32 Dura nerves. **Left:** Innervation of the dura V1 provides three branches to the falx: (1) anterior ethmoid n. to anterior third, (2) a direct branch of V1 to the middle third, and (3) recurrent branch to the posterior third and to the tentorium. **Right:** Innervation of the dura showing extensive distribution of V1 to both the anterior and middle cranial fossae. Neuromeres r4-r7 have no sensory representation so V1 and V2 must take over. Posterior fossa has no dura, being lined by *peri-*

osteum only (blue). It is supplied by C2-C3 as a substitute for absent representation in r8-r11. Note C2-C3 access the posterior fossa by traveling with vagus (X) to the r8-r9 zones (lower supraoccipital) and with hypoglossal (XII) to zone r10-r11 (upper occipital). [Reprinted from Standring S. Gray's Anatomy, 40th edition. Philadelphia, PA: Churchill-Livingstone; 2008. With permission from Elsevier.]

sentation—the first three cervical levels are forced to “take up the slack.”

Does C1 Participate or Not?

C1 is considered unique among spinal nerves because it is said to be purely motor. Both cervical skin and scalp are devoid of C1 sensory fibers. Some neuroanatomists continue to represent C1 over the clival surface of basioccipital. Does it have any role? If so, where?

The central idea is the in the transition between cranium and neck, somites get progressively larger “portfolios” in terms of what they produce. Occipital somites

S1-S4 can only make bone and hypaxial (but not epaxial) muscle. S5 is the first to make epaxial muscle but no skin. However, a fascial sleeve unites foramen magnum with axis. C1 dura could conceivably exist within this envelope, and; it could be limited to anterior to foramen magnum but not posteriorly. S6 is a full-fledged “blue ribbon” producer of both dermis and periosteum. C2 fibers are both hypaxial in the neck and epaxial in the scalp. They appear over the clivus and in the back of the skull.

It is thought that basioccipital is supplied directly by C1 (some) and by C2. C1 does *not* connect with superior cervi-

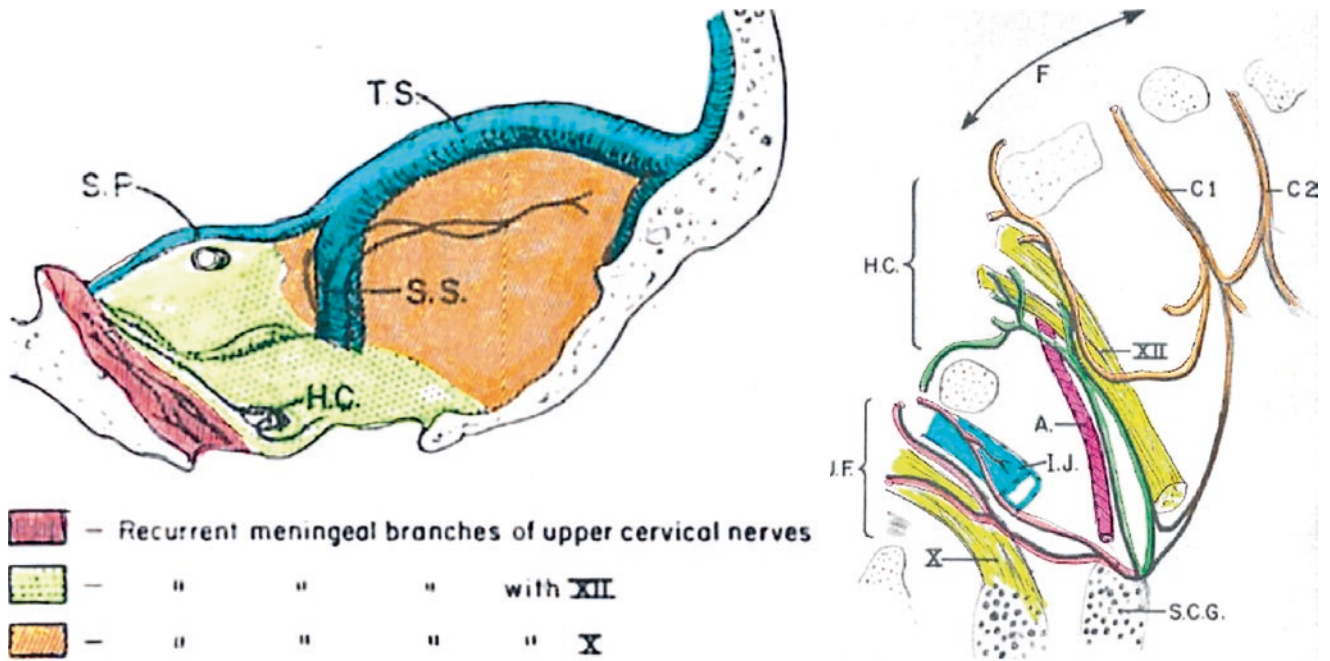
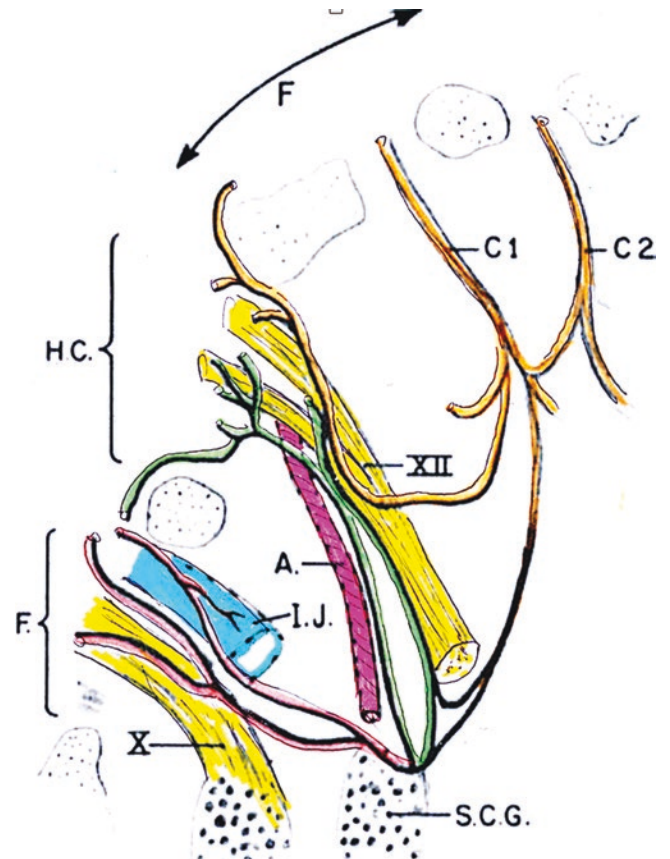


Fig. 12.33 Distribution of sensory nerves to posterior fossa. (1) Recurrent branches direct (pink) supply basioccipital and all zones S1-S4. (2) Recurrent via XII (yellow) enters via hypoglossal foramen, supplies opisthotic, exoccipital, and S3-S4 of supraoccipital. (3)

Recurrent via X enters via jugular foramen to supply opisthotic and S1-S2 of supraoccipital. [Reprinted from Kimmel DL. Innervation of the spinal dura mater and dura mater of the posterior cranial fossa. *Neurology* 1961; 11(9):800-809. With permission from Wolters Kluwer Health, Inc.]

Fig. 12.34 Cervical fibers arrive in three formats. (1) Isolated neurons c1 and c2 (not shown) climb up the clivus to supply basioccipital. (2) C2 (yellow) via superior cervical ganglion follows the more posterior CN XII via hypoglossal foramen into skull. It distributes to opisthotic, exoccipital, and S3-S4. (3) C2 (orange) via superior cervical ganglion follows the more anterior CN X through the jugular foramen. It distributes to prootic and S1-S2. [Reprinted from Kimmel DL. Innervation of the spinal dura mater and dura mater of the posterior cranial fossa. *Neurology* 1961; 11(9):800-809. With permission from Wolters Kluwer Health, Inc.]



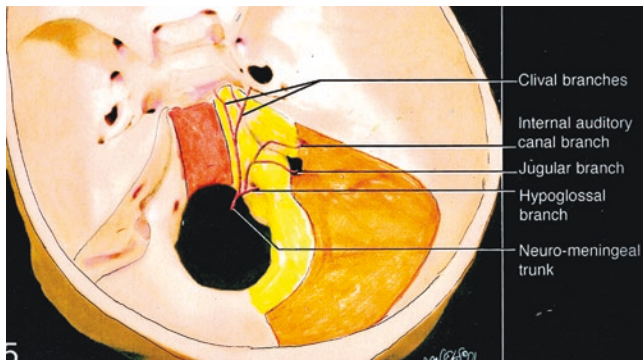


Fig. 12.35 Neural territories per Kimmel marked: (1) direct branches C1-C2 to basioccipital (pink). (2) Indirect branches of C2 distributed to prootic, medial exoccipital and lower zones (S4-S3) of supraoccipital are supplied by ascending pharyngeal representing r6-r7 (yellow). (3) Indirect branches of C2-C3 distributed to opisthotic, lateral exoccipital, and upper zones (S2-S1) are supplied by occipital artery representing r4-r5 (orange). Note the congruency of lamination between innervation and blood supply. [Reprinted from Haccin-Bey L, Daniels DL, Ulmer JL, Mark LP, Smith MM, Strootmann JM, Brown D, Meyer GA, WackLyn PA. The ascending pharyngeal artery: branches, anastomoses, and clinical significance. *Am J Neuroradiol* 2002; 23:1246-1256. With permission from the American Society of Neuroradiology.]

cal ganglion. C2 enters via jugular foramen with distribution to r4-r5 and upper zone of supraoccipital. When it enters hypoglossal foramen, it is distributed to r6-r7 and lower supraoccipital bone. This pattern makes perfect sense for the exoccipital and supraoccipital bones. The Huang model would predict that the upper zones (S1-S2) would be irrigated by branches of r4-r5 occipital artery while the lower zone (S3-4) would be supplied by r5-r6 branches of ascending pharyngeal.

An Astounding Misconception

Occipital and ascending pharyngeal supply structures of the 2nd and 3rd arches, respectively. This does NOT imply dura is as pharyngeal arch derivative. It simply means that our model of external carotid as being strictly relating to pharyngeal arches is *wrong*. We really should be talking about these arteries as in register with neuromeres. In this manner, we can explain the presence of structures such as squamous temporal bone and parietal cartilage that are clearly supplied by ECA and are unrelated to the arches.

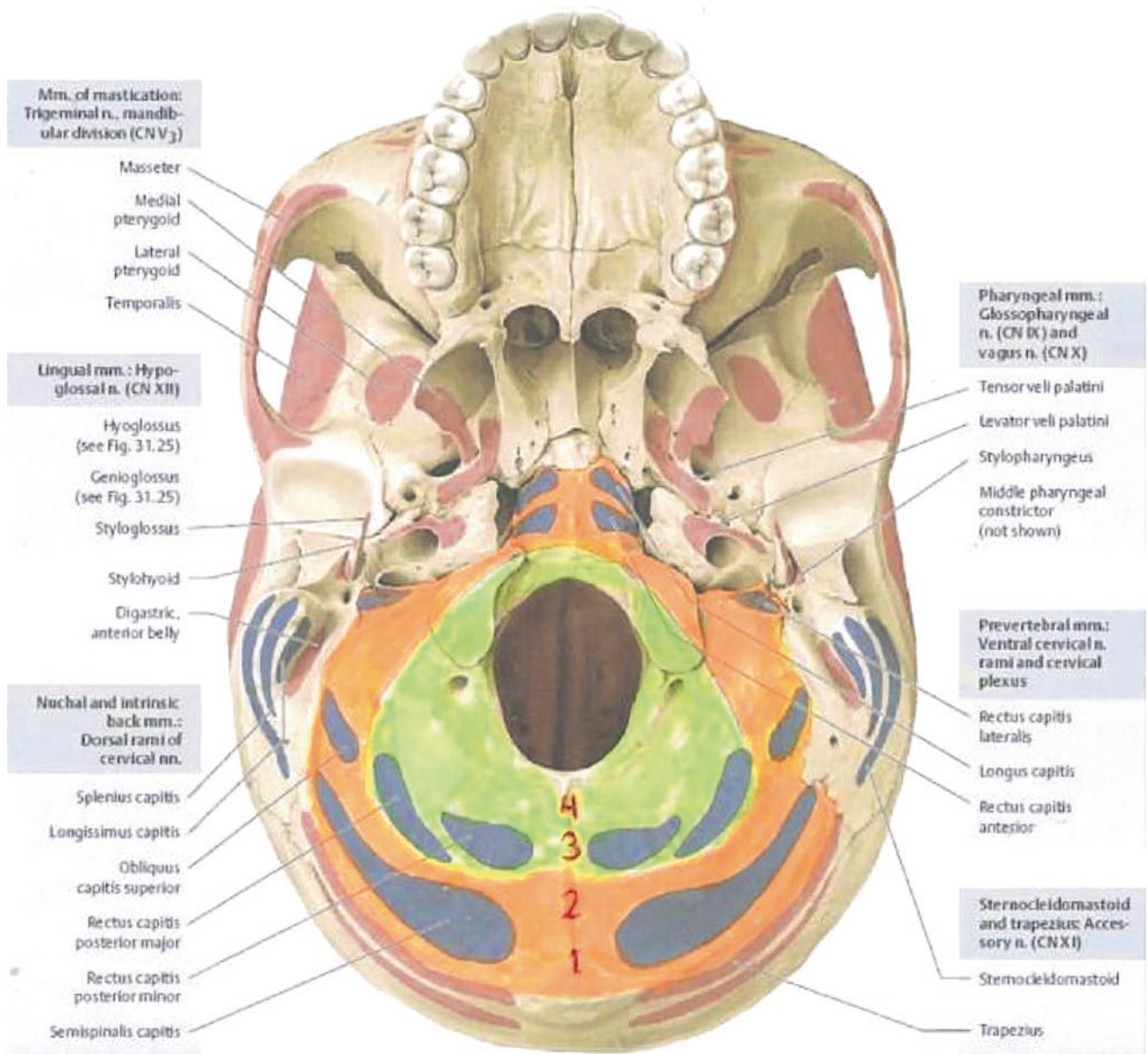


Fig. 12.36 Occipital somites are laminated, one upon the other, like Russian dolls. S1 is the largest and S4 is the smallest. Their bone products are in concentric rings. Somites S1 and S2 (orange) are lateral and form the superior half of supraoccipital. Somites SS3 and S4 are medial

and produce lower supraoccipital. Hypoglossal foramen is between S3 and S4. Muscle insertion sites are also zonal. [Reprinted from Lewis, Warren H (ed). Gray's Anatomy of the Human Body, 20th American Edition. Philadelphia, PA: Lea & Febiger, 1918.]

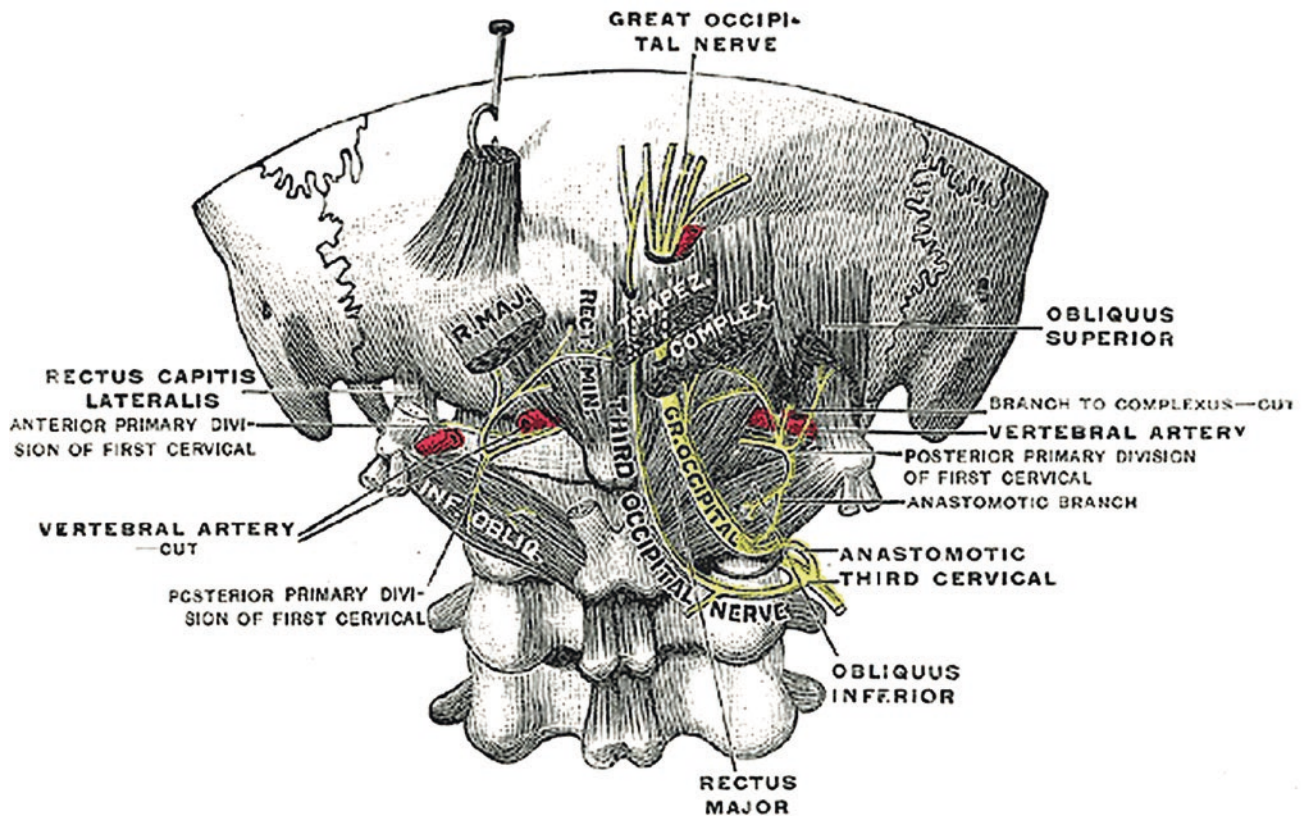


Fig. 12.37 Posterior branches of cervical nerves C1-C3. C1 suboccipital nerve is strictly motor. The anterior branch is smaller, having limited muscle targets. C2 greater occipital and C3 lesser occipital have small anterior branches contribute to cervical plexus and clival periosteum. These do not make contact with superior cervical ganglion. They enter foramen magnum directly to supply basioccipital periosteum. Posterior branches of C2 and C3 send sensory neurons to pick up SANS

fibers from superior cervical ganglion. These are then distributed to occipital and supraoccipital periosteum. C2 posterior division is also motor whereas that of C3 is sensory only. Sensory distribution for the membranous calvarium is C2 lateral and C3 medial. [Reprinted from Lewis, Warren H (ed). *Gray's Anatomy of the Human Body*, 20th American Edition. Philadelphia, PA: Lea & Febiger, 1918.]

Mesenchyme of the Meninges

Pia Arachnoid Mesenchyme

These tissues maintain vascular relationships with underlying brain on a neuromeric level. This probably determines the penetration patterns of the cortical vessels which are subsequently organized around the “feeder branches” of the cerebral circulation. Neuromeric mapping is on the basis of the underlying brain tissue.

Dural Mesenchyme

This is a relatively simple affair being provided by the PAM from levels r0-r3 and by neural crest from midbrain and r0-r3. Neuromeric mapping is on the basis of the trigeminal system.

Mesenchyme of the Posterior Cranial Fossa: Periosteum

In the absence of accurate rhombomeric mapping of these bone fields, we can make a best-guess assumption that the posterior fossa is an “equal opportunity employer” that makes use of paraxial mesoderm from all eight levels (r4-r11). In the case of temporal bone complex we know that r4-r7 are represented. Likewise, mapping by Huang in the avian model demonstrates the development of the occipital complex as a ring-like distribution of mesoderm from each occipital somite. The mammalian situation should be no different.

We have been able to account for the blood supply as the external carotid.

The dura of the occipital lobe is neural crest is r3 neural crest, innervated by V3 and supplied by StV3 meningeal arteries. Note that the occipital foramen admits 2nd arch

occipital artery into the skull below tentorium. The bones above it are membranous in formation. Interparietal has two zones, the central postparietals are neural crest while the lateral tabulars are paraxial mesoderm likely from level r3 as well. What determines the “chondrality” of a bone whether it forms in membrane or not depends on the intrinsic source and the dura with which it interacts.

The infratentorial periosteum come from two sources depending on the bone fields. PAM from r4 to r7 covers petromastoid. The periosteum lining of the occipital complex is made from r8 to r11 PAM and covers basioccipital, exoccipital and supraoccipital. The territories of distribution for the occipital complex can be ascertained from the model by Huang. Mesenchyme from r8 to r9 produces occipital somites 1-2. It is distributed in an arc bordering posterior lateral exoccipital and the upper zone of supraoccipital. is likely derived from r8 to r9 while the lower zone originates r10-r11. The upper zone is supplied by branches from the occipital artery correlating with the 2nd arch while the lower zone is supplied by branches of the ascending pharyngeal correlating with 3rd arch. It is to be emphasized that these bone fields. The designated sensory supply is hyaxial C1-C2 to basioccipital and epaxial C2 to exoccipital and supraoccipital.

As previously stated, the internal periosteum covering the ones of posterior fossa represents the stem cell layer “donated” to the bone by the underlying somitomeres and somites. In the case of the temporal bone complex, its external periosteum contains stem cells from overlying mesodermal structures, such as muscle insertions, and neural crest fascia. The internal periosteum of the occipital bone complex is derived from the four occipital somites while the external periosteum bears the stem cells of the multiple muscles insertion into the posterior cranial base [Cf Figs. 12.36 and 12.37].

The fusion plane between neural crest and PAM mesenchymes results in triangular spaces that create the dural sinuses. These smooth fascial tubes have no lining endothelium and consequently no valves. *Continuity of periosteum between neural crest and mesoderm at the level of the sinuses means that the sinuses can be safely reflected away from the bone.*

The combination of arterial supply and innervation beneath supraoccipital bone divides it into four (and perhaps eight) distinct zones, each one receiving a C1 muscle. The muscles are inserted into an exterior periosteum that is continuous between the chondral supraoccipital complex and the membranous interparietal complex. The posterior fossa represents coverage over both chondral and membranous bone. It contains the suboccipital fossa of muscles from C1 to C2. It continues upward bringing C1-2 PAM into contact with r3 neural crest. There is a zone overlying the membranous occipital where dura is covered externally by C2 dermis

and DIF supplied by occipital artery. But above the highest nuchal DIF continues as the periosteum. Thus, the origin of posterior fossa dura is a mixture of neural crest as described plus PAM contributions from Sm7 to C2-C3.

In sum, the development of the posterior fossa has these key anatomic points.

- (1) No dura exists below tentorium cerebelli.
- (2) Venous sinuses form the superior boundaries of posterior fossa.
- (3) The sinuses are boundary zones between neural crest and PAM.
- (4) Posterior fossa is lined by internal periosteum: PAM from r4 to r11.
- (5) Petromastoid and its periosteum are products of r4-r7, somitomeres 4-7.
- (6) Occipital complex and its periosteum are products of r8-r11, somites S1-S4.
- (7) The external periosteum of the occiput is a product of cervical somites C1-C3.

Themes of Meningeal Development

Stages 7–10: Mesenchyme Surrounds the Neural Tube

During early development, the component parts necessary for synthesizing an immediate blood supply to the CNS parenchyma are laid down. These are (1) mesodermal endothelial cells to form the tubular structures of blood vessels, (2) neural crest-derived pericytes to surround the tubules, and (3) neural crest to provide a primitive covering layer that coats the vessels as they enter the brain parenchyma to maintain a blood-brain barrier. Gastrulation (completed in stages 7–8) organizes mesoderm into the paraxial, intermediate, and lateral plate sectors. At stage 8 the neuroectoderm forms the primordium of the brain. Immediately lateral, at the junction between the neuroectoderm and paraxial mesoderm, neural crest cells develop. Prechordal mesoderm is present just cranial to the notochord—at future level r0, it is positioned directly opposite from where the 1st pharyngeal arches will appear. By stage 9, the neural crest cells begin to migrate. Stage 10 involves further proliferation of prechordal mesoderm. Migration of MNC into the midline splits prechordal mesoderm: MNC forms the nasoethmoid mesenchyme and PCM moves out to the orbits.

Neurulation at stage 8 involves the rolling-up of the neural plate into the neural tube. At all levels from r1 backward, this pulls adjacent paraxial mesoderm upward into contact with the neural tube, thus creating an immediate source for blood vessels over the hindbrain. Hindbrain and spinal cord PAM is self-sufficient to make both endothelial tubes and

pericytes—neural crest cells *are not required*. Forward from r1, paraxial mesoderm coverage of forebrain/midbrain is accomplished by a process of *tissue expansion*. As the forebrain arises from the plane of the embryo. PAM from r1 to r3 is mechanically pulled forward to cover it.

By stage 9, neural crest cells migrate over the forebrain and midbrain where they are critical for the development of the head plexus. At these levels, NCCs *are required* to produce pericytes necessary for support the blood vessels. The stage 9 brain is now completely surrounded by a primitive head plexus. Nutrients come from surrounding fluid, as the connection with the heart is not yet established.

At stage 10, in the presence of neural crest, these primitive vessels acquire pericytes and penetrate into the neuropil. The primitive head plexus is now directly supplied from the heart via segmental arteries that interconnect with dorsal aortae. Conditions are now present for development of pia mater which becomes visible at the next stage.

Stages 11–13: Peri-CNS Mesenchyme Organizes: Pia Mater

Nota bene: *As soon as a cell layer appears in between the wall of the brain and the vascular layer, this layer is identified as **pia mater**.*

By stage 11, pia mater first presents over the caudal medulla. It develops from local neural crest and contains primitive blood vessels. *Subsequent pial development proceeds cranially*, arriving at the mesencephalon by stage 12. Complete pial coverage of the telencephalon is achieved by stages 13–14.

By stage 15, the entire primary meninx is in place but the leptomeninges have not differentiated. During stages 17 and 18 *leptomeningeal development* takes place. The mesenchyme just above the brain is fluid-filled, *presumably from blood vessels of the original head mesoderm* spanning between the cerebrum and the overlying peripheral mesenchyme. This zone develops into a meshwork, first above the fourth ventricle and then spreading throughout the hindbrain/midbrain and later over the forebrain.

In summation: pia formation takes place in two ways. Hindbrain and cerebellar pia arises from the *internal migration* of neural crest which flows downward over the neural tube to achieve complete coverage. The coverage is immediate (even before closure of the neural tube) and local: neural crest participates from every neuromeric level of the neural tube, from r1 backward. Pia maturation into identifiable layers follows exactly the caudal-rostral progression of CNS vascular development. Vascular supply of the pia makes use of peritubular somitomic mesoderm to form a succession

of structures. Primitive head plexus matures into longitudinal neural arteries. The LNAs connect with the primitive internal carotid to supply each neuromere, one-by-one. They eventually connect with the vertebral arteries. The arterial supply to the brain is deep to the dura, remaining isolated from the external carotid system.

Forebrain pia is limited to the cerebral coverage because midbrain and diencephalon are enclosed within the hemispheres. PNC has no role in forebrain meninges due to its limited developmental potential—it only makes frontonasal dermis. Hindbrain neural crest (r1-r3) must be imported.

Stage 13 marks the beginning of the notochordal sheath and the consolidation of the posterior fossa cranial base.

Stages 14–17: Primary Meninx in a New Location: Tentorium Cerebelli

At stage 14 the cellular sheath of the notochord has reached the r1 and the midbrain. The forward progress of this tissue reflects the posterior to anterior development of the paraxial cranial base. By stage 15 the cellular sheath extends all the way forward.

Cerebellum arises from r0 to r1 (collectively called r1). Primary meninx (PAM and neural crest) from r1 undergoes three forms of expansion. (1) One population surrounds cerebellum; it will morph into secondary meninx with pia and arachnoid. (2) A second population extends outward as a T-shaped sheet interposed between cerebellum and forebrain and also extending backwards between the two lobes of cerebellum. The transverse limb becomes tentorium and the sagittal limb becomes falx cerebelli. (3) A third population migrates forward over both the medial and lateral surfaces of cerebrum. It will develop to frontal lobe dura and falx cerebrii.

This structure, the *protentorium*, is first observed (as expected) at the level of the mesencephalic flexure. It is medial, just behind diencephalon and forward from the termination of basilar artery, that is, exactly at rhombomere r1. This medial tissue is a placeholder. It is not yet dura. Later in development (stage 19) with development of the cerebellum, protentorium undergoes apoptosis and is replaced by lateral components.

Nota Bene At stage 16 cranial nerve outgrowth takes place. These will provide the programming for the subsequent arterials. In particular V and VII organize the stapodial system in plane immediately superficial to future dura propia.

By stage 17 lateral parts of the tentorium grow medially from the otic capsule and tentorium appears.

Stages 17–18 Secondary Meninx: Leptomeninges and Dura

Exactly how the secondary meninx develops varies depending upon its location along the neuraxis.

Mesenchyme closest to the brain forms a fluid-filled meshwork, the vessels of which are connected with veins located at the periphery. Vascularization takes place and new cellular elements appear. These will form scaffold of arachnoid. At the deep margin arachnoid is separated from pia by the blood vessel network but its definition at the periphery depends upon events in the overlying dura.

Two external condensations take place in the dura. The more internal one becomes the identifiable *dural limiting membrane* and will define it vis-a-vis the arachnoid. External to that, a thicker condensation becomes the osteogenic *skel-etogenous layer*. It is external to the veins. Although this layer interacts with overlying soft tissues to form the membranous calvarium, the cell source for the bone is predominantly from dura. Having given up its mesenchyme to the skull, the skeletogenous layer retreats, differentiates. Left behind immediately beneath the bone is the internal periosteum; the arteries lie just beneath. Subjacent is the dura propria and finally the dural limiting membrane.

Dura mater begins to develop at stage 17. The dural limiting membrane develops in the same caudal-to-cranial and ventral-dorsal sequence as the pia. During stage 18 the many branches of the stapelial system become dependent of the external carotid system for supply. This process causes the dura to mature and thicken.

Stage 19–23 Dural Venous Sinuses Appear

At stage 19 tentorium extends in the midline; the falx cerebri is present at stage 20. The presence of parietal plate, otic capsule, obitosphonoid and alisphenoid indicates formation of periosteum, likely at the same time as the full development of tentorium. Dural limiting membrane continues to advance forward, covering the hindbrain by stage 22 and the midbrain by stage 23. Note that forebrain will expand backward into the space such that this dura becomes basal beneath the posterior cerebral lobes. Sinuses are defined as soon as the dural limiting membrane appears in the region because of the interface with posterior fossa periosteum.

At stage 23 falx has now reached its most forward extent over crista galli. Dural lining layer, now complete basally, extends upward over the lateral walls of cerebrum.

Skin Coverage of the Brain

How does skin coverage over the nervous system take place? In the case of the spinal cord, the process is simple. The neural tube rolls up on itself like a cigar. As the two edges of non-neural ectoderm (future epidermis) approximate each other they drag along with them subjacent paraxial mesoderm as well. As these two layers fuse, the neural tube sinks beneath the skin. Local neural crest from each neuromere immediately migrates: (1) outward beneath the skin, (2) adjacent to the somites to form the sympathetic chain, (3) ventrally to populate the lateral plate mesoderm of future viscera, and (4) downward to cover the neural tube circumferentially.

Craniofacial skin is utterly different. Its epidermis comes from discontinuous sources. Frontonasal epidermis is a product of prosencephalic non-neural ectoderm from the anterior neural folds. The remaining epidermis is true ectoderm from r1 to r3, including anterior tympanic membrane. The upper eyelid epidermis and the conjunctiva are the only sites in the embryo where r1 ectoderm is expressed. Note V1 fibers supply the cornea via lacrimal gland as well as from the superior orbital fissure. This gives us a potential “roadmap” for r1 ectoderm to reach the upper eyelid. Innervation of the upper eyelid by The first 12 somitomeres (head mesoderm + occipital somites + 1st cervical somite) are incapable of producing dermis. Thus dermal tissues must come from remote sources. *Underlying all non-somitic skin is the single unifying structure of the face and skull: the 2nd arch superficial investing fascia SIF (also as the superficial musculo-aponeurotic system or SMAS).* It conveys the vessels of the external carotid system to support the overlying skin. It also interacts with the underlying dura to produce the membranous bones of the calvarium.

Frontonasal Skin and Scalp (FNO)

Recall from our previous discussion that the frontonasal skin is radically different from the other five skin types. Here, epidermis and dermis both come from non-traditional sources. This *non-neural ectoderm* (NNE) of the anterior prosencephalic folds. This ectoderm is *not* produced via gastrulation. The populations “assigned” to NNE correspond to the p6-p4 zones of the old Puelles prosomeric system. There are no neural crest cells in the anterior folds but they do contain placodes. The dermal supply for frontonasal skin is neural crest from zones p3-p1. The dermal precursor populations

migrate forward beneath the NNE. Together this composite tissue covers the upper face like a baseball cap pulled forward over the eyes.

Note that PNC frontonasal fields have no intrinsic neurovascular supply. The PNC dermis is layered upon the underlying r1 mesenchyme. In this way it acquires StV1 stapedial arterial vessels and V1 nerves. Later in development 2nd arch mesenchyme interposes itself between the two pre-existent layers. It brings with it intrinsic blood supply from the external carotid (transverse branch of superficial temporal) but only into the facial muscles. For this reason, both supraorbital and supratrochlear neurovascular pedicles split around the SMAS fascia. The deep branches go to periosteum and the superficial branches supply the skin. Thus, even though portions of frontalis are irrigated by ECA, the vertical pedicles run all the way upward to the vertex.

Of clinical importance is the susceptibility of frontonasal skin to underlying pathologies of the V1 stapedial neuroangiosomes. Deficits can occur in eyelids, eyebrows, and dermis. The skin is at risk for neurodegenerative states such as Perry Romberg disease and neurocutaneous disorders.

Non-Frontonasal Skin

This skin covers all of the face and scalp innervated by V1, V2, and V3. Its components originate from rostral rhombomeres r1-r3. Midbrain neural crest does not participate nor is dermis produced anywhere else in the hindbrain. Gastrulation occurs at level r1. It does not supply frontonasal skin with ectoderm of neural crest. So what happens to the r1 tissues? They produce a very small component of ectoderm which is likely assigned to upper eyelid and the conjunctiva. Dermal and subconjunctival tissues from r1 are likewise extremely thin. Despite these limited efforts r1 is definitely not a “second-class citizen.” Its contributions are vast, being the required mesenchyme of dura, bone, and fascia for the anterior cranial base and orbit.

Migration of PNC brings it into contact with r1 dura and the V1 stapedial neurovascular axes. At the same time, SIF invades the frontonasal zone, passing over the orbit (previously populated by midbrain neural crest) into the forehead and down over the nose. Frontal bone forms at the interface with r1 dura and SIF.

Comments About Scalp Hair

Skin coverage is timed with neural tube closure—between stage 11 when the rostral neuropore closes and closure of the caudal neuropore at stage 12. At stage 13 the first hair in the entire body appears at the parieto-occipito junction, the boundary between dermis from epaxial r3 neural crest and dermis from the epaxial dermatomes of c2 and c3. From this spot, the

occipital whorl, hair growth radiates outward. Scalp formation demonstrates the epithelial-mesenchymal interaction required to induce dermis. One can hypothesize that the distinctions between the hair-bearing scalp and beard-forming facial skin relate to genetic differences between epaxial versus hypaxial populations of neural crest. Occipital hair could represent that neural crest from c1 to c2 does not have any hypaxial.

Bilaminar Programming of Membranous Calvarial Bone

Membranous calvarial bone is bilaminar with an intervening marrow space. This bilaminar model has to do with two sources of programming. Obviously, in the most primitive state, mesenchymal tissues of the meninges are apposed with overlying neural crest dermis from either PNC or r2-r3. Later in development neural crest fascia and muscle from the r4 to r5 differentiate and are *interposed between the dura and dermis* – this is superficial investing fascia, SIF, or galea.

So which layer is responsible for programming the external table? Is it r2-r3 neural crest dermis, r4-r5 neural crest fascia, or both? Neuromeric mapping has not been done to date but we can draw some conclusions from the embryology. The vascular supply of the scalp, primarily from superficial temporal system, appears very late in embryogenesis, ascending from in front of the ear at stage 20 and reaching the vertex at stage 23. Dissections of the epicranium by this author [4] demonstrated perforating blood vessels passing downward through the subgaleal fascia and into the external periosteum. Temporo-parietal bone flaps can survive on superficial temporal pedicle designs. Substantial galeal-subgaleal flaps can be harvested from beneath the scalp with necrosis of the overlying skin. For these reasons, it is reasonable to assign a histologic role to r4-r5 neural crest over the entire extent of the calvarium. Superimposition of these zones is clinically useful with parietal bone to explain different forms of synostosis and with the interparietal bone complex to give histologic basis to its various fields.

Fascial Planes of the Brain and Calvarium

Our final topic is of great surgical relevance as it explores planes of separation and the differential synthesis of craniofacial bones. We are going to deal with three separate systems.

In our previous discussion of the blood supply to the skin we defined the fascial and vascular planes involving the structures of the face and scalp. These are:

1. Pia/arachnoid: primitive head plexus/internal carotid
2. Dura/fronto-orbito-nasal mesenchyme/jaws: the stapedial system

3. Deep investing fascia (pharyngeal arch mm.): deep branches of ECA
4. Superficial investing fascia/galea (facial mm.): superficial branches of ECA.

The reader will note that in the face and in the non-temporal cranium only three of these planes are relevant. The temporal region is unique, as it has all four fascial layers and therefore offers the most complexity because here SIF and DIF are both present.

At this juncture, the reader may well ask, “Since the sensory nerves and arteries of the dura and scalp appear to arise from common sources of mesenchyme, by what mechanism do they develop in different planes? And why should the neurovascular supply of these two structures vary in orientation? Those of dura mater run obliquely forwards and backwards whereas the superficial temporal system is essentially vertical. Our approach to the temporal fossa follows the Rule of Fours. *The coverage of the brain consists of four distinct layers, each with its own dedicated blood supply. The four vascular systems develop in four different spatial planes and develop at four different points in time.*

Layer 1: Endomeninx

Pia and arachnoid arise in situ as neural crest/PAM derivatives. It is directly exposed to signal from the underlying brain. It is vascularized by the vessels of the *primitive head plexus* at stages 8–9. These vessels develop from paraxial mesoderm immediately adjacent to the neural tube and paraxial mesoderm. They ultimately connect with the internal carotid circulation. By stage 14 pial development reaches the telencephalon and the vascularization process is largely complete.

Layer 2: Ectomeninx

Dura is a mixture of neural crest and PAM. It is further away from the brain and receives different differentiation cues, hence its three layers. It is vascularized by the *stapedial artery system*, beginning at stage 17. Stapedial development continues through stage 23.

Layer 3: Deep Investing Fascia

DIF encloses muscles of mastication arising from Sm4 and innervated by V3. It forms a muscle-enclosing mesenchymal sandwich from the midline of the cranial base upward to the squamosal-parietal boundary. It is vascularized by ECA arteries from the 2nd segment of internal maxillomandibular artery corresponding to 1st arch structures. As such, it provides external coverage for the middle cranial fossa contain-

ing r4-r5 petrous complex, the synthesis of these which is chondral and unrelated to DIF. DIF development is completed by stage 17.

Layer 4: Superficial Investing Fascia

The non-temporal calvarium is straightforward. It is composed of r4-r5 neural crest. Depending upon the anatomic zone, galea/SIF/SMAS may or may not enclose 2nd arch muscles. The muscle-free zone between frontalis and occipitalis is a good example of a strictly fascia-only zone. This layer is vascularized by the superficial temporal branch of ECA corresponding to 2nd arch structures. These arteries run along its external surface of dura directly below the dermis. Although the vessels are tightly related to the dermis, a thin fascia separates the layers, permitting dissection in an avascular plane, save where they send out superficial branches. Below the galea is a loose layer, the subgaleal fascia, the anatomy of which has been previously described by this author. Of note, the SGF is not avascular but has a delicate pattern of vessels representing a deep division of the overlying arterial arcade. Multiple small vessels pass from the SGF into the external periosteum. SIF development takes place between stages 20 and 23.

In the temporal region, SIF splits to enclose the periosteum of zygomatic arch and then proceeds cranially to form galea. The *triangular fat pad* between the two laminae of SIF is surgically useful because it can be entered, permitting subperiosteal elevation of the external lamina fascia away from the bone, thus preserving the facial nerve branch at its crossing point. Deep investing fascia encloses the temporalis muscle which passes beneath the zygomatic arch to insert into the temporal fossa, its superior termination being the superior temporal line. The temporalis muscle is supplied by the anterior and posterior deep temporal arteries from the 2nd part of the composite maxillo-mandibular artery. This marks the cranial limit of the deep division of external carotid system. Forward (rostral) from this point there are no further derivatives of the original first pharyngeal arch. The 3rd part of MMA is exclusively stapedial; it supplies the zygomatico-maxillary complex and the fronto-naso-orbital mesenchyme

Physiologic Role of the Meninges

Development and Vasculature

The meninges are, in essence, a vascular organ responsible for the proper development and ongoing nutrition of the underlying CNS. As such they constitute a stem cell niche. Formation of the meninx primitive is essential for survival. Formation of the meninges is virtually simultaneous with that of the neural tube at stage 7. Rapid assembly of a super-

ficial vascular plexus is accomplished by stage 8 with vascular connections with the heart beginning at stages 9–10 and with the underlying intracerebral internal carotid system at stage 11. Every penetrating vessel is accompanied by a pial sheath which constitutes a microenvironment.

Although the territory of dura is limited, leptomeninges cover the entire brain, with pia-arachnoid extending into all sulci and fissures. Meninges form non-neural structures within the brain. Choroid plexus, the roof of the 3rd ventricle, lateral ventricle, and the 4th ventricle are all pial structures. CSF manufactured by choroid at about stage 17 exactly when arachnoid begins to differentiate as does the dural limiting membrane. Intercalation of arachnoid villi into the subdural space sets up access of CSF to the venous circulation and permits fluid exchange with the brain. Every penetrating blood vessel is surrounded by pia and the arachnoid space provides for lymphatic drainage.

Forebrain meninges are required for actual development of the underlying cortex. Penetrating blood vessels receive mesoderm required for construction of their endothelial walls, while neural crest provides pericytes and connective tissue. Ablation of the posterior diencephalic and the mesencephalic neural folds causes apoptosis of the entire forebrain [5]. Meninges secrete trophic factors such as retinoic acid, stem cell proliferation factors, and are themselves responsive to mitogens, such as BMP-2. Meningeal SDF-1 guides the migration of Cajal-Retzius cells. The pial basement membrane constitutes an insertion site for the endfeet of processes sent upward by neural progenitor cell residing in ventricular zone.

Cerebral dura provides the osteogenic precursors necessary for synthesis of membranous calvarial bone. When BMP-2 added to demineralized bone matrix or tricalcium/trimagnesium phosphate is placed on dura, membranous bone produced.

The meninges, specifically the dura mater provide stem cell components that respond to injury and are required to reestablish the blood-brain barrier. Pericytes (the putative source of mesenchymal stem cells) migrate into the perivascular space and demonstrate stem cell activity. Boundary cap cells, derived from neural crest can differentiate into different neural tissues depending upon where they are located. Thus, the meninges constitute an injury-responsive stem cell niche [6].

Clinico-Anatomic Correlation: Headache, the Perigrinations of V1 Neural Crest, and the Development of Tentorium and Falx

The referral patterns of supratentorial headache from various locations in the dura demonstrates a disproportionate representation of V1 with pain perceived in the eyes, nose and

forehead. The entire extent of tentorium as well as both the anterior and posterior sectors of falx, refer via V1. These tissues are located at a great distance from r1. Why should recurrent V1 pursue a *bidirectional* course? What does this tell us about the migration patterns of neural crest from r1? [Figs. 12.38, 12.39, 12.40 and 12.41].

Anterior migration of r1 NC along the basal forebrain brings it into the midline to form the sphenethmoid complex. It then sweeps upwards over the dorsum of prosencephalon, covering the future frontal lobe and then narrowing dramatically to pursue a posterior course. The narrowing represents the invasion of r2-r3 neural up the sides of the brain. With division of the forebrain, r1 NC plunges downward until it dead-ends against the midline communication between the hemispheres, corpus callosum. At the same time, recurrent V1 indicates the posterior basal migration pathway of r1 NC. The initial binding of tentorium is lateral, following along the superior petrosal sinus. It is as if r1 were following a pathway backward from r4 to r11 until it reaches posterior midline at the future torcula. Here the two columns of r1 NC join together and proceed cephalically, in retrograde fashion to form posterior falx. Thus, almost the entire falx is r1 save in the parietal-interparietal regions. There, I suspect it is admixed with r2-r3 but the latter populations are dominant and have their own nerve supply from V2 to V3.

What about the blood supply of the falx and tentorium? In Chap. 6, the development of the anterior cerebral system was reviewed. From its A5 segment becomes the *pericallosal artery* supplies the entirety of corpus callosum, extending beyond the genu to anastomose with posterior cerebral. The A4 segment of ACA, as the *callosomarginal* artery supplies the entire medial cortex of frontal and parietal lobes backward to the genu. In point of fact, ACA is the exclusive supply of the falx. Callosomarginal *paracentral branches* arch over the vertex to supply a strip of marginal cortex on either side of sagittal sinus. V2 and V3 ascend to this zone and then halt. This maps out headache and also maps out the developmental zones of the parietal bone we discussed previously. Recall that all craniofacial arteries of the ICA and ECA have neural crest cells in their walls and, from Etchever's work, these crest cells relate to specific locations along the neuraxis. We can reasonably surmise that the all the NC necessary for the synthesis of ACA originates from r1. [Fig. 12.42, cf Fig. 12.22].

Tentorium presents a similar model. Here the basal spread of r1 neural crest mesenchyme requires vascularity from the same neuromeric level. Thus, the medial and lateral tentorial arteries arise from immediately proximal to the ACA itself, that is, from the cavernous sector of internal carotid artery. This is also in keeping with the direction of maturation of the cranial base. Basisphenoid forms prior to presphenoid. Its blood supply originates more proximal than that of its distal partner and is therefore more readily available. Neural crest

Fig. 12.38 Referred pain pathways of the dura. Note the disproportionate representation of vV1 dura referring pain the eye and forehead. This reflects the contribution from r1 to the dural system. [Courtesy of Michael Carstens, MD]

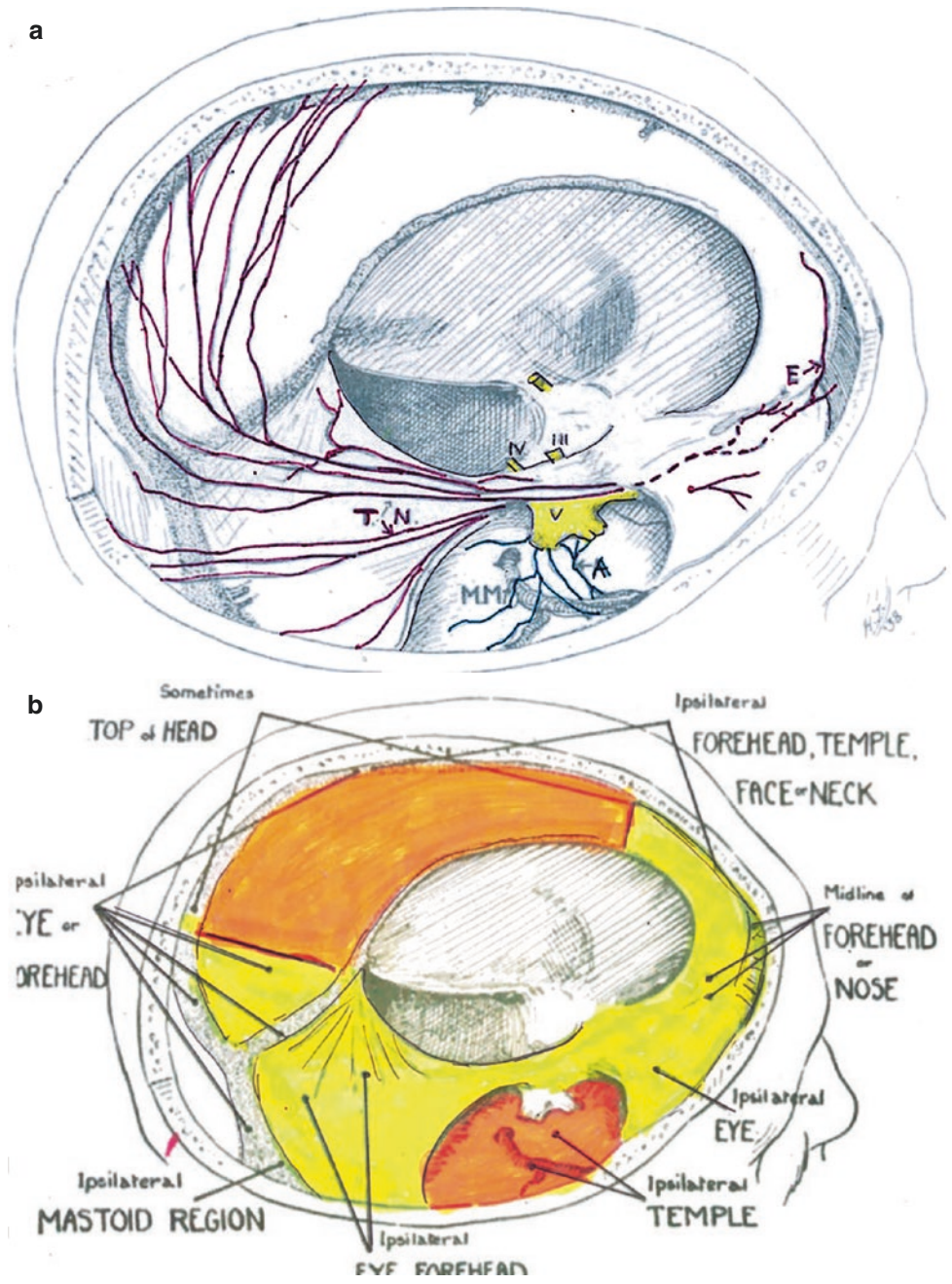


Fig. 12.39 Migration pathways of r1 neural crest. It along with r2-r3 defines the medial boundary of dura of the neural crest cranium and paraxial mesoderm periosteum of the posterior fossa. [Reprinted from Puelles L, Harrison M, Paxinos G, Watson C. Developmental ontology for the mammalian brain based on the prosomere model. *Trends in Neurosciences*. 2013;36(10):570–578. With permission from Elsevier.]

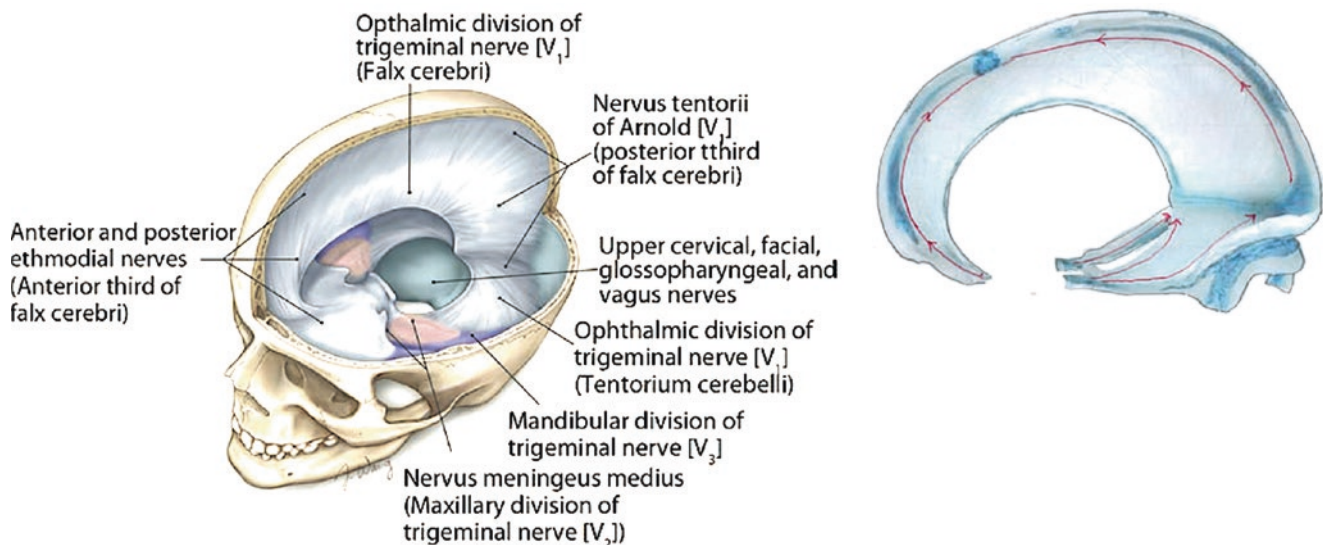
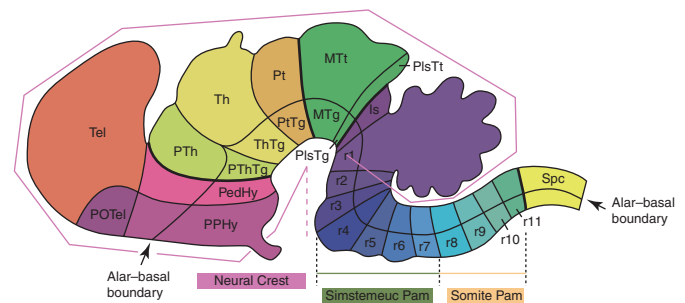


Fig. 12.40 Development of the falx and tentorium. The falx is not a structure per se but rather the fusion of opposing layers of dura. Venous sinuses develop in the folds. It can be detached from corpus callosum. Forward attachment: r1 ethmoid plate/crista galli. Lateral attachments: r4 petrous apex backward to r11 internal occipital protuberance. Medial border: non-adherence to cerebellum. Starts out as a flat sheet with a partition for cerebellum. Attaches at torcula. Free border of falx cerebri

follows the corpus callosum. Problems with the division of the prosencephalon affect the corpus callosum. Note flow of r1 neural crest along the base of the brain both anteriorly and posteriorly. Left: [Reprinted from Kemp WJ, Tubbs RS, Cohen-Gadol AA. Innervation of the cranial dura mater: Case correlates and Review of the Literature *World Neurosurgery* 2012; 78(5): 505–510. With permission from Elsevier.] Right: [Courtesy of Michael Carstens, MD]

flow from r1 backwards takes place before that along anterior cranial base. For this reason tentorial development precedes that of falx. The tapering of saggital sinus as it runs forward indicated that falcial structures are posterior dominant.

What we can conclude from all this seemingly picayune detail is that r1 NC is a very large population that spreads along the base of the brain both forward and backward. It does seem to follow patterns of bone development, especially in the middle and posterior fossae. Its course over petromastoid recognizes a biologic boundary with r2-r3 NC which may have to do with signaling in the medial and lateral parts of the r4-r7 bone complex. It may also simply be a case of competing populations. In any case, from it knife-

edge insertion, V1 tentorium expands medially until it encounters midbrain and ceases to grow, creating the so-called *free edge* of tentorium.

What sort of mechanism could explain this? The combination of trigeminal innervated dura and tentorium versus c2-c3 periosteum defines the boundary between r1-r3 neural crest derived bone and r4-r11 paraxial mesoderm bone. The extent of migration from r1 simply reflects a large amount of mesenchyme that migrates along the base of the brain unimpeded. It recognizes and attaches to the boundary until reaching the posterior terminus. With growth of the brain, the previously flat tentorium is pulled upward like a sail, being attached via the falx along the undersurface of the expanding calvarium.

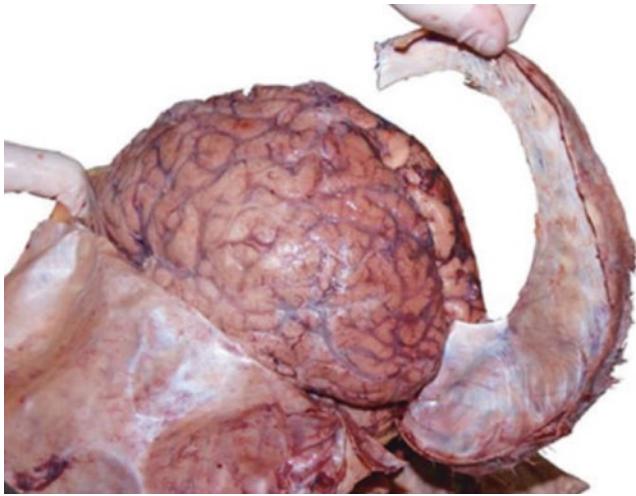


Fig. 12.41 Falx being reflected backward. At its junction with tentorium, the straight sinus is seen. Tentorium has been reflected away from falx and from its interposition between posterior cerebral lobe and cerebellum, a small triangle of which is visible here. [Reprinted from Adeeb N, Mortazavi MM, Tubbs RS, Cohen-Gadol AA. The cranial dura mater: a review of its history, embryology, and anatomy. *Childs Nerv Syst* 2012; 28(6):827–837. With permission from Springer Nature.]

Clinico-Anatomic Correlation: Is Tentorium Bilaminar? Is the Occipital Lobe the Posterior Pole of the Brain?

Tentorium serves a dual function. It acts as a dural layer for the occipital lobe and separates cerebellum from cerebrum. It also contains the straight sinus. The only topological way the sinus can form is for tentorium to have two neural crest layers. The cranial layer, likely r3 belongs to the subjacent occipital lobe; the caudal layer is, of course, r1.

The original posterior pole of primitive telencephalon before 9 weeks is translocated inferiorly to become temporal lobe. Prior to folding, temporal is located at the posterior pole. Forward from it, the dorsal wall contains occipital and ventral wall is made up of insula. Temporal rotates downward and forward, coming into line below the insula, thus creating the Sylvian fissure. Occipital moves backwards to fill in the space. Optic radiations are connected straight back through the dorsal wall. When occipital is posteriorized it drags its visual cortex and connections backwards as well. Thus, although the initial connections between geniculate ganglia and visual cortex may have be

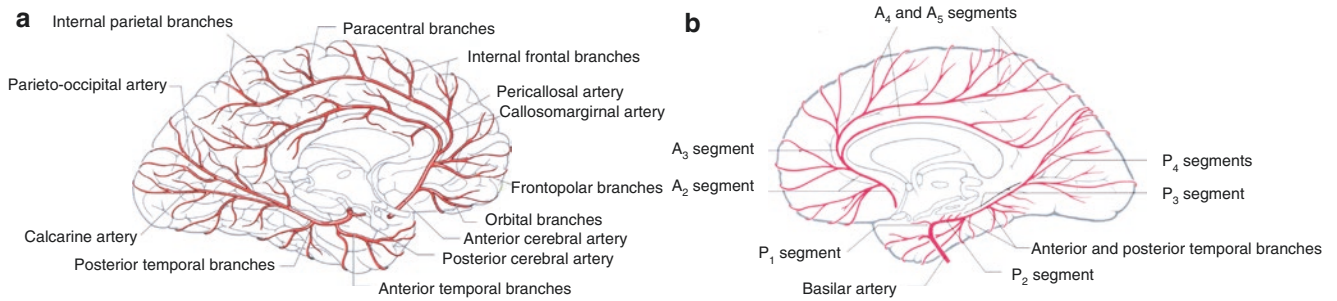


Fig. 12.42 (a,b) Blood supply to the falx. Anterior cerebral artery and its branches are constructed from r1 neural crest. A4 callosal marginal supplies the upper half of falx and extends “over the top” to supply cerebral cortex on either side of the sagittal sinus. A5 pericallosal artery

supplies the lower half of falx and the midline communicating system of corpus callosum. [Reprinted from Haines D, et al. *Fundamental Neuroscience for Basic and Clinical Applications*, 3rd ed. Elsevier; 2006. With permission from Elsevier.]

quite direct, the eventual pathways, running deep to parietal cortex, make sense.

We can trace the relocation of temporal and occipital lobes by comparing the initial geometry of the vascular system. Posterior cerebral is the final branch of the ICA before posterior communicating. For reasons discussed in Chap. 6 PCA is often mis-interpreted to be a branch of vertebral but this is not embryologically correct. In the initial iteration PCA has a common stem which supplies occipital lobe first and then terminates with temporal lobe. As the latter rotates downward its blood supply from PCA turns about 120 degrees downward and anteriorly. This is readily observed in the adult state [Fig. 12.43]. The common stem is seen by the arterial axes to both lobes displaced directly opposite one another.

Final Thoughts

In this chapter, we have discussed in detail the formation of meninges, with emphasis on different neuromeric zones based upon the origin and composition of its mesenchymal components. We created a “dural map” based upon sensory supply to help explain the migration patterns of neural crest. We have seen that somitomeres and somites are positioned

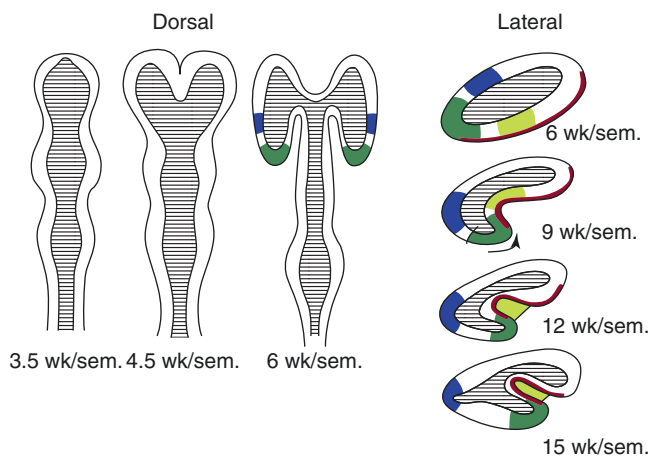


Fig. 12.43 Relocation of the occipital lobe. This drawing of the telencephalic flexure illustrates its development from a ventral bending of the telencephalic hemisphere to form the operculum and finally the Sylvian fissure. The posterior pole of the primitive telencephalon before 9 weeks becomes the temporal (green), not the occipital, lobe. The occipital lobe derives from the dorsal wall of the primitive telencephalon (blue); the insula derives from the ventral wall (yellow). Both lips of the Sylvian fissure are from the ventral margin of the primitive telencephalon, so defective ventralizing genes in the vertical axis would be expressed in the cortex forming both the frontal and temporal lips. wk/sem. 1/4 gestational weeks/semaines (French) or semanas (Spanish). (Illustration by Laura Rodríguez-Flores, graphic designer). [Reprinted from Sarnat HB, Flores-Sarnat L. Telencephalic Flexure and Malformations of the Lateral Cerebral (Sylvian) Fissure. *Pediatric Neurology* 2016; 63:23–38. With permission from Elsevier.]

below the brain to provide regional contributions of paraxial mesoderm sidewalls and posterior fossa. We have seen how the developmental sequence of the blood supply is spatially preserved in fascial layers of the face and skull. It is hoped that a better knowledge of how dura is synthesized will lead to insights about the mechanisms of skull osteogenesis and the pathologic states that can arise when zonal deficiency states of dura and/or SIF lead to synostosis.

SUMMARY OF DEVELOPMENTAL EVENTS (as per O’Rahilly and Müller) Stage 07 Gastrulation

- Stage 08 Future brain, surrounded by PAM
- Stage 09 Cranial neural folds, 1st occipital somite
- Stage 10 Prechordal mesoderm organizing, neural crest migration
- Stage 11 Brain vascularization, pia in hindbrain
- Stage 12 Closure of neural tube, pia lateral midbrain
- Extraocular muscles organizing in Sm1, Sm2, Sm3, and Sm5
- Stage 13 Lateral rectus appears
- Stage 14 Cell sheath of notochord – paraxial mesoderm of cranial base
- Medial tentorium condenses
- Blood vessels connect in the brain
- Stage 15 Entire brain covered with primary meninx
- Stage 16 Cranial nerves emerge, these will program meningeal vessels
- Stage 17 Pia complete as part of entire brain
- Skeletogenous layer (future dura) appears
- Dura limiting membrane appears (first definition of the dura)
- Stage 18 Cavitation in primary meninx initiates arachnoid
- Roof of 4th ventricle
- Stage 19 Transverse, sigmoid sinuses indicate completion of dural layers
- Choroid plexus fourth ventricle produce CSF for arachnoid
- Stage 20 Cartilage in skeletogenous layer
- Choroid plexus lateral ventricle
- Falx cerebri – rostral-caudal development
- Annexation ophthalmic
- Stage 21 Completion of ophthalmic ocular and StV1 periorbital system
- Stage 22 Cerebello-medullary cistern
- Stage 23 Bone: frontal/interparietal
- Choroid plexus 3rd ventricle

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