Diagnosis and natural history of hemangiomas.

And the blots of Nature's hand

Shall not in their issue stand;
Hemangiomas are the most common tumor of infancy and childhood. About 30–40% are nascent at birth (et al., 1983); the incidence is reported to be 1.0–2.6% in Caucasian neonates (hemangiomas appear during the first to fourth week of life; the median age is 2 weeks. Deep (subcutaneous) hemangiomas are often not discovered until 2–3 months after birth. By age 1 year, approximately 4–12% of Caucasian children have a hemangioma (Holmdahl, 1955; Jacobs, 1957; Hoornweg et al., 2012 et al., 1986). The incidence has been reported to be 1.4% in African American infants (much lower in our Vascular Anomalies Center. Hemangiomas were initially reported to occur in an equal frequency in premature and full-term infants (however, this study included few neonates of less than 1,500 grams (g). In a report many years later, the incidence at birth of hemangioma was 23% in premature infants who weighed less than 1,000 g and 15% in babies who weighed less than 1,500 g (Amir et al., 1986). This was corroborated by an unpublished study from our newborn nursery in which hemangioma appeared in 30% of premature infants weighing less than 1,000 g. In a large, case-control study, multivariable logistic regression showed that low birth weight (defined as less than 2,500 g) was the most significant risk factor for hemangioma, as was a positive family history (Drolet et al., 2008). This analysis also showed that for every 500 g decrease in birth weight, the risk of hemangioma increased by 40%. Earlier studies had shown that premature infants with a birth weight greater than 1,500 g have the same frequency of hemangioma as full-term infants (are also more frequent in preterm infants; however, female preponderance is less than in term infants (Hemangiomas arising in prematures occurs in the same location and have the same age of postnatal onset and time of regression as tumors in full-term infants. Gutiérrez and colleagues (2007 weighed less than 1,500 g who developed postnatal hemangioma to a similar group of prematures who did not have hemangioma. In the hemangioma group, they found a high incidence of placental pathology, including retroplacental hematoma, ischemic infarction, vasculitis, and chorioamnionitis. These investigators speculated that hypoxic/ischemic changes in placental circulation could be related to hemangioma-genesis.

A large prospective study from seven U.S pediatric dermatologic clinics showed that infants with hemangioma were more likely to be female, white, premature, and the product of multiple gestations (found that maternal age was significantly higher and that the pregnancy was often complicated by placenta previa and pre-eclampsia. The finding that hemangioma occurred more commonly in twins is confounded by prematurity and low birth weight in multiple gestations. There are other compounding factors: premature infants are known to be more common in multiple pregnancies, and prematurity is more likely following assisted reproductive technologies (Judah Folkman hypothesized that the common pathway for these prenatal predisposing factors (prematurity, pre-eclampsia, placenta previa, etc.) involves decreased endogeneous angiogenic surveillance.

The female-to-male ratio for hemangioma is 3:1 (Bowers et al.
higher (90%) with problematic tumors (Enjolras et al., 1990; Enjolras et al., 1997). Infantile hemangioma is associated with structural anomalies (Gorlin et al., 1994). Prematures who develop hemangioma is closer to 1:1 (Amir et al., 1986). Preterm infants are more commonly male. There are reports if women who have had transcervical chorionic-villus sampling (Amir et al., 1995; Bauland et al., 2010). A higher incidence of prematurity higher (90%) with problematic tumors (Enjolras et al., 1990; Enjolras et al., 1997). Infantile hemangioma is associated with structural anomalies (Gorlin et al., 1994). Prematures who develop hemangioma is closer to 1:1 (Amir et al., 1986). Preterm infants are more commonly male. There are reports if women who have had transcervical chorionic-villus sampling (Amir et al., 1995; Bauland et al., 2010). A higher incidence of prematurity

**Location**

Infantile hemangioma (IH) most commonly arises in the head (60%) and the extremities (25%) (Finn et al., 1983). This region tendency for parents to bring a child with a facial hemangioma that the distribution and morphologic forms of facial hemangiomas. This distribution is probably skewed because of the natural tendency for parents to bring a child with a facial hemangioma to medical attention. Waner and colleagues hypothesized that “segmental” hemangiomas are predetermined to cease growing, respecting embryonic boundaries that have otherwise disappeared.

The term “segmental” is confusing when used in the clinical context of recording the location of facial hemangiomas. Embryologic texts describe craniofacial development in terms of pharyngeal arches, pouches, clefts and prominences—not segments. The word “segmentation” denotes very early patterning along the embryonic axes that occur in primates and in lower life forms, such as annelids and arthropods. In later craniofacial development, this process of segmentation influences the complex interplay of germ layers and neural crest to form the facial regions. At this stage of our knowledge, it is arguable whether “segmental” speculation provides heuristic insights into the etiopathogenesis of infantile hemangioma. Until more is known of etiopathogenesis at a molecular level, this author prefers simple designations for infantile hemangiomas as either focal (solitary), multifocal (multiple), or regional (territorial). Rather than enumerate facial “segments,” use conventional terms for facial anatomic regions, that is, frontal, temporal, nasal, periocular, maxillary, and mandibular.

**Familial Hemangiomas**

Infantile hemangiomas are not considered inheritable. Nevertheless, these tumors are, in a sense, familial in that they occur more frequently in fair-skinned families and in those with a predisposition to produce female offspring. There was no strong evidence for Mendelian inheritance in a study of monozygotic versus dizygotic twins (Blei et al., 1998). Anencephaly was elicited in 10% of infants (Amir et al., 1995). These “familial” hemangiomas are indistinguishable from common “sporadic” hemangiomas. In some pedigrees there appears to be coexistence of hemangioma and vascular malformation in different members of the same family, as well as in the same individual. A putative locus was identified on chromosome 5q in three such families (Blei et al., 1999).

**Precursor Lesions**

Approximately one-third of infantile hemangiomas are present at birth. Signs of nascent hemangioma include: erythematous macular patch or spot, blanched area (“herald spot”), ecchymotic-like mark, and localized telangiectasia, surrounded by a pale halo. Approximately one-third of infantile hemangiomas are present at birth. Signs of nascent hemangioma include: erythematous macular patch or spot, blanched area (“herald spot”), ecchymotic-like mark, and localized telangiectasia, surrounded by a pale halo.
Ulceration may also be a harbinger of hemangioma. Although exceedingly uncommon, infantile hemangioma can be nearly fully grown at birth and thus confused with congenital hemangioma (lesions exhibit some progression and slow regression, just as tumors that appear postnatally).

**Figure 4-1**
Precursor lesions of hemangioma. A. Newborn male with pink superficial dome-shaped tumor with central ulceration. C. Newborn girl with pink patch on left cheek and surrounding pallor. D. At 8 months, this deep/superficial hemangioma at apogee of growth.
Nascent hemangioma. A. Newborn female with pale patch and telangiectasia on right cheek and upper lip. B. At 4 days of life, vascular lesion is a macular stain. C. At 1.5 months, raised superficial hemangioma throughout the predetermined field.

Premonitory hemangioma. A. Newborn with large pale patch and faint reticular vessels on the shoulder. B. At age 2 months, the superficial tumor is more obvious and beginning to elevate.

Multifocal Hemangiomas (“Hemangiomatosis”)

Eighty percent of infantile hemangiomas are focal, whereas 20% present as multiple cutaneous lesions (Museles, 1965). The purported first description of multiple necromatous hemangiomas was by a remarkable case report of a 6-day-old neonate with 834 lesions 3–4 millimeters (mm), raised, and dome-like. There can also be larger hemangiomas of more typical shapes and sizes in the same infant (Figure 4-4A). These tiny hemangiomas are often present at birth or appear shortly thereafter. They grow for a short time, and often blister, blacken, and disappear. The mechanism for accelerated regression of these tiny hemangiomas is unknown. It is also curious that new, tiny lesions can appear while the older lesions have either stabilized or are regressing.
Multifocal hemangiomas. A. Multiple dome-like lesions and large plaque-like tumor in female infant with multifocal intrahepatic tumors and cardiac decompensation due to shunting. B. Characteristic tiny dome-shaped lesions in 1-month-old boy's superior-medial segment with multiple cutaneous and intrahepatic hemangiomas. (Courtesy of Dr. Madina Holmuhamedova)

Multifocal cutaneous hemangiomas often occur with intracranial or visceral involvement. In the past, this presentation was termed “miliary” or “disseminated hemangiomatosis” (Kundstadter, 1933). Other authors have used the terms “benign” or “diffuse” (Alexander, 1970; Stern et al., 1981). The modifier “diffuse” is incorrect. “Diffuse” derives from the Latin diffusus, past participle of diffundere about.” Thus, “diffuse” more accurately denotes an extensive tumor of the face or neck, a large area of an extremity, or the entire upper body. Unfortunately, the term “hemangiomatosis” is inexact because it also has been used to designate intraosseous vascular anomalies.

Extracutaneous hemangiomas have been found at autopsy in virtually every organ system: brain, lymph nodes, spleen, pancreas, gallbladder, liver, thymus, thyroid, gastrointestinal tract, lungs, heart, kidney, urinary bladder, and adrenal glands (Kundstadter, 1933; Andries and Kaump, 1944; Cooper and Bol, 1965; Stern et al., 1981; Balaci et al., 1999). The most common extracutaneous site is the intestine (Lopriore and Markhorst, 1999) (Figure 4-4B). In our experience, pulmonary involvement is exceedingly rare. It is not known whether multifocal hemangiomas are the result of embolization from a common source or whether cells from one hemangioma can emigrate to another site. Another possible explanation is that nests of hemangioma stem cells (in the past called “angioblasts”) are present in multiple anatomic sites and make their postnatal appearance as multifocal tumors.

It is rare that an infant with visceral hemangiomas does not have multiple cutaneous lesions. The corollary is also true, that is, some infants with multiple cutaneous lesions do not have hepatic involvement. In a study from Great Ormond Street Hospital, hepatic lesions were found in 45% of infants with multifocal hemangiomas.
cutaneous lesions; and 12–14% with one large or three or more small hepatic tumors do not develop congestive cardiac failure. Hemangiomas is a suspect for having visceral tumors, particularly in the liver. There are severe hemangiomas of the iris, often involving the eyelid margins or vascular lesion of the iris in one or both eyes (Haik et al., 1983) include hyphema, vitreous hemorrhage, and subretinal hemorrhage. Confirmed the typical findings of infantile hemangioma in the retina (Chang et al., 1998). Glaucoma is a potential complication (Weiss and Ernest, 1976). Follow-up ocular examination should include indirect ophthalmoscopy. As would be expected, iridal hemangiomas spontaneously regress (Weiss and Ernest, 1976) and respond to corticosteroid therapy (Ruttum et al., Neuraxial Hemangioma

Intracranial infantile hemangiomas can occur, particularly with large facial tumors (Billson and Gillam, 1984; Tortori-Donati et al., 1999). Vascular Anomalies Center, 15/1,454 (approximately 1%) of infants with infantile hemangioma had involvement of the central nervous system (CNS): intracranial, intraspinal, or both. In our center, the true frequency of neuraxial hemangioma is probably much lower. In most cases, extension into the neuraxis was traced from a cutaneous extracranial or extraspinal tumor. The usual portals of entry included the superior or inferior orbital fissure, foramen rotundum, and hypoglossal canal. There were no instances of a CNS hemangioma without an accompanying extra-CNS tumor.

Intracranial hemangioma grows in the subarachnoid space and other typical locations are the cavernous sinus and fourth ventricle. Colleagues (2009), none of the neuraxial hemangiomas invade the effect. Other findings were hydrocephalus (n=3), thrombosis or association (n=3). Two of the intraspinal hemangiomas had an overlying reticular variant of the tumor (Figs. 5C, D). Two of the seven patients with intraspinal hemangiomas had an intramedullary angiolipofibroma. There is a report of an intraspinal hemangioma in a 2-month-old infant; this was ascribed to intratumoral hemangioma.
Figure 4-5
Neuroaxial hemangioma. A. Large upper eyelid hemangioma occluding visual field. B. CT demonstrates orbital hemangioma traversing orbital foramen and extending into left cavernous sinus and continuing along trigeminal nerve to abut ventral surface of brainstem. Reticular hemangioma on posterior thorax is “tip of the iceberg.” Yellow arrows indicate intraspinal, extradural tumor posterior to thecal sac; blue arrow points to hemangioma in right neuroforamen; and red arrows show tumor in prevertebral space.

PHACE(S)-Associated Malformative Anomalies

Geneticists often mistakenly include “hemangioma” on the list of features in a syndrome. Most of these appellations are terminologic errors. These mislabeled vascular lesions are usually a fading macular stain rather than a vascular neoplasm (Burns et al., 1991; Hand and Frieden, 2002). Capillary malformation (“port-wine stain”) is often mislabeled “hemangioma” in the genetic literature. Because infantile hemangiomas are so common, they occasionally coexist, although not pathogenically associated, in a rare syndrome. Nevertheless, telangiectasia and other vascular malformations (capillary, lymphatic, venous, and arterial) are either associated anomalies or the major component of the particular disorder.

An International Working Group of geneticists recommended defining a syndrome to be pathogenically related and occurring in non-contiguous embryonic fields (Cohen, 1997). A syndrome is defined as a nonrandom occurrence of several morphologic abnormalities in two or more individuals and not yet identified as either a sequence or a syndrome (Cohen, 1997). Association connotes that the anomalies may be causally related, although the etiology is unknown. Association alerts the clinician to further examine a patient for other possible anomalies. As a working criterion, an abnormality must occur more frequently than 10% with another in order to be designated as “associated” rather than an aleatory finding.

There are curious, and relatively uncommon, instances wherein a “true” infantile hemangioma in the head and neck region occurs in association with structural anomalies that are not always vascular in nature. There are scattered reports of facial hemangioma in the presence of malformations of the hindbrain, cardiac system, ocular structures, and sternal defects. Honey
and colleagues (1975) described two patients with coarctation of the aorta and smaller tumors on the face. Pascual-Castroveijo (1978) identified cerebellar anomalies (including cerebellar malformations) by angiography in seven females with extensive facial hemangiomas. Schneeweiss and coworkers (1982) described four cases of facial hemangioma with aortic coarctation and dilatation of other great vessels. Goh and Lo (1993) proposed the term “3C syndrome” to designate the combination of cavernous facial hemangioma, cerebellar hypoplasia, and coarctation of the aorta. Some infants with large facial hemangioma and anomalies of the hindbrain were mistakenly labeled as having Sturge-Weber syndrome (Billson and Gillam, 1984) or Wyburn-Mason syndrome. The association between cerebellar, cerebrovascular, and aortic anomalies and infantile hemangioma was underappreciated, until Frieden and colleagues designated the catchy acronym PHACE: face; arterial abnormalities; cardiac defects and coarctation; and other anomalies. Often these malformations are ipsilateral to the face. In 70% of affected patients have only one extracutaneous abnormality. Curiously, females are affected more than males, 9:1; this ratio is much higher than in isolated hemangioma. In one report, the prevalence of hemangioma in association with a structural or genetic abnormality was 6.9%. This prevalence is probably higher in a selected population of patients who were referred with problematic hemangiomas; therefore, the true incidence is probably much lower. In a large, inter-institutional prospective cohort study, PHACE association was discovered in 2.3% of children (Metry et al., 2006). Ascertainment of the true incidence would require radiologic imaging of all infants with a large cervicofacial hemangioma. Comparison of PHACE infants to a large cohort of non-PHACE cases showed no major demographic or perinatal differences (Metry et al., 2008).

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Figure 4-6
PHACES association: Clinical spectrum. A. Infant female with deep frontonasal hemangioma; hypoplastic corpus callosum; stenotic left intracranial internal carotid artery; persistent right subclavian artery. B. 3-month-old female given corticosteroid for regional (frontal) and lower labial hemangioma. MRI revealed hypoplastic cerebellar vermis and dysmorphic cerebellar hemisphere. C. Female infant with bilateral reticular type...
facial hemangioma and anisocoria (small right pupil), esotropia, and hyperopia. Radiologic imaging revealed occlusion right internal carotid artery and persistent trigeminal artery; echocardiography showed ventricular septal defect. D. 1-year-old girl with deep right frontal hemangioma presented with seizures at age 10 months. MRI demonstrated right middle cerebral arterial stroke and moyamoya. Fundoscopic examination revealed gliosis of right optic nerve and peripapillary pigmentation. E. Neonatal female with reticular hemangioma (right mandibular distribution), repaired upper cleft sternum, and stenosis of left (contralateral) internal carotid artery. F. 15-month-old female with bilateral cervicofacial and subglottic hemangioma (necessitating tracheostomy) and bilateral congenital cataracts. Note small hemangioma above long sternal raphe and split manubrium.

**Posterior Fossa**

Dandy-Walker malformation is the most common developmental malformation of the posterior fossa associated with hemangioma; others include: subependymal and arachnoidal cysts and hypoplasia or agenesis of the cerebellar hemisphere or vermis, corpus callosum, cerebrum, and septum pellucidum. Malformation, only 10% had a facial hemangioma (Hirsch et al., 1984). Several cerebral (supratentorial) abnormalities are associated with PHACE, including focal dysgenesis and neuronal migration anomalies. Encephalomalacia, microcephaly, and cortical anomalies cannot be ascribed to vascular stenoses, such as pachygyria, lissencephaly, schizencephaly, and cortical heterotopias (Grosso et al., 2004).

There are several reports documenting intracranial hemangiomas in infants with PHACE association, particularly with periorbital hemangioma (Poetke et al., 2002; Bhattacharya et al., 1998). Intracranial base and posterior fossa; they seem to have a predisposition for the cerebellopontine angle cistern, fourth ventricle, and internal auditory meatus (Tortori-Donati et al., 1999; Judd et al., 2007). As noted above, intracranial hemangiomas extend within the subarachnoid space but do not invade the cerebral cortex.

**Hemangioma**

Facial hemangioma in PHACE manifests at birth as a regional erythematous macule and glows rapidly to become plaque-like, pebbly, or reticular. Although the reticular form is the most common, the more typical, localized, and raised (combined deep and superficial) type of hemangioma also can occur (Rossi et al., 2001). PHACE association is with tumors in the frontal and temporal distribution alone and when combined with involvement of the maxillary and mandibular areas. PHACE association may be present in 2% of infants with facial hemangioma and in as many as 20–30% with a large, regional facial hemangioma (Metry et al., 2006). Mandibular areas are involved (“beard distribution”), laryngeal hemangiomas are often ipsilateral to the intracranial and cervical hemangiomas.

An epidemiologic study showed that these regional facial hemangiomas are more likely to occur in children born at a later gestational age with a higher birth weight, and that there is a higher prevalence among Hispanics (Metry et al., 2006). Internal hemangiomas have also been found with PHACE (Metry et al., 2004). PHACE vascular abnormalities have also been observed in association with reticular type hemangioma of the upper limb.

**Arterial and Cardiac**
Arterial and Cardiac Angiography and magnetic resonance angiography (MRA) have demonstrated that cerebrovascular arterial anomalies are the most common finding in PHACE association. There are two types: malformations and progressive lesions; these can be difficult to differentiate (Heyer et al., 2008). The structural anomalies include: persistent embryonic intra- and extracranial arteries (such as, primitive trigeminal artery, hypoglossal artery, stapedial artery, and pro-atlantal intersegmental artery), carotid-vertebrobasilar anastomoses, segmental agenesis, hypoplasia, or absence of the ipsilateral carotid or vertebral vessels (Pascual-Castroviejo, 1978; Pascual-Castroviejo et al., 1996). Development of the vertebral arteries and posterior communicating arteries. Persistence of the trigeminal artery is rare (less than 1% of the population), but the prevalence is 17.4% in PHA basilar segment (foramen lacerum) of the internal carotid and basilar segment (foramen lacerum) of the internal carotid and vertebral arteries, often with cortical dysplasia (Castroviejo et al., 1996; Aeby et al., 2003; Grosso et al., 2004). Progressive development of arterial aneurysms can also occur (Oza et al., 2008). These cerebrovascular abnormalities tend to be ipsilateral to the facial hemangioma, but they can also be contralateral and bilateral. Serial imaging has documented progressive arterial anomalies, including evidence of worsening stenosis a vessels, resembling moyamoya (Burrows et al. 1998; Baccin et al., 2007). Neurologic sequelae include stroke, and developmental delay. These ischemic events are usually progressive cerebrovascular stenosis can cause neurologic dysfunction, seizures, stroke, and also late-onset migraine headache. Narrowing/non-visualization of at least one great cerebral vessel and aortic arch anomalies (there are rare patients in whom hypoplasia of the aortic arch have regressed (Pascual-Castroviejo et al., 2003).

There are also examples of intracranial AVM/AVF with PHACE association. There is a case report of an infant girl with hemangiomas of the posterior scalp and subglottis, typical intracranial arterial anomalies, along with a cranial base osteodural AVF, likely a separate arteriovenous shunt at T5, an example of pial-dural AVM/AVF and other examples in the literature are reported by Brandon and (2011). They also noted that the intracranial fast-flow anomalies Extracranial vascular anomalies in PHACE association include branches (Burrows et al., 1998); aberrant subclavian artery; coarctatus arteriosus, septal defects, aortic valvular stenosis, pulmonic stenosis, anomalous coronary arteries (1982; Vaillant et al., 1988); and dilatation of the carotid siphon. The facial hemangioma and the side of the aortic arch anomaly common vascular malformation (Metry et al., 2001). Coarctatic and shoulder. Aortic aneurysms found in PHACE association often involve the ascending aorta, at the origin of the innominate artery, both with and without predisposing aortic arch anomalies, particularly aortic aneurysm, can evolve.

**Eye**

Ocular abnormalities of PHACES include microphthalmia, iridoglioma, lens coloboma, persistent papillary membranes, nerve hypoplasia or atrophy, and excavated optic disc anomaly (Coats et al., 1999; Metry et al., 2001; Lasky et al., 2004) (Figure 1). Anomaly of the optic disc; it is usually unilateral, or it can be bilateral. A glial tuft, retinal vessels that exit in a radial fashion from an enlarged posterior scleral opening (where the optic nerve exits the globe), and variable peripapillary pigmentation. It is not pathognomonic of PHACE association. It can occur in isolation (idiopathic) or in association with other disorders, for example...
anomalies (e.g., basal encephalocoele, pituitary dwarfism, and al., 1998), moyamoya disease (Massaro et al., 1998; Lenhart et al., 1998; Massaro et al., 1998; Lenhart et al., 2006). Abnormal development of the intracranial and pharyngeal arch vasculature may be the common thread that ties morning glory fundus to these various conditions. Horner syndrome and congenital third nerve palsy can also be part of the PHACE spectrum.

Figure 4-7
PHACE association: Ocular anomalies. A. 5-year-old girl with reticular facial hemangioma and other anomalies: corectopia (eccentric location of the pupil) giving a coloboma-like appearance; ectasia of the left internal carotid artery; dysmorphic cerebellum; ophthalmological findings reported by Lasky et al. (2004). B. 2-year-old girl with infantile hemangiomas of left parotid and occipital scalp. Normal MRI/MRA. Exotropia and nystagmus prompted ophthalmologic evaluation and fundoscopy revealed "morning glory disc" O.S. (Left) Funnel-shaped excavation of posterior fundus surrounds and incorporates an enlarged dysplastic optic disc—notable for peripheral displacement of central retinal vasculature and straightening of vessels emanating from disc. Yellowish central glial tuft pulls temporally causing traction on temporal retina. (Right) Normal fundus O.D.

Sternum

The original acronymic designation PHACE did not include extracraniofacial and cervical hemangioma can be associated with sternum (Hersh et al., 1985; Igarashi et al., 1985; Gorlin et al. 1994). Some most common sternal cleft involves the manubrium (Figure 4-6 E-F, the letter S was added to make PHACES (Metry et al., 2001). S a diastasis recti, other rare midline abdominal anomalies in the aortic arch anomalies and in the absence of a facial hemangioma Figure 4-8.
PHACES Diagnostic Evaluation and Management

An infant with an extensive temporal-frontal or lower facial hemangioma (especially the reticular type) should be evaluated for possible PHACE association. An echocardiogram should be obtained early; if suspicious, then MRI/MRA of the chest is indicated for possible aortic arch abnormalities. Ultrasonography of the brain, head, neck, and chest is needed to demarcate any diffuse periorbital hemangioma in order to rule-out retrobulbar vascular anomalies, including intracranial hemangioma (Judd et al., 2007). CT angiography is fast and can be done without sedation, but it involves considerable radiation dosage. Timing of these radiologic studies is debatable. In some centers, imaging is done without sedation; the baby is simply fed and bundled. In other units, general anesthetic is recommended prior to age 3 months; sedation will usually suffice after this age. Ophthalmologic consultation is also indicated to rule out ocular anomalies. Neurologic evaluation is required for an infant with cerebral/extracranial vascular anomalies or intracranial structural defects. A coagulative assessment for prothrombotic disorders is indicated if MRI reveals evidence of intracranial venous sinus thrombosis or cerebral infarction or if there are neurologic sequelae.

Children who have suffered an acute ischemic stroke have been empirically given antiplatelet therapy (aspirin) (2006). It is unclear whether an asymptomatic infant with anomalous intracerebral arterial circulation (stenosis) should be prophylactically anticoagulated (with low molecular weight heparin) or aspirin. MRI should be repeated every 3 months if there are cerebral vascular anomalies and until it is certain that there are no cerebrovascular changes on the initial examination in a child with obvious PHACE anomalies. Neurologic symptoms of cerebrovascular involvement can present in a young adult, as illustrated in Figure 4-8. A. Infant girl with focal sternal defect and small reticular hemangioma on lower abdomen. B. Sagittal MRI revealed fusiform aneurysm in ascending and transverse portion of aortic arch.

Figure 4-8
Extra-craniofacial PHACES. A. Infant girl with focal sternal defect and small reticular hemangioma on lower abdomen. B. Sagittal MRI revealed fusiform aneurysm in ascending and transverse portion of aortic arch.
PHACES association: Late presentation. A. Female infant with cobblestone-like left frontal hemangioma causing visual obstruction; treated successfully with systemic corticosteroid. 1 year later, she presented again at 3 years. She presented with migraine headaches and a transient ischemic episode. MRI showed occluded right internal carotid artery and left moyamoya. “Pial synangiosis” done promptly; thereafter, yearly MRI-MRA showed revascularization of hemispheres, persistent tortuosity of intracranial vessels, and an aneurysm of posterior communicating artery.

**PHACES Association-Plus**

PHACES is a useful acronymic mnemonic. More initials might be on the spectrum, such as lingual thyroid (Metry, 2001); agenesis of the corpus callosum and sinus pericranii (2006); and hypopituitarism due to partially empty sella turcica (There are also rare cases of hemangioma arising along the lateral and medial labial margins of infants with common cleft lip/palate (Lo et al., 1994; Williams et al., 1997; Sarifakiouglu et al., 2002). It is appealing to envision that such hemangiomas arise along embryonic lines of fusion; Virchow called these “fissural angiomas.” More accurately, labial clefts result from failure of mesodermal penetration of the ectodermal envelope (merging).

Figure 4-10

Cleft lip and hemangioma: Association or coincidence? A. Bilateral complete cleft lip with hemangioma on right lateral labial element. (Courtesy of Dr. Fernando Ortiz-Monasterio) B. Bilateral symmetrical cleft lip: right complete (after adhesion) and vermilion hemangioma on left incomplete side.
Associated Ventral-Caudal Anomalies

Focal hemangioma located over the cervical or thoracic spine would not be expected to be associated with underlying structural defects, and usually imaging is not necessary. In contrast, a plaque-like, macular, or reticular form of hemangioma, located in the thoracic, lumbosacral, or perineal regions, may well be associated with ventral-caudal structural anomalies. The concurrence of hemangioma and ventral-caudal structural malformations is analogous to and is the extracraniofacial counterpart of PHACE association (Mulliken et al., 2007b). Also common; however, solitary and raised tumors occur as well. A plaque-like, macular, or reticular type of tumor is common; however, solitary and raised tumors occur as well. A plaque-like, macular, or reticular type of tumor is common. Hemangioma is one of several ectodermal lesions known to signal underlying occult spinal dysraphism, for example, lipoma and lipomeningocele (Gr. “space” or “cleft” + myelos, “marrow” or “spinal cord”) (Goldberg et al., 1986). Hemangioma can extend to involve an intraspinal lipoma or extrathecal space, causing distortion of the cord and spastic paraparesis. Signs and symptoms of spinal dysraphism may not appear until the child is 3 years of age or older, for example, paresis of the lower extremities, muscular atrophy, and incontinence. Early recognition and operative repair is necessary to prevent permanent neurologic sequelae. Ultrasonography (U/S) will demonstrate a tethered spinal cord in infants up to age 4 months because of incomplete ossification of the posterior spine. Screening lumbosacral MRI (and sedation) is necessary after that age. If the initial U/S of the spine is highly suspicious or inconclusive for tethering, MRI is mandatory. MRI (with contrast), plus MRA, will also show possible spinal extension of the hemangioma and other vascular anomalies.

Figure 4-11
Hemangioma and associated ventral-caudal anomalies. A. Reticular type tumor with acrochordon and tethered cord. B. Pebbly lumbar tumor with acrochordon and meningocoele. C. Reticular hemangioma involving buttock and entire right lower limb with imperforate anus, duplex left kidney, and tethered cord. D. Hemangioma and penoscotal transposition. (Courtesy of Dr. Steven J. Fishman)

Perineal hemangioma can also be associated with urogenital anomalies, such as anterior, vestibular, or imperforate anus (often with fistula), renal anomalies, bladder extrophy, ambiguous genitalia (e.g., hemiclitoris, atrophy or...
absence of the labia minora), and hypospadius (Goldberg et al., 1986). There may be a persistent sciatic artery, hypoplastic iliofemoral artery (Mulliken et al., 2007b; Kircher et al., 2010); perhaps these correspond to the anomalous embryonal intracranial vessels in the PHACE association. We also described an infant at the extreme end of the spectrum who had an extensive, deeply infiltrative reticular hemangioma, dilatation of the common iliac artery with extensive arteriovenous shunting in the pelvis and lower limb, and cardiac overload (Mulliken et al., 2007b).

The acronyms PELVIS (Girard et al., 2006) and SACRAL (Stockman et al., 2007) incorrectly labeled a “syndrome” and, as in many acronyms, it is necessary as a mnemonic aid, LUMBAR is the most inclusive: lymphangiomyelopathy, bony deformities, anorectal malformations and arterial anomalies. The u also denotes the likelihood of ulcerations in this setting.

This same combination of congenital abnormalities (in the absence of hemangioma) has been designated as the septum malformation sequence (Wheeler and Weaver, 2001). The pathogenic speculation is that during the fourth to sixth weeks of development there is incomplete breakdown of the cloacal membrane and insufficient mesodermal penetration in the caudal region of the embryo.

**Pathogenesis of Hemangioma and Associated Structural Malformations**

The concurrence of infantile hemangioma and malformative anomalies has generated speculation about the possibility of a common pathogenesis. Perhaps these associations represent a defect in mesodermal development and angioblastic tissue (Hersh et al., 1985) and neural crest cells give rise to the cellular components of infantile hemangioma, that is, endothelial cells, pericytes and smooth muscle cells, as well as most connective tissues in the craniofacial region (of infantile hemangioma and associated structural anomalies). The structural anomalies that occur in PHACES and ventral-caudal hemangiomas are intriguing. The remarkable preponderance of females (over 90%) suggests an X-linked dominant monogenic disorder that is usually lethal in males. Some males would survive, depending on the mutation in their genome. Males with PHACE association do not have more severe anomalies (hypothesis was provided by Levin and Kaler (2007), who analyzed a family with hemangioma in two generations. They determined that an unaffected mother had skewed X-inactivation (which could protect her against the theoretical X-mutation), whereas her daughter with PHACES showed a random X-inactivation (which could result in greater expression of the mutated X chromosome). Nevertheless, molecular and genetic studies must continue to focus on the etiology and pathogenesis of sporadic infantile hemangioma. Solving the mystery of hemangioma-genesis should clear the way for investigation of mechanisms that cause the rare associated malformations.

**The Proliferating Phase**

Infantile hemangioma’s hallmark is rapid neonatal growth. The concurrence of infantile hemangioma and malformative anomalies has generated speculation about the possibility of a common pathogenesis. Perhaps these associations represent a defect in mesodermal development and angioblastic tissue (Hersh et al., 1985) and neural crest cells give rise to the cellular components of infantile hemangioma, that is, endothelial cells, pericytes and smooth muscle cells, as well as most connective tissues in the craniofacial region (of infantile hemangioma and associated structural anomalies). The structural anomalies that occur in PHACES and ventral-caudal hemangiomas are intriguing. The remarkable preponderance of females (over 90%) suggests an X-linked dominant monogenic disorder that is usually lethal in males. Some males would survive, depending on the mutation in their genome. Males with PHACE association do not have more severe anomalies (hypothesis was provided by Levin and Kaler (2007), who analyzed a family with hemangioma in two generations. They determined that an unaffected mother had skewed X-inactivation (which could protect her against the theoretical X-mutation), whereas her daughter with PHACES showed a random X-inactivation (which could result in greater expression of the mutated X chromosome). Nevertheless, molecular and genetic studies must continue to focus on the etiology and pathogenesis of sporadic infantile hemangioma. Solving the mystery of hemangioma-genesis should clear the way for investigation of mechanisms that cause the rare associated malformations.
appearance (Figure 4-12A). If the tumor arises in the superficial elevated surface and a vivid crimson color. Many superficial hemangiomas are small and localized, ranging from 0.5–5.0 centimeters (cm) in diameter (Figure 4-12B). In general, the area of the lesion is delineated early; this has been called a “field transformation” (Mulliken, 1991). Once the territory of a superficial lesion is defined, further growth occurs in depth. This causes the tumor to protrude and present with a red, often circular, cap over an enlarging bluish deep component. The hallmark of the combined (deep and superficial), as well as the primarily deep, hemangioma is large draining veins radiating from the tumor.

Entirely superficial lesions are diffuse, slightly raised, with a pebbled surface, and disposed in a geographic pattern. There can be continued growth at the periphery, while the central area may remain stable or show signs of early regression. A less common form of reticular hemangioma remains flat (macular); however, scattered or peripheral pebbles of nodular tumor may appear within the involved area. Parents often comment that their child’s hemangioma changes color during the day; it looks better in the early morning. This observation is ascribed to increased adrenal excretion of corticosteroid during the sleeping hours.

Deep hemangioma proliferates in the lower dermis, subcutis, or muscle; the overlying skin is only slightly raised, warm, and normal or slightly bluish in color (Figure 4-12C). The covering telangiectatic vessels. Deep hemangioma often grows unnoticed until 3–4 months of age. Combined lesions, in which there is proliferation in both the superficial and deep dermis, as well a cavernous” hemangioma (Figure 4-12D). Histologic examination of axial sections through these hemispherical hemangiomas shows that the proliferative endothelial pattern is remarkably consistent throughout the depth of any particular tumor (Mulliken and Glowacki, 1982). Thus, the time-honored histologic adjectives “capillary” (denoting superficial hemangioma), “cavernous” (denoting deep hemangioma), and “capillary-cavernous” are confusing, inaccurate, and should be discarded (Mulliken and Glowacki, 1982).

There are few indicators that predict the eventual volume of an evolving hemangioma or that forecast accurately the onset or outcome of involution. The apogee of growth is around 6–7 months. A large prospective cohort study showed that most hemangiomas reach 80% of their maximum size by 5 months (Chang et al., 2008). Therefore, a young infant with emerging h
tumor’s growth, anticipate complications, and consider treatment. The spectrum of growth is broad. Small tumors seem to stabilize earlier. It has been written that deep hemangiomas have a longer growth phase than superficial lesions; furthermore, deep lesions seem to regress more slowly (Nakayama, 1981) due to the difficulty in monitoring the life cycle of a deep hemangioma, which is more easily appreciated than diminishing volume.

There is a small subset of errant hemangiomas that continue to proliferate beyond age 1 year, even into late childhood (Figure 4-13 A–C). It is traditionally believed that an involuted hemangioma is a stable lesion, nothing more than fibrofatty tissue and a few residual vessels. A rare example of recrudescence prior to onset of puberty is shown in Figure 4-13D.

Differential Diagnosis

Clinical history is foremost in differentiating infantile hemangioma from vascular malformation. Whether or not there is a premonitory cutaneous sign at birth or the tumor appears postnatally, growth of a hemangioma is rapid, out of proportion to that of the infant. In contrast, a vascular malformation, whether noted at birth or later, usually enlarges commensurately with the child. The color of a vascular birthmark also helps in establishing the diagnosis. A superficial hemangioma has a bright scarlet color that gradually deepens during the first year. Vascular malformations have a persistent hue, depending on whether there are arterial, venous, capillary, or lymphatic components.
While palpating a vascular anomaly, it is helpful to imagine what its microscopic appearance might be. Infantile hemangioma feels firm or rubbery; it is a dense cellular tumor with relatively little luminal area. A hemangioma cannot be completely emptied of blood with compression, unlike a flat capillary malformation or a protuberant venous malformation. In contrast, a venous malformation is soft, easily compressible, and sponge-like because it is composed of dilated channels and sparse parenchyma. Palpation of thrombi or phleboliths confirms the diagnosis of venous malformations. Capillary malformations, arteriovenous anomalies, and infantile hemangiomas are warm to the touch, in contrast to lymphatic and venous malformations.

In most instances, hemangiomas can be differentiated from vascular malformations without resorting to radiologic diagnostic techniques (Finn et al., 1983; Mulliken, 1984). An accurate history, often with the help of the baby’s earlier photographs, and physical examination should permit proper diagnosis. For confirmation, or if there is any uncertainty, a handheld (continuous wave) Doppler unit demonstrates the typical to-fro sound of proliferative hemangioma. This rechargeable instrument is very useful, particularly in the diagnosis of a deep lesion, and also can save the time and expense of a radiologic assessment. If the diagnosis remains unclear, formal ultrasonography can be done, followed, if necessary, by magnetic resonance imaging. Alternatively, if the diagnosis is uncertain, although it appears to be a harmless lesion, the physician can honorably suggest that the infant come back for another visit in 2–3 weeks. Usually parents accept an explanation of the most likely diagnoses, especially if immediate therapy is not necessary. Clearly, this kind of consultative plan requires an understanding of the parents’ concern and their confidence that an accurate diagnosis is forthcoming.

There are two axioms that help to distinguish infantile hemangioma from other tumors and vascular malformations.

**Not All Hemangiomas Look Like Strawberries**

The diagnosis of hemangioma is usually possible based on a history of rapid growth, characteristic appearance, and palpation. Nevertheless, hemangiomas appear in a wide variety of guises. The most common form is a localized, bright red, raised tumor with a variable deep component. Less common is a large, patch-like, or more diffuse tumor. Multifocal lesions can be variable, from pinpoint tumors to large nodules. Deep hemangioma and reticular hemangioma are variations that are easily diagnosed by pattern recognition. Some of hemangioma’s many disguises are shown in...
Figure 4-14
Axiom I: Not all hemangiomas look like strawberries. A. 4-month-old boy with recent appearance of macular vascular stain on left cheek with indistinct border. Lesion stopped growing by “Arrested” infantile hemangioma. B. Raised hemangioma left cheek mucosa limits elevation of tumor. C. 2-year-old girl with vascular lesion that appeared at 3 months, grew rapidly, and remained unchanged thereafter. Fast-flow suggested AVM. Sin Histolopathology: tightly packed capillary-like vessels, plump hemangioma.

Deep Hemangioma

The skin can be normal overlying a deep hemangioma in subcutaneous tissue; however, usually there is a faint bluish hue and a few telangiectasia. A fibrofatty feel on palpation and the hemangioma can be confused with other vascular lesions in the malformation (Figure 4-15). Hemangioma is the most common (50%), followed in frequency by pleomorphic adenoma (29%) (Welch, 1986). Malignant epithelial tumors of the parotid are uncommon in infancy; they typically present in childhood and adolescence (Lack and Upton, 1988).

Figure 4-15
Deep hemangiomas. A. 2-year-old girl with spheroidal tumor right lateral supraorbital area first noted at age 2 months. First diagnosed as angular dermoid cyst; fast-flow noted by Doppler examination. Dx: Deep hemangioma. B. Spherical swelling right lower neck manifested at 2 months, simulating macrocystic lymphatic malformation. Ultrasonography and MRI confirmed Dx: Infantile hemangioma. C. 5-month-old female infant with enlarging tumor in left parotid region. Dx: Deep hemangioma. Telangiectasia or tiny circular red spot usually confirms diagnosis; sometimes overlying skin is normal and duplex ultrasonography needed.

Lymphatic anomalies are not always obvious at birth; they can suddenly appear, due to intralesional bleeding or cellulitis. Lymphatic lesions are either cystic and soft or tense; they can be transilluminated, unless there is intralesional blood. Lymphatic anomalies may have an overlying capillary stain; tiny cutaneous vesicles are pathognomonic.

A handheld (continuous wave) Doppler unit usually confirms the diagnosis of a deep hemangioma. If necessary, duplex ultrasonography or MRI (with gadolinium) will precisely define the lesion and its extent. If there is still clinical or radiologic ambiguity, consider fine needle biopsy, under fluoroscopic guidance.

Arrested Hemangioma

Hidano and Nakajima (1972) described two infants who presented with well-demarcated pale spots that betoken
hemangioma; however, only “telangiectases” developed, and called “port-wine like” and “telangiectatic” (Martínez-Pérez et al., 1995). An inchoate hemangioma presents as a flat, telangiectatic lesion. There is a predilection for the lower body and lower limbs; there may be elsewhere (Figure 4-16). Often the central area of an arrested hemangioma presents as a flat, telangiectatic lesion. An inchoate hemangioma presents as a flat, telangiectatoid patch, sometimes with a pale halo. There is a predilection for the lower body and lower limbs; there may be elsewhere (Figure 4-16). Often the central area of an arrested hemangioma begins to involute as it regresses while tiny papules form at the periphery and coalesce. These stunted hemangiomas tend to involute earlier in childhood as compared to other forms of infantile hemangioma that appear postnatally and exhibit a prominent growth phase. There is the same female preponderance as the more typical infantile hemangioma.

Most arrested hemangiomas look reticular but not all reticular hemangiomas are “arrested.” At the opposite end of the spectrum is the regional reticular hemangioma that occurs in PHACE association (Figure 4-17A) or in the lower trunk with associated lumbo-sacral anomalies (Figure 4-17B). Reticular hemangioma in an extremity can be a patch or more diffuse, often in a distal glove or stocking pattern (Figure 4-17C). Extensive (regional) reticular hemangiomas exhibit postnatal growth and usually darken in color or

Figure 4-16
Arrested hemangiomas. A. Infant born with pale patch and central blotchy pink on lateral calf; however, the tumor failed to evolve and began fading before 1 year. B. Neonate with “telangiectatic” lesion (and faint pale halo) on left upper abdomen that never progressed. C. 2-month-old girl born with pink patch on the calf; this darkened; few tiny papules appeared; lesion failed to evolve further and slowly regressed. She also had 3 other more typical forms of infantile hemangioma. D. 5-week-old infant with stunted hemangioma on calf and multiple intrahepatic hemangiomas.

Reticular Hemangioma

Infantile hemangioma can infiltrate the dermis, staining and slightly elevating skin, thus simulating a capillary malformation (“port-wine stain”) (Martínez-Pérez et al., 1995). This variant typically presents as a precursor lesion at birth and may show few signs of rapid growth, further adding to possible confusion with capillary malformation. On close examination, the hemangiomatous stain is inhomogeneous and network-like (unlike a capillary malformation); there are fine vessels, variegated color, and irregular margins; often there are large draining veins, and the involved skin is slightly puffy. These lesions have also been called “telangiectatic” (hemangioma) histopathologically a telangiectasia. The adjective “reticular” is suggestive of a fine network of cells or connective tissue. Dictionary (27th edition) defines reticular as “a fine network formed by cells…or by connective tissue between cells.”

Reticular hemangioma is a variation of infantile hemangioma; protein-1) positive. Reticular hemangioma phenotype present localized macular lesion, usually in a limb, that fails to grow arrest not all reticular hemangiomas are “arrested.” At the opposite end of the spectrum occurs in PHACE association (Figure 4-17A) or in the lower trunk (Figure 4-17B). Reticular hemangioma in an extremity can be a patch or more diffuse, often in a distal glove or stocking pattern (Figure 4-17C). Extensive (regional) reticular hemangiomas exhibit postnatal growth and usually darken in color or
become raised. The plantar or palmar surfaces remain macular and are often homogenously stained, whereas more proximally, the tumor exhibits the characteristic network-like appearance. Reticular hemangioma has been mistaken for capillary malformation, cutis marmorata telangiectatica congenita, and Parkes Weber syndrome. Reticular hemangioma of the limb can also be accompanied by the more typical forms of the tumor, as well as with intrahepatic hemangiomas (as in PHACE association), gastrointestinal hemangiomas, and tiny macular cutaneous lesions. Structural abnormalities have not been reported with reticular hemangioma in the upper extremity.

Figure 4-17
Reticular hemangiomas. A. Female infant with left facial reticular type hemangioma. MRI and echocardiography ruled out PHACE association. B. 2-month-old female with reticular hemangioma on right lower extremity and perineum associated with tethered spinal cord, imperforate anus, omphalocele and capillary malformation. C. 10-month-old girl with reticular her postnatally and darkened over ensuing months. D. Diffuse reticular hemangioma of right lower limb with ulcerations. Fast-flow resulted in cardiac overload with a minor contribution by demonstrating enlarged right common iliac artery with multiple distal extremity.

Reticular hemangiomas often progress to acral, proximal, and perineal ulcerations (with or without ventral-caudal anomalies); these tend to be deep and recalcitrant to the usual and sometimes skin grafting may be necessary. Fast-flow through an extensive reticular hemangioma in a limb can cause cardiac overload. In one such infant, embolization was necessary because of extensive necrosis (microscopy showed infiltrative growth of deep tissues, including bone).

Reticular hemangioma sometimes regresses rapidly, but usually localized form of the tumor. Axial overgrowth of the limb is possible following involution.

Reticular hemangioma over the thoracic spine is another, albeit uncommon, location. MRI may reveal intraspinal extension, both intra- and extrathecal. The tumor may cause compression of the thoracic cord.

Not All Strawberries Are Hemangiomas
Tumors

Other vascular tumors of infancy can masquerade as common tufted angioma, and various types of hemangioendothelioma (nasal glioma, juvenile xanthogranuloma, infantile myofibroma, al., 1995), cutaneous lymphoid hyperplasia, solitary (“self-hea angiofibroma, giant cell angiolobra, and pilomatrixoma (Hassanein et al., 2011) have been misdiagnosed and mistreated as infantile hemangioma (ready to burst), purple-red with radial vessels, and firm to palp infantile hemangioma include rhabdomyosarcoma, extraosseous metastatic neuroblastoma (Hassanein et al., 2010) (Figure 4-2c cutis”) can be mistaken for hemangioma (Burnett et al., 2007) (lipoblastoma of the forehead that was initially misdiagnosed a mandatory if there is any inconsistency in the findings or any s examination, or radiologic imaging.

Figure 4-18
Axiom II: Not all strawberries are hemangiomas. Multiple vasc trunk and extremities. Curiously, only one tiny lesion grew on (unspecified type, GLUT1 negative).
Figure 4-19

(Courtesy of Dr. Arin K. Greene)

Figure 4-20

(Courtesy of Dr. Chantal van der Horst)
Cutaneous leukemia. A. Glabellar mass appeared at 6 months, leukemic infiltrate in muscle. B. 6-month-old child with swelling skin; lesion slightly firm. Biopsy Dx: precursor B-cell acute lymphoblastic leukemia. (Courtesy of Dr. Trevor J. McGill)

Pyogenic Granuloma

This common fruit-like cutaneous vascular tumor can be confused with infantile hemangioma when it occurs in the pediatric age group. Unfortunately, pathologists have muddied the term hemangioma." A better term would be “lobular capillary (or endothelial) hyperplasia.” Pyogenic granulomas arise in older infants and children, at a mean age 6.7 years; 12% occur in the first year of life (Patrice et al., 1991). Usually there is no history of trauma or a preexisting dermatologic condition. These lesions appear to arise sui generis; however, they often appear in a preexisting capillary stain. The characteristic locations are the central face, eyelids, or extremities. Less frequently, pyogenic granuloma occurs on the lips, oral mucosa, tongue, and nasal cavity (Patrice et al., 1980). Typically they appear suddenly and grow rapidly. They begin as a papule and, in time, they erupt to form a stalk or pedicle. The typical pyogenic granuloma is small (average diameter 6.5 mm) (Figure 4-21). Repeated, often copious, bleeding episodes initiate visits to the local emergency room or the physician’s office. Bleeding is notoriously difficult to stop despite pressure or cauterization. Frequently the child arrives with an adhesive bandage covering the lesion. This typical presentation prompted Thomson to call this entity “Band-Aid disease.” Pyogenic granulomas exhibit rapid flow by Doppler examination. Ultrasonography demonstrates a characteristic vertically oriented central feeding artery and draining vein.
Figure 4-22
Pyogenic granuloma. A. Pedunculated lesion. B. Dome-like lesion. Continued to appear until age 6 months. Several lesions excised. GLUT1 immunonegative capillaries in edematous stroma with epithelial collarettes. No recurrence at age 19 years. C. Multiple pyogenic granulomas at birth; new lesions continued to appear until age 6 months. Several lesions excised because of bleeding. Histopathologic examination showed GLUT1 immunonegative capillaries in edematous stroma with epithelial collarettes. Remaining lesions shrunk and fell away; no recurrence at age 19 years. D. 10-year-old girl born with capillary stain on posterior thorax; multiple pyogenic granuloma-like lesions appeared at age 1.5 years. Doppler and MRI reveal Stage I AVM without spinal extension.

Not all pyogenic granulomas ulcerate; some remain sessile, circular, slightly raised, and covered by epithelium (Figure 22B). This papular form can be mistaken for a small infantile hemangioma. Multiple congenital pyogenic granulomas vary in size; often they are pedunculated, and they always bleed, which necessitates excision. Nevertheless, they have a limited life span and gradually begin to regress in late infancy and disappear in early childhood. Multiple pyogenic granuloma-like lesions can also arise in the stain overlying an AVM (Figure 22D). Pyogenic lesions are GLUT1 negative, whereas multiple, tiny, and rapidly regressing hemangiomas are GLUT1 positive. Multiple pyogenic lesions (“satellites”) can also appear in the area of a previously excised solitary lesion.

The cause of pyogenic granuloma is unknown. Although they contain inflammatory cells, these lesions are not thought to be induced by infection, nor are they granulomatous by histologic examination. They have a similar appearance to the eruptive vascular lesions in bacillary angiomatosis and in verruga peruana (Carrión disease) caused by species of Bartonella. Nevertheless, immunohistochemical and molecular profiling of 45 specimens failed to reveal any of the protein or DNA sequences of *B. quintana* or *B. henselae* (Levy et al., 2005).

**Vascular Malformations**

Capillary, venous, and arterial malformations can be confused at birth and commensurate growth, plus the findings by observation and palpation, should assure the diagnosis. Both hemangioma and AVM are warm on palpation. Hemangioma exhibits a prominent Doppler signal, whereas a nascent AVM may not. AVM in an infant typically presents as telangiectasia expanding during the first year, forming a tumor-like mass, sometimes with ulceration. In some cases, imaging studies are necessary to evaluate the lesion. Biopsy may be necessary.
Figure 4-23
Vascular malformations. A. Vascular birthmark on philtrum; note capillary malformation. B. Purple vascular lesion of lower eyelid misinterpreted as “hemangioma.” Dx: venous malformation. C. Exhibited postnatal nodular expansion. MRI and angiography confirmed Dx: AVM (Stage II). Tiny helical ulceration followed embolization. D. 5-month-old girl born with purple, enlarged right ear and patchy stains on face. Epistaxis prompted angiography, interpreted as “hemangioma” because lesions discontinuous and localized. Auricular biopsy was GLUT1 negative and interpreted to be AVM.

Proliferating Phase Complications

Ulceration

Superficial hemangiomas, those proliferating just beneath the epidermal crusting and dark discoloration are the immediate localizations. Maguiness and colleagues (2010) have shown that an earlier whitish discoloration (at age 3 months or younger) is a sign of impending ulceration, rather than an augury of early involution.

The frequency of ulceration was 16% in a large multicenter prospective cohort study, occurring around 4–6 months, at the height of the proliferative phase. For example, ulceration was documented in 59% of commonly occurs in lower labial and anogenital hemangiomas and post-auricular sulcus. If the tumor grows in the form of hillocks, ulceration frequently occurs in the valleys. These observations suggest that localized trauma, friction, and maceration of any tense superficial tumor (Figure 4-24A, B, C). Congenital ulcers occur around 4–6 months, at the height of the proliferative phase. For example, ulceration was documented in 59% of commonly occurs in lower labial and anogenital hemangiomas and post-auricular sulcus. If the tumor grows in the form of hillocks, ulceration frequently occurs in the valleys. These observations suggest that localized trauma, friction, and maceration of any tense superficial tumor (Figure 4-24A, B, C).

Once it was believed that ulceration was secondary to infection; bacterial colonization of an ulcerated wound. A retrospective study of so-called “infected” hemangiomas documented polymicrobial cultures, either aerobic or anaerobic or mixed organisms (uncommon; the usual offenders are *Pseudomonas* and *Staph. aureus*). Hemangioma progresses to extensive necrosis and destruction of soft tissue and the cartilaginous framework of the nose or ear (Figure 24-D). Thomson (1979) called these aggressive lesions “wild-fire hemangioma.” Small punctate and often quite large recalcitrant ulcerations characterize reticular hemangioma in an extremity and perineum. Ulcerated hemangiomas often bleed, but this is usually minor.

Ulcerated hemangioma is notoriously slow to heal, despite all measures. The ulcerated area is exposed to air or physical contact. Nor do the parents sleep well. Cutaneous and sensory nerves have been shown to be increased in the proliferative phase (Jang et al., 2000).

**Mechanism**

The cause of ulceration is not precisely known. The old speculation was that localized ischemia is the cause of epidermal breakdown and ulceration—either as the result of microvascular shunting or the tumor simply “outgrowing its blood supply.” Another possible explanation is that the loss of normal keratin barrier and abnormal hyperplastic and parakeratotic changes in the overlying epidermis (Beilenberg et al., 1999) predispose to desquamation and ulceration.

**Bleeding**

In 1940, Kasabach and Merritt described thrombocytopenic purpura.
with a rapidly enlarging “giant capillary hemangioma” of the left thigh (years, the double-eponym “Kasabach-Merritt syndrome” was a variety of vascular anomalies. By the end of the last century, it cause coagulopathy. Primary platelet-trapping is almost exclusively associated with tumors, kaposiform hemangioendothelioma (KHE) and tufted hemangioma also bleeds, but usually more slowly.

**Obstruction**

**Visual**

Amblyopia is defined as poor vision in an eye in which there is no structural defect. Any visual perturbation in one eye results in failure of normal development of binocular cortical cells. The best-known is deprivational amblyopia (caused by visual failure to develop binocular vision (Robb, 1977; Stigmar et al., 1978; Thomson et al., 1979; Haik et al., 1979). Longer periods of obstruction are even more injurious (Figure 4-25). Periocular hemangioma can also cause amblyopia because of anisometropia (asymmetrical refractive error), secondary to pressure on the highly elastic infantile cornea and globe. A difference in refraction of 2 diopters or more is significant enough to cause amblyopia. These refractive errors are usually astigmatic and sometimes myopic (Robb, 1977; Haik et al., 1979). Hemangioma exerts pressure on the globe in a direction perpendicular to the axis of greatest corneal curvature (Robb, 1977; Stigmar et al., 1978) and strabismic. The best-known is deprivational amblyopia (caused by blepharoptosis) and failure to develop binocular vision (Robb, 1977; Stigmar et al., 1978; Thomson et al., 1979; Haik et al., 1979). Paralysis (secondary to extraocular muscle infiltration by tumor) also can be a primary cause of amblyopia (Stigmar et al., 1978).
Figure 4-25
Proliferative phase complication: Ocular obstruction. A. Newborn on day 1. B. On day 5, faint geographic stain on left supraorbital area and upper eyelid. C. By day 14, stain darker with slight swelling of eyelid. D. By 7 weeks of age, fronto-orbital hemangioma obscures visual field.

Figure 4-26
Proliferative phase complication: Corneal deformation. 3-month-old female with small left medial upper eyelid hemangioma causing astigmatism (2.5 diopters); she is at risk
Retrobulbar hemangioma usually does not cause astigmatism or ambylopia. It is more likely to cause displacement of the globe (usually proptosis or dystopia), ocular muscular imbalance, or hyperopia (due to relative shortening of the globe).

Epiphora and recurrent conjunctivitis is another relatively frequent complication of periocular hemangioma. It is caused by hemangiomatous obstruction of the nasolacrimal drainage system, and it is usually temporary.

Ultrasonography is useful in determining the anatomic extent extraconal, or intraconal (Bowman et al., 2004). It can be accomodated without the need for sedation or a general anesthetic.

MRI is indicated if there is concern about possible intraorbital extension of an eyelid hemangioma. Imaging should also include attention to the brain, looking for possible PHACE cerebral vascular anomalies. Intraorbital hemangioma can extend intracranially.

Every child with a periocular hemangioma should be refracted using retinoscopy after cycloplegia. Whenever the tumor is in the upper eyelid or supraorbital area, frequent periodic refraction is mandatory. Large hemangiomas of the lower eyelid and cheek should also be followed closely, although lesions in this area is because... globe to rotate upward during sleep—babies’ usual mode. Newborns should be evaluated by an ophthalmologist. Rarely, a large hemangioma can obstruct vision. One possible mechanism is that the tumor elevates with supine positioning of the baby. Even when infants are propped up, they may not be able to raise the head to look over a malar tumor.

Absence of an asymmetrical refractive error is a favorable prognostic sign for normal vision after involution of a periocular hemangioma (Robb, 1977). Late residual complications of periorbital and adnexal hemangiomas include ocular proptosis, blepharoptosis, and even optic atrophy (Stigmar et al., 1978).

Airway

Proliferative phase hemangioma could possibly block the nasal air passage early on, when the infant is an obligatory nasal breather. In clinical practice, this is an extremely rare occurrence. Nasal obstruction usually occurs slowly such that the infant adapts and learns to breathe through the oral passage. It has also been written that a rapidly proliferating nasal tip hemangioma can destroy the lower lateral cartilages. This is apocryphal. The cartilages are entirely normal, although distorted, when exposed during resection of the tumor.

More insidious and life-threatening is hemangiomatous proliferation in the subglottis. Typically, these infants are asymptomatic at birth, but within 6–8 weeks they slowly develop inspiratory, then biphasic, stridor, which is especially noticeable during feeding, crying, or upper respiratory tract infection. The majority of infants present before the age of 6 months; the mean age is 3.6 months (Shikhani et al., 1986). Often the symptoms fluctuate. The treating physician may misdiagnose the problem as protracted laryngotracheitis or recurrent croup, despite the absence of fever (Approximately one-half of infants with subglottic hemangioma have cutaneous hemangiomas, usually in the cervicofacial area (Ferguson and Flake, 1961). Thus, the absence of cutaneous appearance of the cutaneous lesion indicate the presence of, or early involution in the cutaneous lesion (e.g., softening and a dull gray color change) at the same time that the subglottic hemangioma is slowly narrowing the airway. The term “beard” distribution serves as a useful reminder that cervicofacial hemangioma can be associated with subglottic hemangioma (inappropriate since most hemangiomas occur in little girls.

Any infant who is suspected of having subglottic hemangioma should be endoscoped. A flexible endoscope in an awake infant does not permit full visualization of the subglottis. General anesthesia is necessary for direct laryngoscopy and bronchoscopy. The typical finding is a localized, smooth, compressible mass in the subglottic area (Figure 3). There may be a few telangiectatic vessels in the submucosa. Subglottic hemangioma can also be diffuse, exhibiting a bright red-
stain subglottis and trachea in the absence of mucosal elevation. There also can be supraglottic staining of the epiglottis, aryepiglottic folds, and piriform fossae. Extension into the hypopharynx and base of the tongue is uncommon. Subglottic hemangioma can also be circumferential and can encroach on the airway also may be compromised due to extrinsic compression by mediastinal hemangioma. CT or MRI (with contrast) is indicated whenever there is circumferential narrowing.

Figure 4-27
Proliferative phase complication: Airway obstruction. A. Localized right subglottic hemangioma seen through laryngoscope. Unilateral tumor more commonly seen on left side. (Courtesy of Dr. Reza Rahbar) B. Endoscopic view of circumferential subglottic hemangioma with 95% narrowed airway. (Courtesy of Dr. Reza Rahbar)

Hemangioma in the postcricoid region of the hypopharynx is rare. In this location, the hemangioma may be asymptomatic, or obstructive symptoms can be subtle and appear late; these include dysphagia, hypersalivation, and intermittent aspiration (Awwad and Mortelliti, 2006). If the infant is straining, flexible laryngoscopy reveals a bulging, vascular mass in the postcricoid region. Postcricoid lesions are less easily visualized when the infant is relaxed, particularly when under general anesthetcic (Awwad and Mortelliti, 2006).

Auditory

Obstruction of the external auditory canal, unilateral or bilateral, typically occurs with hemangiomatous involvement of the parotid gland (Figure 4-28A). Narrowing of the canal can result in minor to moderate conductive hearing loss; however, this is relieved with regression of the hemangioma. This should not be a problem unless bilateral obstruction persists beyond 1 year, when auditory conduction is necessary for normal development.
Figure 4-28

It is curious that facial nerve palsy is almost never seen, given that parotid hemangiomas can grow to a large size and hemangiomas have a predilection to invade nerves. In our unit, we have seen transient facial nerve weakness in an infant with a parotid hemangioma. This was likely caused by a separate intracranial hemangioma located within the course of the nerve in the temporal bone, that is, in the internal auditory canal. This same rare presentation has also been documented by Judd and coworkers (2007).

Skeletal Distortion

Infantile hemangioma rarely affects nearby bone. A minor deformity can result from a mass effect by the tumor. Examples include deviation of the nasal pyramid caused by a tumor of the cheek or a slight depression of the outer calvaria caused by a large scalp lesion (Boyd et al., 1984). Extensive intra- and extraconal hemangioma typically expands the infantile orbital cavity (Williams, 1979; Boyd et al., 1984), just as in experimental models (typically overgrows in the presence of a large parotid hemangioma (Figure 4-28B). Malar enlargement can also cause elevation of the ipsilateral orbit (Figure 4-28C). Bony and cartilaginous hypertrophy is presumably the result of hypervascularity. Localized hemangioma in a limb does not cause longitudinal overgrowth; nor does a diffuse tumor. Nevertheless, a minor limb length discrepancy can occur with reticular type hemangiomas (Greene et al., 2004).

Cardiac Overload

An extensive infantile hemangioma can divert enough blood to produce high output cardiac failure. This scenario most commonly occurs with multifocal intrahepatic hemangiomas, usually in association with multiple cutaneous tumors. The infant typically presents in the early postnatal period with hepatomegaly and signs of cardiac overload (Boon et al., 1996). The cutaneous lesions are usually tiny (less than 5 mm diameter) and dome-shaped; they can also have the other typical morphologic features of solitary cutaneous tumors. Clinical and radiologic features of intrahepatic hemangiomas are discussed in Chapter 5; diagnosis and management are presented in Chapter 5.

In rare instances, a large infantile hemangioma, whatever the location, can shunt sufficient blood as to cause increased high cardiac output. Perhaps the most common site is the parotid gland. This complication occurred in 3% of children in a series of 100 parotid hemangiomas (Greene et al., 2004). Cardiac decompensation can also occur with an extensive reticular type infantile hemangioma involving an extremity; the large tortuous feeding arteries and dilated draining veins can simulate an AVM (Mulliken et al., 2007b).
Fetal (congenital) hemangiomas, either cutaneous or solitary intrahepatic lesions, can cause hydrops fetalis or present with cardiac failure at birth (*vide infra*).

**Hypothyroidism**

Type 3 iodothyronine deiodinase (D3) is normally present in the brain and placenta, where it catalyzes thyroxine and triiodothyronine to biologically inactive metabolites. Placental D3 is thought to protect the fetus from maternal thyroid hormones. The finding of severe hypothyroidism in an infant with a large hepatic hemangioma led to the discovery of D3 in the tumor (*Huang et al., 2000*). Elevated D3 has also been found in small hemangiomas in children less than age 12 months, and also in a 21-year-old female with hepatic hemangioblastoma. The hemangioma degrade the thyroid hormones at rates that exceed the synthetic capacity of the infant’s thyroid gland. TSH levels should be checked in an infant with a large hemangioma and rechecked periodically during pharmacologic therapy. This “consumptive hypothyroidism” should be promptly treated with high doses of levothyroxine. Three to five IQ points are lost for each month in which an infant with hypothyroidism is untreated (*Newborn serum TSH screening is useful in the differential diagnosis of hypothyroidism. Elevated thyrotropin secretion in an infant with hemangioma could also indicate coincidental, congenital athyreosis, or there may be a tiny lingual thyroid. In such an infant, the TSH level promptly falls to normal level following administration of levothyroxine.*

**The Involuting Phase**

Hemangioma’s growth stabilizes by the end of the first year of life, follows thereafter by slow regression. Nevertheless, some hemangiomas continue to grow beyond age 1 year, particularly during the proliferating and involuting phases (*Brandling-Bennett et al., 2008*). Gradually, apoptosis begins to predominate after age 1 year, as the tumor enters the involuting phase. The central region of a superficial hemangioma can appear involuting, while proliferation may continue at the periphery of the lesion. Histologically, proliferation and involution can be seen in the same high-powered field. Tritiated thymidine uptake into endothelial DNA (*Mulliken and Glowacki, 1982*) have demonstrated diminishing cellular turnover until age 4–5 years. Apoptosis reaches its maximum rate at 2 years of age (*Razon et al., 1998*).

One of the first signs of regression is fading of the shiny crimson color to a dull purplish hue. The surface of the hemangioma assumes a mottled, grayish mantle, and on close examination, tiny white flecks can be seen. The lesion softens, and the involved skin becomes slightly wrinkled. Bleeding and ulceration cease to be a problem. The cutaneous signs of involution often begin centrally and spread, in a centrifugal fashion, toward the periphery of the hemangioma.

Whereas a young, tense hemangioma is often tender to the touch, the hemangioma seems less painful and that their child is not as fussy. The parents may also notice that when the child cries and strains, the hemangioma does not swell up the way it once did. Diminishing flow in the tumor can be documented by a handheld Doppler probe, as initially described by *Bingham (1979)* and subsequently by *Lister, 1938; Pratt, 1953; Simpson, 1959*. The disappearance of fast-flow Doppler signal in involuting phase hemangiomas. The Doppler signal vanishes around age 2–3 years in some children; it persists longer in many children. There is likely a wide range.

The involuting phase extends from 1 year until 5 to 7 years of age. Two examples of regression are shown in Figure 4-29. Clinical resolution occurs in over 50% of children by age 5 years and in over 70% by age 7 years, with continued improvement in the remaining children until age 10–12 (*Lister, 1938; Pratt, 1953; Simpson, 1959*).
298 hemangiomas, 80% of lesions that had not completely involuted by age 6 years left behind a significant residual deformity, as opposed to 38% "imperfect" results for lesions that involuted before age 6 years (Bowers et al., 1960; Finn et al., 1983). There is a lingering perception that large hemangiomas are less likely to regress than smaller tumors. Our experience (Finn et al., 1983) confirmed the unexpected finding, first noted by coworkers (1960), that the rate and completeness of resolution are not influenced by sex, site, size, nascent presence at birth, duration of the proliferating phase, nor morphology. Neither sex, race, nor site influences involution (Bowers et al., 1960; Finn et al., 1983). There is a lingering perception that large hemangiomas are less likely to regress than smaller tumors. Our experience (Finn et al., 1983) confirmed the unexpected finding, first noted by coworkers (1960), that the rate and completeness of resolution are unrelated to the size of the lesion. Furthermore, there is no correlation between the final result of regression and the age at which the lesion appeared.

Figure 4-29
Involuting-involuted phases. A. 4-month-old girl with superficial cheek hemangioma; treated with corticosteroid. B. Accelerated regression underway at age 1.5 years. C. Minor cutaneous residuum at age 13 years. D. Deep hemangioma of cheek relatively unchanged at age 2 years. E. Some regression complete at age 14 years. Nasal deviation barely noticeable with excellent skin quality.

The clock of regression begins ticking as hemangioma’s growth reaches its apogee during late infancy. Involution proceeds on a similar time schedule for both deep and superficial tumors. In low-birth-weight prematures follows the same time course as hemangiomas in full-term infants. That is, the duration of proliferation in a premature infant is determined at the time of birth, not by the biological age. Curiously, the tiny cutaneous lesions of multiple hemangiomatosis usually involute more rapidly, beginning in infancy and disappearing by age 2 years.

It is also commonly observed that involution proceeds more slowly in certain locations, particularly the nose and lips (Bowers et al., 1960). At the cellular level, all infantile hemangiomas involute, whatever the location. Proliferation and involution are often seen in the same microscopic field; however, there are no studies that correlate clinical and histologic findings by anatomic region. A likely explanation is that hemangiomas in some locations, such as the lips, nasal tip, and cheek, deposit more fibrofatty tissue during regression. This variable fibrofatty residuum gives the appearance of slow regression and persistent “tumor.”

Although uncommon, an infantile hemangioma can have a prolonged proliferative phase lasting well beyond one year. In some cases, pharmacologic therapy may have to be continued or reinstituted in early childhood. Whenever there are no signs of regression, the tumor should be excised. Histopathologic examination of these
reveal features characteristic of a much earlier stage in hemangioma's life cycle.

**The Involute Phase**

Nearly normal skin is restored in approximately 50% of children whose hemangioma atrophies, telangiectatic vessels, and slightly pale skin. A crepe-like matrix and the destruction of elastic fibers (*anetoderma*). This type of damaged skin is more likely after involution of a sharply demarcated, superficial, bossed tumor. Extra skin after regression also occurs because hemangioma acts as a tissue expander. Involuting tumors often have residual purplish draining veins. If ulceration occurred during the proliferating phase, this area will become a pale or discolored patch of scar. This skin is never of the same quality as that following involution without intervening ulceration. Another curious observation is that there is a predisposition for comedones and adolescent acne in skin of an involuted hemangioma.

Protuberant hemangioma of any size is more likely to result in a fibrofatty residuum. Nevertheless, even bulky deep (subcutaneous) hemangiomas may well regress totally, leaving residual fat. In general, it is difficult to accurately foretell the outcome in terms of the quality of the involved skin and the amount of residual fat (Figure 4-30). Hemangioma in certain anatomic locations produces observable permanent changes after regression. Tumor in the scalp can expand or destroy hair follicles, resulting in decreased density. Expansion of the eyebrow is common with a supraorbital hemangioma. Periorbital hemangioma can cause proptosis, blepharoptosis, and imbalance of the extraocular muscles. Nasal hemangioma splays the lower lateral cartilages and leaves fatty residuum, producing spherical enlargement of the tip. Labial hemangioma effaces the vermilion-cutaneous junction, and pale discoloration of the vermillion. Reticular hemangioma of a limb typically leaves behind dark blue veins, fine telangiectasias, and sometimes a slightly puffy subcutaneous layer (Figure 4-30). Rare instances of recurring, deep, well-localized ulcerations years after regression of the reticular type lesion in the lower extremity.
Fetal (Congenital) Hemangiomas

There are neonatal vascular tumors that do not follow the expected postnatal course and life cycle of the common infantile hemangioma. These tumors are distinguished as fully grown at birth, and thus they are defined as congenital hemangioma (Boon et al., 1996). Congenital hemangioma can also be called rapidly involuting congenital hemangioma (RICH). The defining feature of congenital tumors is that they do not exhibit rapid proliferation. Some regress rapidly, typically within the first year of life, whereas others do not regress at all and grow proportionally to the child. These two subgroups are designated by acronyms: RICH, hemangioma; NICH, rapidly involuting congenital hemangioma. Both forms of congenital hemangiomas have a different biologic clock from hemangiomas that appear postnatally. RICH’s clock runs fast and stops, whereas NICH’s clock never stops ticking. Curiously, both types of congenital (fetal) hemangioma occur in a 1:1 sex ratio, just as the common form of hemangioma that arises in premature infants.

Rapidly Involuting Congenital Hemangioma (RICH)

Accelerated regression of a large “strawberry nevus” was probably first described by Bowers and in seminal paper on the natural history of hemangioma. Two other examples were illustrated in the first edition of this book, but the significance of this unusual behavior was underappreciated (Boon et al., 1995). The following year, the vascular anomalies teams in Boston and Paris reported 31 such lesions and introduced the term “congenital hemangioma” to designate the type that exhibits rapid involution (Voisard et al., 1996). Increasing use of prenatal ultrasonography has generated several descriptions of fetal hemangioma (Treadwell et al., 1993; Maynor et al., 1995), often the tumor is detected in the first trimester; the earliest in our series was in a 12-week fetus (Boon et al., 1996). Doppler study demonstrates a fetal hemangioma as a fast-flow parenchymatous mass. Shunting in a large fetal vascular tumor can cause hydrops fetalis, a complication associated with a high mortality rate. The case described by Daniel and Cassady (1968) was retroperitoneal-mesenteric “hemangioendothelioma.” Many reports in the ultrasonic literature describe a large single tumor in the scalp/occiput (Khoury, 1994). These lesions have often been confused with occipital “hemangioma” was detected in a 14-week fetus and confirmed after termination (Boon et al., 1996). Intrathoracic fetal hemangioma can also cause hydrops fetalis (Viora et al., 2000), vascular tumors either regressed rapidly during early infancy (Tokuda et al., 1990; Boulot et al., 1996; Carlotti et al., 2000), were excised in early infancy (Tokuda et al., 1995; Boulot et al., 1996; Carlotti et al., 2000), or, less commonly, the neonate died of complications of the tumor (Carlotti et al., 1998; Shiraishi et al., 2000). Based on careful examination of these prenatal sonographic reports, the solitary fetal tumors, called “hemangioma” or “hemangioendothelioma,” are examples of RICH.

RICH reaches its greatest size during the final weeks of the third trimester; often there are ultrasonic signs of shrinkage just prior to delivery. At birth, RICH presents as a solitary tumor with a raised grey or violaceous mass with ectatic, radial veins, central telangiectasias, and a pale surrounding halo (Figures 4-12B, C). Involuted reticular hemangioma, age 7 years, only few telangiectasias remain; prominent ear secondary to retroauricular intracranial vascular anomalies. See proliferative phase Figure 4-12B. C. Minor crepey skin. See proliferative phase Figure 11 years. Note pigmented, atrophic skin, nasal deviation, and ear E. Multiple thoracic hemangiomas regressed at age 5 years, lea F. Involuted reticular hemangioma, age 13 years. Foot/toes slightly puffy, toes with scattered telangiectasias and few draining veins. See proliferative phase Figure 4-17C.
There may be central ulceration, scar, or nodular brown, corrugated patch. Initially there is fast-flow, but the typical variant is likely the result of rapid regression toward the end of the third trimester (Figure 4-33 C, D). There are rare cases of multiple RICH tumors (Figure 4-34). RICH has a predilection for the craniofacial region and lower limbs. Diagnosis for a solitary hepatic lesion (see Chapter 5). Being in full-bloom at birth does not always signify RICH (or NICH). In rare instances, infantile hemangioma can be protrusive in a newborn (Figure 4-31).
Figure 4-32
Plaque-like RICH. A. 2-month-old with a slightly raised, violaceous lesion with lighter halo. Likely involution began prior to birth. B. Accelerated regression at 6 months of age. C. Atrophy and slightly prominent veins at age 2 years. D. Appearance at age 4 years; residual ectatic veins.

Figure 4-33
Figure 4-34
Multiple RICH. A. Newborn with congenital vascular tumors of umbilical cord and anterior abdomen. Biopsies confirmed diagnosis. B. Accelerated regression at one year. Note more common (postnatal) cervical hemangioma.

Figure 4-35
Congenital or infantile hemangioma? A. Newborn with raised, discoid vascular tumor. Note halo and subcutaneous extension in temple. No subsequent rapid growth. B. Ulceration at 7 months and some signs of regression by age 10 months. Dx: Tumor resected at age 2 years. Histopathology: GLUT1 negative.

There are two complications with RICH, although both are uncommon: cardiac overload and transient thrombocytopenia. Fast-flow can cause sufficient shunting in a cutaneous or intrahepatic tumor so as to produce neonatal congestive heart failure. There are documented examples of resection for this complication (Price et al., 1972). Sometimes the excised tumor is mistaken for an AVM (50,000 platelets/µL (sometimes lower) can be caused by a large thrombocytopenia also can occur in an infant in response to a thrombocytopenic coagulopathy was considered to be a complication in our original description of RICH (Boon et al., 1996), and was labeled "Kasabach-Merritt phenomenon" (KMP). There are older reports of vascular tumors treated for this indication with radiation therapy and resection (Inglefield et al., 1961; Hill and Longino, 1962). In our original description of RICH (Boon et al., 1996), we mistakenly applied the double-eponym "Kasabach-Merritt phenomenon."
to describe minor thrombocytopenia in two patients. The hematologic profile in RICH is more akin to a minor consumptive coagulopathy, that is, low platelets, low fibrinogen, and elevated D-dimers. Petechiae are uncommon and visceral bleeding has not been observed with thrombocytopenic RICH. Platelets rapidly rise to normal levels as RICH regresses (2008) (Figure 4-36).

![Figure 4-36](Click to view larger)

**Complications of RICH.** A. Neonate with vascular tumor right medial thigh causing anemia, thrombocytopenia (11,000/µL), and high output congestive cardiac failure. Dx: RICH confirmed by duplex ultrasonography and MRI. B. Given corticosteroid; by 2 months, normal platelet count and cardiac function. C. Tumor regressed at age 6 months, leaving lax skin. Ultrasonography with color Doppler, MRI/MRA, and angiography demonstrate rapid flow within parenchyma, just as in the common infantile hemangioma that evolves postnatally (Rogers et al., 2002). Indeed, RICH does not exhibit the same homogenous enhancement as infantile hemangioma. Furthermore, MRA and angiography may demonstrate calcifications, focal aneurysms, and direct arteriovenous fistulae, which are likely the cause of cardiac overload. Thrombi with focal calcifications can also be seen radiographically. There is a report of a fatal pulmonary thrombo-embolus originating in a RICH in the lower extremity.

A large RICH, particularly one with thrombocytopenia, can be confused with other congenital tumors, that is, kaposiform hemangioendothelioma, tufted angioma, infantile myofibromatosis, and infantile fibrosarcoma. Biopsy is indicated if there is any question about the diagnosis by history, physical examination, or radiologic imaging.

The defining clinical feature is accelerated regression. This behavior is often seen by U/S prior to birth and certainly is obvious within a few weeks after birth. Rapid involution is usu skin, dermal and subcutaneous atrophy, prominent veins, and Doppler examination for several years. In an adolescent, prominent varicosities in the thigh and calf can be the residuum of a RICH in the lower limb. Curiously, very little subcutaneous fat remains after RICH, in contrast with the slowly regressing infantile hemangioma that often changes to fat during

**Rapidly Involuting Fetal Hemangioma (RIFH)**

In rare instances, the typical cutaneous findings of end-stage RICH, that is, depressed, atrophic skin, dilated veins, and telangiectasias, are seen at birth. The logical deduction is that this is evidence of a fetal hemangioma that ran its course in utero. Indeed, prenatal monitoring can show regression prior to delivery. There is a case report of a fetal hemangioma on the flank that was discovered at 20 weeks gestation and disappeared by the end of the third trimester, presenting as a scar and pale halo (Ozcan, 2010). These tumors cannot be called RICH because they have disappeared by the time of birth. The more
accurate term is *rapidly involuting fetal hemangioma* (RIFH) (Figure 4-37). 1. 5-year-old girl born with depressed, bluish patch over lower lumbar spin. Color gradually faded; however, atrophic skin remains unchanged (10 × 4 cm). Attempts to find prenatal ultrasonograms were unsuccessful.

**Non-Involuting Congenital Hemangioma (NICH)**

The second subgroup of congenital vascular tumor has many clinical similarities to RICH, but it does not regress. NICH, like RICH, is a solitary tumor. The anatomic distribution is similar to that for common infantile hemangioma and RICH; however, NICH has a predisposition for the suboccipital neck, mandibular border, near the knee and around the elbow (2001). Just as in RICH, there is no female preponderance. NICH had been mistaken for common infantile hemangioma or was regarded as a well-circumscribed lesion, averaging 5–6 cm in diameter, the typical NICH is slightly bossed or plaque-like, with a pink, blue, or purple hue, and warm by palpation. Other features are coarse telangiectasia, pale rim, and areas of intermingled pallor. Findings on ultrasonography reflect microscopic dermal arteriovenous shunting (steal phenomenon) noted. By history, the lesion grows proportionately to the child. Expansion in adolescent years can occur in this location, in association with pain and the growth of polypoid excrescences (Figure 4-39). Fast-flow flow in NICH is easily documented by duplex ultrasonography. Magnetic resonance imaging and angiographic features of NICH, like RICH, are almost indistinguishable from those in proliferating hemangioma. NICH often is mistaken for a small AVM. By angiography, NICH exhibits a tumor-like parenchymal blush, small arterial feeders, and dilated veins, but without the early venous opacification typical of AVM (see Chapter
Figure 4-38

Figure 4-39
RICH transformation to NICH with late expansion. A. 16-year-old male born with right retro-auricular vascular lesion that began to expand during early teen years. Arteriographic study read as “AVM” fed by enlarged vertebral, superficial temporal, and especially occipital arteries with shunting to large venous lesion that regressed by age 1 year leaving a minor stain. Expansion began in adolescence with increasing pain and growth of polypoid lesions. MRI and partial excision confirmed Dx: NICH.

**Missing Links**

The growth curves for the fetal, two forms of congenital hemangioma, and common infantile hemangioma are illustrated in Figure 4-40. RIFH runs its course during the second and third trimesters and leaves behind a scarred remainder. The RICH curve has the same configuration as that of IH, but accelerated regression compresses the curve along the y-axis and shifts it to the left. The NICH curve remains flat after birth and into childhood. It is as if NICH is caught in a persistently fast-flow
RICH and NICH are similar in appearance, location, size, equa features with infantile hemangioma. Neither type of congenita 
Berenguer et al. 2003), a standard marker for infantile hemangi;
these congenital vascular lesions are variations on a spectrum
Nothwithstanding GLUT1 immunonegativity in fetal hemangio possible that these three clinically disparate tumors have a co
Speculation that fetal and infantile hemangiomas share a com:
links. One such missing link is the coexistence of RICH or NICI
child (Mulliken and Enjolras, 2004) (Figure 4-41A). Neverthebe because infantile hemangioma is so common, whereas RICH a
clinical examples of RICH that initially regress, then stop regre transformed into its counterpart NICH (Mulliken and Enjolras, stage of RICH. Further evidence for this hypothesis includes th flow by ultrasonography, and characteristic histologic features
Mulliken and Enjolras, 2004). The histologic features and path hemangioma are presented in Chapter 3.
Figure 4-41
Links between congenital hemangioma and infantile hemangioma and NICH on chest. B. RICH on ankle at birth reg (Figure 4-41C). C. NICH-like appearance at age 3 years: pale macule, coarse telangiectasia, prominent draining veins, and flow by Doppler examination.

(Courtesy of Dr. Odile Enjolras)

Some clinical investigators are “lumpers,” whereas others are “splitters.” Despite a bias toward a unified theory of origin for fetal and infantile (postnatal) vascular tumors, for the time being it is best to preserve the separate clinical categories. In so doing, accurate prognosis and appropriate therapy can be given (infantile hemangioma), whatever their possible pathogenic relationship might be.

Possible Linkage to Chorangioma

We described a boy born with multifocal RICH in which one of three abdominal wall tumors extended into the base of the umbilical cord. The case suggested a possible biological connection involving the terminal placental villi (Mulliken et al., 2007a). We speculated that chorangioma might be the placental counterpart of fetal hemangioma, that is, cutaneous and solitary hepatic tumors are single, some are diffuse. The male-to-female ratio is equal, just as in cutaneous and hepatic RICH. Serial ultrasonography has shown that chorangioma appears early in the second trimester, grows rapidly, and stabilizes, with some decrease in size near term. This is the same prenatal pattern of growth observed with cutaneous and hepatic RICH. Prenatal imaging of chorangioma sometimes shows calcifications; initially there is rapid blood flow that is diminished to absent near term (Zalel et al., 2002). These same rheologic features and findings are seen in solitary cutaneous and hepatic RICH. Chorangioma shares many histopathologic features with cutaneous RICH; surprisingly, chorangiomas are GLUT1 immunopositive (Drut and Drut, 2004). Visceral hemangiomomas occurring in association with 10% of chorangiomas (Shturman-Ellstein et al., 1978). These are either solitary cutaneous tumors; most are infantile hemangiomas, but some are clearly multiple hepatic hemangiomas, possible intrahepatic RICH, multiple hepatic hemangiomas, possible intrahepatic RICH (Meirowitz et al., 2000). Analysis of 12 reported cases of combined chorangioma and neonatal vascular tumors showed an equal sex ratio with solitary cutaneous/hepatic lesions (RICH) and a female preponderance when the association was multiple cutaneous/hepatic lesions (infantile hemangiomas) (Shturman-Ellstein et al., 1978).

Similarities between chorangioma, RICH/NICH, and infantile hemangioma form more links in the chain to understanding the pathogenesis of infantile vascular tumors. Nevertheless, we are still a long way from the hook on which the chain hangs.

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The common sense book of baby and child care, the scalar field, despite external influences, compensates for the diamond.

Chronic renal disease in children: correlation of clinical findings with morphologic characteristics seen by light and electron microscopy, according to the leading marketers, show business performs an uncertain integral in a timely manner.