

# Infantile Hemangiomas: Current Knowledge, Future Directions. Proceedings of a Research Workshop on Infantile Hemangiomas

April 7–9, 2005

Bethesda, Maryland

**Ilona J. Frieden, M.D.,\*** **Anita N. Haggstrom, M.D.,†** **Beth A. Drolet, M.D.,‡** **Anthony J. Mancini, M.D.,§** **Sheila Fallon Friedlander, M.D.,¶** **Laurence Boon, M.D., Ph.D.,\*\*** **Sarah L. Chamlin, M.D.,§** **Eulalia Baselga, M.D.,††** **Maria C. Garzon, M.D.,‡‡** **Amy J. Nopper, M.D.,§§** **Dawn H. Siegel, M.D.,\*** **Erin W. Mathes, M.D.,\*** **Deborah S. Goddard, M.D.,¶¶** **Joyce Bischoff, Ph.D.,¶¶¶** **Paula E. North, M.D., Ph.D.,\*\*\*** and **Nancy B. Esterly, M.D.†††**

*\*University of California School of Medicine, San Francisco, California; †University Dermatology Associates, Washington DC; ‡Medical College of Wisconsin, Milwaukee, Wisconsin; §Children's Memorial Hospital, Chicago, Illinois; ¶University of California, San Diego, California; \*\*St Luc University Hospital, Brussels, Belgium; ††Hospital de la Santa Creu I Sant Pau, Barcelona, Spain; ‡‡Columbia University, New York; §§Mercy Children's Hospital, Kansas City, Missouri; ¶¶Harvard University School of Medicine, Boston, Massachusetts; \*\*\*University of Arkansas School of Medicine, Little Rock, Arkansas; and †††Medical College of Wisconsin, Milwaukee, Wisconsin*

Infantile hemangioma (IH) is the most common tumor of infancy, but understanding of its etiology and pathogenesis has lagged far behind other diseases, in part because of a nearly complete lack of funded research. The exponential growth of research regarding angiogenesis and vascular biology has obvious relevance for the study of hemangiomas, and indeed there has been a modest increase in research and understanding of IH in the past 5 years. Most studies have either been unfunded or funded with small grants from private or local institutional sources, rather than traditional sources such as the National Institutes of Health (NIH).

Although many hemangiomas are benign and innocuous, a significant subset are life altering (causing permanent visual loss, disfigurement, and pain from ulceration), and a smaller subset are life threatening. There are virtually no

rigorous evidence-based studies to guide therapy. Moreover, there are no FDA-approved medical treatments for hemangiomas. Glucocorticoids have been the mainstay of therapy, but their mechanism of action is not well understood, and they have many potential side effects. Other therapies such as interferon- $\alpha$  and vincristine can be effective but also carry the risk of potentially serious side effects. Laser and surgical therapies can be helpful, but have a relatively limited role in larger, more problematic hemangiomas. The lack of a good animal model has greatly hampered in vivo research and the limitations of current cell culture models have made in vitro studies more difficult.

In order to address these issues, an NIH-sponsored research workshop was held from April 7 to 9, 2005, at the Lister Hill Auditorium on the NIH campus and at the Pooks Hill Marriott Hotel in Bethesda, Maryland. This

Address correspondence to Ilona J. Frieden, M.D., Department of Dermatology, Box 0316, San Francisco, CA 94143-0316, or e-mail: [friedeni@derm.ucsf.edu](mailto:friedeni@derm.ucsf.edu).

workshop was the first time that physicians and other researchers gathered together specifically to discuss infantile hemangiomas. It was attended by 112 individuals from 12 different countries, representing a broad range of medical and scientific disciplines. Many pediatric specialties were represented including dermatology, general surgery, plastic surgery, pathology, otolaryngology/head and neck surgery, ophthalmology, endocrinology, neurology, neurointerventional and diagnostic radiology, genetics, and hematology–oncology. Scientists from molecular genetics, cell biology, and developmental biology also participated. In addition, representatives from two patient advocacy groups, the Vascular Birthmark Foundation, and the National Organization for Vascular Anomalies were present. The meeting was initiated by a group of pediatric dermatologists, the Hemangioma Investigator Group, who came together in 2001 with the goal of studying hemangiomas and furthering hemangioma research (Appendix A). The organizing committee consisted of well-respected clinicians and researchers in the field of vascular anomalies (Appendix B). The meeting consisted of a keynote address by M. Judah Folkman, M.D., on the evening of April 7, a full day of plenary talks with discussion on April 8, and three all-day breakout sessions on April 9, followed by a group summation of these sessions. Speakers and moderators were asked to emphasize three key aspects about infantile hemangiomas: What is our current state of knowledge, what is *not* known, and what strategies might help to bring more knowledge and understanding of IH. The following Proceedings represent a composite summary of this meeting.

#### **Keynote address, April 7, 2005**

**M. Judah Folkman, M.D., Director, Vascular Biology Program, Children's Hospital, and Professor, Harvard Medical School, Boston, Massachusetts**

The keynote speaker for the workshop was Dr. M. Judah Folkman, a pediatric surgeon and pioneer in angiogenesis research. Dr. Folkman discussed the history of angiogenesis research starting with experiments he carried out during his surgical training in the 1960s. Dr. Folkman's hypothesis that a tumor stops growing when it outgrows its blood supply was initially met with strong opposition. Despite many harsh reviews and numerous rejected grant proposals, however, Dr. Folkman persevered and helped pioneer an entire field of angiogenesis research yielding many important discoveries and therapies.

After sharing some personal anecdotes about his research career, Dr. Folkman presented the fascinating story of interferon (IFN)- $\alpha$  as an antiangiogenic agent. Interferon- $\alpha$  was the first endogenous antiangiogenic agent identified. In a 1992 *New England Journal of Medicine* article, Ezekowitz et al noted IFN- $\alpha$  to have prominent antiangio-

genic properties in treating infantile hemangiomas at lower doses ( $1-3 \times 10^6$  units/m<sup>2</sup>) than used for other conditions. It was subsequently found to inhibit the synthesis of fibroblast growth factor (FGF) by human cancer cells. The discovery that bFGF could be measured in the urine as a marker of efficacy of IFN- $\alpha$  proved to be a useful tool. Of interest, in proliferating hemangiomas, bFGF expression is increased, whereas IFN- $\beta$  expression is decreased, suggesting that an angiogenesis suppressor gene may be deleted in these tumors. Dr. Folkman spoke about the finding by Slaton et al (1) that endothelial cells demonstrate a U-shaped response to angiogenesis inhibitors and growth factors. That is, at low and high doses, IFN- $\alpha$  has highly antiangiogenic properties per unit tumor volume, but at mid-range doses, it has much lower efficacy. The concept of U-shaped dose responses may be applicable to other antiangiogenic agents as well. Dr. Folkman also explained that although IFN- $\alpha$  synergizes with thalidomide and zoledronate in its antiangiogenic properties, it is critical that these agents must be used at low doses for optimal synergy. Because of neurotoxicity, IFN- $\alpha$  is not widely used for infantile hemangiomas. However, the concepts learned from its use may be applicable to other candidate drugs. Many new agents are in various stages of investigation and some, such as bevacizumab (Avastin®) are now FDA-approved for treating specific malignancies. Future therapies will need to be tailored to the specific vascular phenotype of infantile hemangiomas, but the groundwork has been laid for such an approach.

#### **Plenary Session, April 8, 2005, Lister Hall, National Institutes of Health**

##### **Hemangiomas: Clinical Characteristics**

Moderators: Anne Lucky, M.D., Cincinnati Children's Hospital; Odile Enjolras, M.D., Lariboisiere Hospital, Paris.

##### **Infantile Hemangiomas: Demographic and Epidemiologic Trends**

**Beth Drolet, M.D., Medical College of Wisconsin, Milwaukee, Wisconsin**

Dr. Drolet discussed the incidence and demographics of hemangiomas of infancy (IH). There are several limitations in determining the true incidence of IH. Hemangiomas are not included in the state or federal birth defect registries and they are often not present at birth. The current estimated incidence is 4% to 10% of infants. A female predominance has been described (2.5–4 : 1). This predominance is even more pronounced in PHACE(S) association, where the female to male ratio is 9 : 1. Dr. Drolet discussed the lack of adequate studies defining patient demographics. Previously,

prematurity, low birth weight, and chorionic villus sampling have been associated with IH.

The Hemangioma Investigator Group (HIG) enrolled 1058 patients with IH from the United States between September 2002 and October 2003. All patients were seen as referrals at academic institutions. A questionnaire was administered addressing ethnicity, gender, prenatal history, birth history, perinatal history, and family history. No control group was enrolled, but the findings were compared to National Vital Statistics (NVSS) data for children born in the year 2002. The study population (infants with hemangiomas) had several statistically significantly demographic characteristics when compared to the NVSS data. Infants in the study population were more likely to be female, Caucasian, premature, of low birth weight, and multiple gestation. The mothers of the study population were older and more likely to have pre-eclampsia and placental abnormalities. Several of these factors have been noted in previous studies, but some, such as multiple gestations and advanced maternal age, have not. Future studies will be needed to determine which factors are most important, and which are confounding variables.

*Discussion points:*

When there is a multiple gestation, why is the other twin often unaffected? In several cases in the HIG study, both twins were affected, but this was uncommon. It is difficult to assess accurately from the HIG study because the unaffected twin was not enrolled or examined. The group is considering re-analyzing the twins enrolled in the study (more than 100) to look more closely at their characteristics compared to their unaffected twins. Dr. Drolet referred to a study by Mulliken et al (2), which showed that there was not a significant increase in concordance of hemangiomas in monozygotic twins compared to dizygotic twins.

Is the disproportionate incidence in Caucasians a result of a referral bias? Does it reflect the population seen in the dermatology clinic rather than a true difference in the incidence of hemangiomas in those ethnicities? Dr. Drolet commented that she thinks the difference is real, but an ancillary study enrolling a control group of infants without hemangiomas is currently underway to address this and other demographic trends in the HIG study. The higher percentage of hemangiomas in Caucasian infants has previously been reported, however.

What about the relationship between chorionic villus sampling (CVS) and the incidence of hemangioma? This has been previously reported. Dr. Paul Rieu, a pediatric surgeon from Nijmegen, the Netherlands, mentioned two relevant, as yet unpublished studies. A cross-sectional study was performed that found an overall incidence of 4.5%. Prematurity, female gender, and Caucasian race were etiologic determinants. Dr. Rieu also cited a study

presented at the International Workshop on Vascular Anomalies in February 2004, which found that transcervical CVS had a significant association with hemangiomas, but transabdominal CVS did not. The number of patients in the HIG study having CVS was relatively low – approximately 3% – which, even if truly associated, could only account for a small number of affected infants.

**Infantile Hemangiomas: Clinical Characteristics, Implications for Pathogenesis**

**Iiona J. Frieden, M.D., University of California, San Francisco, California**

While the word “hemangioma” has been used to describe a wide array of lesions, there is now a consensus that the word “hemangioma” needs an adjective to be specific. Infantile hemangiomas, unique tumors that arise only in infancy, are absent at birth or present only as precursor lesions, and have a characteristic natural history of growth early in infancy followed by spontaneous involution. Other types of hemangiomas, such as rapidly involuting congenital hemangiomas (RICH) and noninvoluting congenital hemangiomas (NICH) are fully formed at birth. These are interesting entities, but were not the focus of this workshop.

Many unanswered questions remain about the pathogenesis of IH. A closer look at clinical characteristics, including the marked clinical heterogeneity, the significance of premonitory marks, growth and involution characteristics, anatomic patterns, presence only in certain tissues, multifocal hemangiomas, and associated structural anomalies may all provide clues to pathogenesis.

Premonitory marks often have a blanched, dusky, or ulcerated appearance suggesting the possibility that hypoxemia precedes tumor growth. The territory of the IH is delineated by the premonitory mark, yet in some cases only part of the area proliferates. This may indicate a balance between inhibitory and growth effects.

Growth characteristics of IH are unpredictable, yet seem to be correlated with size. Small hemangiomas typically grow rapidly for a few weeks to months, whereas larger hemangiomas can grow for longer, and in rare cases, growth continues even after the first year of life. Involution time varies from months to years. The postnatal factors that stimulate hemangioma growth are still unidentified. Because of the variation of IH growth characteristics, clinicians should be more vigilant in the first few weeks to months of growth, and should always warn parents to return if the IH changes in an unexpected fashion.

Even though most IH involute on their own, they carry the risks of scarring and disfigurement as well as medical morbidities. Anatomic patterns have implications for prognosis. Segmental hemangiomas (IH that involve a

broad anatomic region or developmental unit) have a worse prognosis than localized IH, with more complications, more frequent need for treatment, poorer cosmetic outcomes, and more associated structural anomalies. IH that have a thick dermal component or steep slope, are exophytic or ulcerated, and present in certain sites on the face (especially the nasal tip, perioral area, ear, and glabella), also have a worse prognosis. The concept of treating the “tiny red dot,” often the first sign of the hemangioma, is an appealing one, but at present, there is little evidence to guide our selection of which precursor lesions to treat and whether treatment would necessarily be effective, as the dot may denote the beginning of a very superficial hemangioma or a more deep-seated one.

*Discussion points:*

Why doesn't IH grow in utero? What is suppressing growth? The placenta produces inhibitors of angiogenesis (such as 2-methoxyestradiol) that steadily increase throughout pregnancy, potentially affecting hemangioma growth.

How can you tell if an IH is segmental or focal? Is segmental just related to size? Segmental is independent of size and involves the location and distribution of the IH. As we understand the anatomic patterns of segments, defining them will become easier. (See discussion below)

**Infantile Hemangiomas: Ulceration**

**Maria Garzon M.D., Columbia University, New York, New York**

Ulceration is the most common complication of IH, with an incidence of between 5% and 13% of all lesions. Ulceration is also the most common reason for hemangioma referral to specialists, since it causes pain as well as parental concern and anxiety. Only a few retrospective studies of IH ulceration exist, and there have been no prospective studies. Ulceration can lead to a number of significant complications, including pain, scarring and disfigurement, and, less commonly, infection and anemia secondary to bleeding.

Dr. Garzon reviewed what is clinically known about ulceration: ulceration has a propensity to affect hemangiomas at certain anatomic sites, at particular growth phases in the hemangioma life cycle, and it is associated with certain hemangioma patterns. Ulceration most often involves hemangiomas of the head and neck, and perineal regions (particularly the lip, perioral, and intertriginous areas), and less commonly those on the extremities and the trunk. Ulceration most commonly occurs during the peak of hemangioma proliferation (3–4 months of age), and often persists for several weeks to months, requiring multiple physician visits. However, ulceration can also

occur in so-called precursor lesions prior to the development of an obvious IH, later in infancy during the involution phase, or as a side effect of treatment, such as laser, corticosteroids, or imiquimod. Hemangiomas that ulcerate are often large, with a prominent superficial component. It is unclear whether the increased risk of ulceration in larger lesions is related to overall size or subtype (focal versus segmental), but data from a recent HIG study strongly implicate segmental hemangiomas as having a much greater risk than focal ones: 8% of focal IH showed ulceration compared to 29% of segmental hemangiomas.

The pathogenesis of ulceration is unknown, but Dr Garzon cited three factors that may play a role: (i) sites of trauma (maceration or friction or both), (ii) local factors such as bacteria (either infection or colonization), and (iii) tissue hypoxia such that ulceration occurs when a hemangioma “outgrows its blood supply.”

Treatment of ulceration falls into three categories: halting proliferation with therapy [e.g., corticosteroids, interferon  $\alpha$ , pulsed dye laser (PDL)], altering the local environment (e.g., wound care, topical or systemic antimicrobial agents, alteration of the local vasculature), and pain management (acetaminophen, limited application of topical lidocaine ointment, occlusive dressings). The role of PDL in treating ulcerated hemangiomas is controversial. Reports of PDL effectiveness vary, but several have claimed increased healing, subjective improvement of pain, and accelerated involution. Laser treatment has also been temporally associated with onset of ulceration, however, particularly for larger lesions treated early in the proliferative phase. Recently, topical platelet-derived growth factor, becaplermin, has been described to be effective in a few cases, although the mechanism of action is unclear (3).

Many questions remain concerning why ulceration occurs and how it should be treated. Dr. Garzon raised a few questions for future research:

- What is the role of local growth factors in promoting ulceration?
- What is the relationship between hemangioma vasculature and the overlying epidermal keratinocytes?
- What role does apoptosis play in ulceration?

*Discussion points:*

A study looking at ultrasounds of cutaneous hemangiomas performed in Montreal did not show a correlation between blood vessel flow characteristics and likelihood of ulceration.

Early laser treatment of segmental (referred to by some as diffuse) hemangiomas has been demonstrated to lead to very bad outcomes, especially if treatment is performed in the first six months of life, during the proliferating phase.

In the mouse hemangioendothelioma model, treatment with imiquimod led to apoptosis of both the hemangioendothelioma and the overlying epidermal keratinocytes, and resulted in ulceration in the overlying epidermis. Thus, apoptosis of overlying epidermal keratinocytes may play an important role in the pathogenesis of hemangioma ulceration.

**Infantile Hemangiomas: Orbital and Ocular Issues**  
**Douglas R. Fredrick, M.D., University of California, San Francisco, California**

Dr. Fredrick discussed periocular and orbital hemangiomas, and their complications. The first step in evaluation is establishing the diagnosis. Usually this can be performed clinically, but imaging studies should be considered if the presentation is atypical (such as presence of a mass at birth or development after a few months of life), if there is a concern regarding other orbital soft tissue tumors such as rhabdomyosarcoma, if there is evidence of involvement of the orbit itself, and when considering the PHACE association.

Periocular hemangiomas most often involve the upper lid, but involvement of the lower lid and retrobulbar space is also relatively common. Development of amblyopia is the complication of most concern. In some series, amblyopia is reported in 40% to 60% of infants, but this likely represents an overestimate because of ascertainment bias. Amblyopia occurs when abnormal visual input to the immature developing striate cortex results in abnormal cellular development, with resultant vision impairment, which can be permanent if not detected and treated early in life. Anisometropic amblyopia refers to unequal refractive error, which in the case of hemangiomas is usually a result of astigmatism or myopia or both. In the case of hemangiomas, astigmatism is usually secondary to pressure from the tumor on the globe, which causes an irregular corneal curvature. Strabismic amblyopia can occur if the hemangioma(s) affect the movement of extraocular muscles. Deprivation amblyopia arising from partial or complete eyelid closure is particularly devastating if it occurs during the first few months of life, when it can cause profound visual impairment. Visual deprivation on a sustained basis up to age 6 years can result in amblyopia. Several tests useful in diagnosing amblyopia include visual fixation with a vertical prism and the preferential gaze test.

Dystopia can result from displacement of the globe as a result of pressure on the globe or abnormal orbit development. It can result in upward or downward displacement of the eye, proptosis, or exophthalmos, if the eye is pushed forward. Another relatively common complication of IH is lacrimal duct obstruction because of pressure in the

region of the lacrimal duct, resulting in increased tearing and recurrent conjunctivitis.

Treatment of amblyopia consists of addressing the underlying cause (in this case hemangioma) and occlusion therapy, patching the unaffected eye. Patching has a greater benefit if initiated earlier in the course of the disease. The patch should be used only part time; usually 1 to 2 hours per day is enough. If physical patching is not tolerated, pharmacologic patching or so-called penalization therapy can be used. Atropine 1% or cyclopentolate 1% can be instilled to pharmacologically blur the good eye.

Dr. Fredrick discussed some additional ocular complications of periocular hemangiomas. Strabismus occurs secondary to involvement of extraocular muscles. Blockage of the lacrimal duct may lead to epiphora (tearing).

Ideally, treatment of sight-threatening hemangiomas should begin early, either before or at the first sign of visual compromise, and well before amblyopia develops. Treatment options include systemic corticosteroids, intralesional corticosteroids, topical corticosteroids, and excisional surgery. Systemic corticosteroids are preferred for hemangiomas that have a high probability of or are already causing visual compromise, particularly for segmental hemangiomas, and those with clinical or radiographic evidence of intraorbital involvement or both. Intralesional corticosteroid injections, first pioneered by Kushner, have been used for more than two decades. They can be quite effective, but there is a rare but real risk of inadvertent intravascular/ophthalmic artery embolization with permanent visual loss. Other potential side effects include dermal atrophy, pigmentary alteration, skin necrosis, and adrenal axis suppression. Embolization is thought to be caused by retrograde flow into the retinal artery. This risk is probably higher with larger volumes of medication injected at higher pressures. As large volumes also can have systemic effects, the use of this modality is probably best reserved for small hemangiomas, especially those where the area of involvement is limited to the eyelid itself. Topical corticosteroids can be considered for superficial lesions, but has not been demonstrated to be effective in lesions that are already causing ocular compromise. Early surgical excision is usually reserved for vision-threatening hemangiomas that are well localized and likely to leave permanent skin changes even after involution. Surgical debulking is also sometimes considered in children who have failed pharmacologic therapy. Referral to a surgeon experienced in operating on hemangiomas is essential.

Finally, Dr. Fredrick mentioned the importance of seeing patients at frequent intervals during the growth phase. Not all ophthalmologists, even pediatric ophthalmologists, are familiar with the growth characteristics of hemangiomas. Seeing patients frequently during the growth phase and

working closely with other treating physicians are essential for optimal management.

*Discussion points:*

The volume and speed of injection with regard to risk of embolism was discussed. Dr. Fredrick uses small aliquots spread over a diffuse area and injects with a 30-gauge needle. However, he warned that even when employing these methods, there have been reports of embolism. He counsels patients about this risk, but continues to inject when indicated. He carries out an eye examination immediately following the injection.

How do we monitor for glaucoma and cataracts? The main risk for glaucoma is with topical steroids; the second greatest risk for glaucoma is with oral corticosteroids. The risk with intralesional corticosteroids is low. Given the short duration of use, there is not a significantly increased risk overall.

### **Hepatic Hemangiomas**

**Steven Fishman, M.D., Children's Hospital Boston, Boston, Massachusetts**

Dr. Fishman began by discussing misconceptions regarding hepatic hemangiomas: that they are a homogeneous group of disorders, and that they always present with the triad of hepatomegaly, high-output congestive heart failure (CHF), and anemia. Our understanding of hepatic hemangiomas is also hindered by confusing terminology. For example, the term hemangioendothelioma is often applied to lesions in the liver, yet there is no evidence that hepatic vascular tumors are unique and differ substantially from the hemangiomas described in the skin and other tissue sites. Although mild thrombocytopenia is often seen in liver hemangiomas, especially congenital hemangiomas, true Kasabach–Merritt phenomenon does not occur in liver hemangiomas. Liver hemangiomas found in adulthood are not actually hemangiomas, but venous malformations. These misconceptions can be damaging, in part because the treatments used can be harmful and in some cases worse than the disease itself. When should imaging studies be performed on infants with cutaneous hemangiomas? Most agree that infants with five or more hemangiomas should be screened for liver hemangiomas. Recent studies suggest that children with large segmental hemangiomas may also be at risk.

Two recent papers suggest that the clinical course of hepatic hemangiomas can be predicted by imaging and clinical findings (4,5). For the remainder of the session Dr. Fishman discussed the clinical characteristics of focal, multifocal, and diffuse hepatic lesions.

Three distinct clinical scenarios are well recognized: solitary, large lesions typically present at birth are often

detected antenatally. They may be asymptomatic, but are sometimes accompanied by mild thrombocytopenia and anemia, and occur without skin hemangiomas. They have a heterogeneous appearance without central enhancement on imaging, and may have arteriovenous (AV) or portovenous (PV) shunts that can lead to congestive heart failure. These focal lesions are similar to rapidly involuting congenital hemangioma (RICH), are Glut-1 negative, and resolve on their own. Management depends on the level of symptoms, but generally consists of either observation or embolization of high-flow shunts.

Multifocal lesions most commonly occur in the presence of multiple skin lesions. On CT they are spherical, homogeneous, and hypodense with centripetal enhancement. These lesions may also have macrovascular AV or PV shunts that can result in CHF. They are true IH and are Glut-1 positive. Multifocal lesions may be asymptomatic, in which case they can be managed with observation and serial imaging. Symptomatic multifocal hemangiomas can be treated with pharmacotherapy and embolization of shunts if necessary.

Diffuse lesions cause massive hepatomegaly with abdominal compartment syndrome, impaired ventilation, impaired venous return, and renal vein compression, but they do not cause high-output CHF. On imaging there are so many hemangiomas that they cannot be counted. These diffuse lesions express type 3 iodothyronine deiodinase, which degrades thyroid hormone and causes profound hypothyroidism. Management of diffuse hepatic hemangiomas includes aggressive pharmacotherapy, thyroid replacement in very high doses, and consideration of liver transplantation if there is no response to pharmacologic therapy. The natural history of these liver hemangiomas is that they eventually involute and the hypothyroidism resolves, but there is a high mortality rate during the early phases of the disease.

*Discussion points:*

Which lesions are Glut-1 positive? Solitary congenital hepatic lesions are Glut-1 negative. Diffuse and multifocal lesions are Glut-1 positive.

Are there cases in which pharmacotherapy worked for diffuse lesions? Yes.

What about duration of thyroid disease? The form of hypothyroidism caused by hepatic hemangiomas can resolve if the hemangiomas involute and we would expect this to be true with liver transplantation as well. Cases with resolution of hypothyroidism after hemangioma involution have been reported. Close collaboration with endocrinology is imperative in managing these patients.

Is there a time period after which we do not have to worry about liver involvement? Do we even need to screen with imaging or can we just wait for symptoms?

Heart failure typically presents early in the first few weeks of life. Mass effect from diffuse hemangiomas typically occurs around 3 to 4 months.

When evaluating hepatic vascular lesions, the differential diagnosis of hepatic hemangiomas includes angiosarcoma, venous malformation, metastatic neuroblastoma, hepatoblastoma, and mesenchymal hamartoma.

### **Airway Hemangiomas**

**Milton Waner, M.B.B.C., F.C.S.C.S.A., Vascular and Birthmark Institute, New York, New York**

Dr. Waner pointed out that hemangiomas involving the airway have been traditionally described as “subglottic lesions,” but the preferable descriptor is “upper airway hemangiomas” as many IH present above the vocal cords. Historically, treatment of airway hemangiomas has varied widely from center to center, including laser ablation, steroids (both systemic and intralesional), interferon- $\alpha$ , and surgical excision including tracheostomy.

Airway hemangiomas need to be differentiated from vascular/lymphatic malformations that occur in the airway. Airway hemangiomas, like their cutaneous counterparts, have localized (focal) and segmental (also called diffuse) morphologies. The majority (85%) are focal, with 15% classified as segmental. Approximately 65% of “beard distribution” hemangiomas (involving the mandibular region) have upper airway involvement. These are more likely to have multiple areas of airway involvement, rather than one nodule. Large parotid hemangiomas can sometimes cause extrinsic airway obstruction at the hypopharyngeal level, with compression resulting from large bulky parotid hemangiomas. Clinically, these patients present with failure to thrive and obstructive sleep apnea.

Classic localized unilateral airway hemangiomas are typically treated with laser therapy (CO<sub>2</sub> laser ablation), intralesional steroid, or surgical resection. Options for segmental hemangiomas with bilateral/circumferential subglottic involvement are limited to systemic agents such as vincristine or systemic steroids. Ideally, tracheostomy and surgical interventions should be avoided in this group as they have a high-risk of morbidity and mortality. Diffuse tracheal hemangiomas can be abortive in some cases; however, they must be monitored closely, and systemic therapy should be considered if progression is observed. The American Academy of Pediatrics Section on Otolaryngology will be having its first meeting in a few months to better classify vascular lesions of the airway and develop guidelines for treatment.

Otolaryngologists are reluctant to treat bilateral airway lesions, as compared to unilateral lesions, with surgical or laser therapy because of the fear of subglottic stenosis. However, if a surgical or laser approach is chosen to treat

bilateral lesions, staged interventions should be considered. Optimal treatment for parotid hemangiomas is 6 to 9 months of systemic steroid therapy; surgery plays a limited role in treating these lesions because of high vascularity, the requirement for preoperative embolization, and difficulty of facial nerve dissection.

### **Segmental Hemangiomas and Associated Structural Anomalies**

**Denise Metry, M.D., Baylor College of Medicine, Houston, Texas**

A small, but significant minority of hemangiomas have associated structural anomalies. The association of segmental lumbosacral hemangiomas with tethered spinal cord or genitourinary anomalies or both has been recognized for many years. More recently, a group of anomalies associated with segmental hemangiomas, particularly those involving the face, have been recognized. PHACE is an acronym for the association of posterior fossa defects, hemangiomas, arterial anomalies, cardiac defects, and coarctation of the aorta, and eye anomalies. An S is sometimes added referring to associated sternal clefting or supraumbilical abdominal raphe or both. There are over 200 reported cases in the medical literature. In the HIG study previously mentioned, PHACE(S) was present in at least 20% of infants with facial segmental hemangiomas. A striking female predominance (90% of cases) suggests a possible X-linked defect. A large variety of structural brain malformations have been described, including posterior fossa malformations; hypoplasia or agenesis of the cerebrum, corpus callosum, and septum pellucidum; subependymal and arachnoid cysts; frontal lobe calcifications; and microcephaly. Cerebrovascular arterial anomalies include hypoplasia, anomalous branches, and stenosis of the carotid artery. Additional ventral developmental defects include sternal agenesis, clefts or pits, supraumbilical raphe, and omphalocele.

Numerous eye anomalies have been described. A few examples include retinal vascular abnormalities, optic atrophy, iris hypoplasia, congenital cataracts, lens coloboma, and excavated optic disc anomalies such as the “morning-glory” anomaly. Aortic arch anomalies include coarctation, aneurysms, and congenital valvular aortic stenosis. Additional cardiac defects include septal defects, pulmonary stenosis, and anomalous pulmonary veins, among others.

Of the reported cases, structural brain and cerebrovascular anomalies were the most common associated findings. Over 50% of these patients will have neurologic sequelae such as seizures, stroke, developmental delay, and late-onset migraine headaches. Of particular concern are reports of progressive neurologic disease, but the scope of this problem is uncertain.

The proposed evaluation of PHACE(S) includes MRI/MRA of the head and neck, neurologic evaluation, cardiac examination and imaging, ophthalmologic examination, and cutaneous examination for ventral developmental defects. Different segments appear to be correlated with different structural anomalies. For example, segments 1 and 4 (frontotemporal and frontonasal) appear to have a higher correlation with structural cerebral and cerebrovascular anomalies, and segment 3 (mandibular) and truncal anomalies appear to have a higher correlation with ventral developmental defects, cardiac defects, and coarctation of the aorta (see Dr. Haggstrom's presentation below for further discussion of segments).

Proposed areas of study include determining who is at risk, developing a uniform approach to evaluation and imaging, and determining predictors of stroke and progressive neurologic complications.

#### *Discussion points:*

The lack of a valid model for hemangiomas in animals was discussed. One example of hemangiomas may be in Viennese horses.

The microphthalmia-associated transcription factor (MITF), which is required for the proper development of several cell lineages including osteoclasts, melanocytes, retinal pigment epithelial cells, mast cells, and natural killer cells was mentioned as a possible gene to look at in future studies.

Regarding appropriate imaging, one participant questioned whether angiogram should be used to evaluate the aorta and cardiac vasculature, given that some anomalies may be missed with echocardiography.

A question was asked regarding the pathology of IH in the setting of PHACE. Is it the same as other IHs? Dr. Paula North commented that both are positive for Glut-1 and other immunohistochemical markers. One small but potentially significant difference is that segmental hemangiomas intermingle more with intralesional nerves.

### **Facial Segmental Hemangiomas: What Do the Patterns Tell Us?**

**Anita Haggstrom, M.D., Washington, DC**

The term segmental hemangioma grew out of a distinction between those hemangiomas that were localized and those that covered a broader territory. Some segmental hemangiomas appear to resemble known developmental units. The segmental hemangiomas on the face seen in association with PHACES are believed to occur because of a developmental error in early gestation, which could explain the coexisting skin, cardiac, CNS, and ocular anomalies.

The pathologic mechanism(s) that explain the coexistence of segmental hemangiomas and the structural

defects found in the PHACE association remains unclear. Several theories have been advanced, including an intrinsic endothelial cell defect, abnormal cell-cell signaling, neural crest cell dysfunction, or a developmental field defect.

One of the problems with segmental hemangiomas is defining "what is a segment?" Dr. Haggstrom discussed the findings of an image analysis study in which 72 facial segmental and 93 indeterminate hemangiomas were mapped to a facial template. Based on the findings in this study, four segments were identified. The frontotemporal segment (S1) includes the lateral frontal scalp, forehead, and anterior temporal scalp, with or without the eyelid. The maxillary segment (S2) includes the medial and lateral cheek, spares the preauricular region, and respects the nasolabial sulcus and the philtrum. The mandibular segment (S3) includes the preauricular region, mandible, chin, lower cutaneous and vermilion lip, and parotid. The frontonasal segment (S4) includes the medial frontal scalp, medial forehead, glabella, nasal bridge, nasal tip, alar base, columella, and philtrum.

Segmental hemangiomas respect anatomic boundaries, suggesting a developmental origin. The hemangioma patterns do not correspond to dermatomes or the lines of Blaschko. The segments best correlate with facial embryologic prominences, particularly the S2 and S3 segments, which resemble the maxillary and mandibular prominences, respectively. However S4, the frontonasal segment, is significantly narrower than depicted in embryologic texts, and S1 is a novel segment, not depicted in standard embryologic schemata. These findings suggest that segmental hemangiomas arise from a defect (or defects) in neuroectodermal development. This, together with the patterns observed, may not only provide insight into hemangioma pathogenesis, but also help in understanding mechanisms of craniofacial development.

The facial embryologic prominences are composed of mesenchyme derived from cranial neural crest and epithelium from non-neural ectoderm. Dr. Haggstrom suggested that perhaps derivatives of neural crest cells influence segmental endothelial cell growth. Understanding these developmental patterns may potentially help clarify the mechanisms of the coexisting anomalies in PHACE association.

#### *Discussion points:*

How often is the occipital region involved? Not often. The occipital mesenchyme region is derived from mesoderm, whereas that of the anterior head is derived from the neural crest.

Do large hemangiomas stop growing at Tessier cleft lines? Possibly. There are many examples of lesions that appear to be predetermined to stop, respecting embryologic boundaries.

Vasoconstriction present in hemangiomas suggests a neural crest progenitor. Nerve growth is influenced by

vascular endothelial growth factor (VEGF) produced by nerves, endothelium, and early in development, mesenchyme.

## HEMANGIOMAS – PATHOLOGY, PATHOPHYSIOLOGY, AND MOLECULAR INSIGHTS

Moderators: Joyce Bischoff, Ph.D., Harvard Medical School  
Miiikka Vikkula, M.D., Ph.D., Christian de Duve Institute and University of Louvain Medical School, Brussels; Paula North, M.D., Ph.D., University of Arkansas School of Medicine.

### Genetics of Hemangiomas

**Douglas Marchuk, Ph.D., Duke University, Durham, North Carolina**

Dr. Marchuk reported on his investigations regarding whether maternal microchimerism (the presence of low levels of maternal cells) plays a role in IH pathogenesis. The rationale stems from two pieces of evidence: (i) endothelial cells (ECs) derived from proliferating hemangiomas are clonal in origin, suggesting that hemangiomas arise from clonal expansion of an endothelial precursor cell (6,7); and (ii) ECs of IH can be distinguished from ECs in other vascular malformations by proteins expressed on their surface that are seen in the placenta, including antigens F<sub>c</sub>R $\gamma$ II (CD32), Lewis Y antigen (LeY), merosin, and glucose transporter 1 (Glut-1) (8,9). Dr. Marchuk pointed out that this placental phenotype could arise from either or both of the following two hypotheses:

- 1 A somatic mutation occurs in a key regulatory gene in a precursor endothelial cell that gives rise to the placental phenotype, or
- 2 Placental endothelial cells embolize and become dislodged into the fetal circulation (placental origin theory). Evidence to support the placental origin theory lies in the increased incidence of hemangiomas in infants whose mothers had undergone chorionic villus sampling.

Two approaches were employed using proliferating hemangioma tissue and peripheral blood samples to determine the genotype of hemangioma ECs and compare them with the maternal genotype relative to the infant's genotype. The first method involved genotyping Glut-1-positive endothelial cell mRNA, and performing SNP analysis. The second method involved genotyping FACS sorted ECs using CD32 (F<sub>c</sub>R $\gamma$ II, a hemangioma EC-specific marker) and CD31 (PECAM1, a pan-EC marker) antibodies. Evidence of maternal microchimerism was not identified with either approach.

A follow-up study using a mouse model showed that maternally derived cells could be found in the liver of mice

offspring. This group of experiments concluded that maternal microchimerism can occur as a result of transfer of maternal cells across the placenta, but that maternal microchimerism does not appear to play a role in the pathogenesis of the investigated infantile hemangiomas. Dr. Marchuk pointed out that these data cannot rule out the possibility of transfer of placental ECs from the fetal side of the placenta.

### Hemangiomas: Histopathology and Molecular Phenotype Paula North, M.D., Ph.D., University of Arkansas, Arkansas

Dr. North discussed how histopathology plays an important role in the analysis of IH by using morphologic clues to make the correct diagnosis. Pitfalls of histologic interpretation of IH include:

- lack of criteria for defining the involutational stage (i.e., that patient age is not useful in determining the growth phase),
- lack of clinical information regarding prior therapies, and
- technical challenges of immunohistochemistry.

Histopathologic analyses have shown hemangiomas to be a complex mixture of cell types including endothelial cells (CD31-positive), pericytes (SMA-positive), dendritic cells (factor XIIIa-positive), and mast cells. The early involution phase is characterized by ICAM-1 (CD54) expression and a sparse infiltrate of CD8<sup>+</sup> suppressor T cells with focal evidence of cytotoxic activity (granzyme B-positive). Infantile hemangiomas have a placenta-like microvascular phenotype that is stable in vivo but lost in standard culture media (e.g., Glut-1 positivity is lost in culture). The shared phenotype of placental endothelial cells and hemangioma endothelial cells overlaps that of the hematopoietic system and endothelial cells of the cardinal vein. As in the cardinal vein, early endothelial cells of hemangioma coexpress LYVE-1 and CD34, but do not express the PROX-1. Their LYVE-1 expression is lost during maturation to a blood vascular phenotype (10). Histopathologic analysis demonstrates that IH associate with a number of normal tissue elements including epithelial tissues and intralesional peripheral nerves. Dr. North referred to this latter association as “endoneural pseudoinvasion.” Involution is accomplished via apoptosis and marked by increased expression of markers of endothelial cell maturity and activation, which are HLA-DR and ICAM-1.

The distinctive molecular phenotype of infantile hemangiomas has been more fully characterized including immunohistochemical positivity for: Glut-1, LewisY Ag (LeY), F<sub>c</sub>R $\gamma$ II, merosin, CCR6, IDO, LYVE-1 (positive in early phase hemangiomas), and CD15. IDO expression is particularly interesting in that it may allow immune tolerance

and thus resist involution pressures. Dr. North pointed out that there has been a recurring theme of hematopoietic markers found similarly in placental and infantile hemangioma tissues, demonstrating the intimate relationship between hematopoiesis and vasculogenesis from the stage of the embryonic yolk sac through the adult bone marrow.

### **Endothelial Progenitor and Mesenchymal Stem Cells in Hemangiomas**

**Joyce Bischoff, Ph.D., Harvard Medical School, Boston, Massachusetts**

Dr. Bischoff reviewed the role of endothelial progenitor and stem cells in IH. The works of Yu (11) and Boye (6) suggest that endothelial progenitor cells (EPC) in hemangiomas may differentiate into the clonal population of hemangioma-derived cells.

One hypothesis is that a somatic mutation causes a defect in endothelial maturation that slows the maturation of EPCs to ECs and results in hemangioma formation. In situ hybridization for VEGF-Rs in proliferating hemangiomas shows that VEGF-Rs are evenly spread throughout the hemangioma and therefore not yet assembled into blood vessels. These EPCs coexpress stem cell markers and endothelial cell markers (CD133, CD34, and KDR). The stem cell marker, CD133 is present in proliferating hemangiomas, but not in involuting hemangiomas or newborn foreskin. EPCs are not present in lymphatic or venous malformations. Questions that remain are whether EPCs acquire somatic mutations in situ or are recruited to the hemangioma and how the EPCs contribute to hemangiogenesis.

Dr. Bischoff also reviewed what is known about the origin of adipocytes in involuted hemangiomas. New studies show that mesenchymal stem cells are present in proliferating hemangiomas. She proposes that mesenchymal stem cells (MSC) reside in hemangiomas and contribute to adipogenesis during involution. MSCs are nonhematopoietic stem cells with self-renewal capability and multilineage differentiation potential. In proliferative-phase hemangiomas, there is an increased number of adipogenic MSCs and adipogenesis as indicated by expression of peroxisome proliferators-activated receptor (PPAR) gamma 2 – a marker of differentiated adipocytes. Of interest, the MSCs are not clonal, whereas the ECs clearly are. MSCs are present in much lower numbers in the involuting phase.

### **Identifying Regulators of Hemangioma Growth and Involution Using Expression Arrays**

**Matthew Ritter, Ph.D., Scripps Research Institute La Jolla, California**

Analysis of gene expression in IH using DNA arrays was employed to identify candidate genes that may play a

role in hemangioma growth and involution. Tissue samples of hemangiomas in proliferating, early involuting/plateau and involuting phases were studied using gene chips, and results were compared to expression arrays of tissue samples of RICH, pyogenic granuloma (similar to hemangioma histopathologically), lymphatic malformation, and adenoid tissue (rich in lymphatics). The gene encoding indoleamine 2,3-dioxygenase (IDO) was found to be expressed at high levels in proliferating hemangiomas. However, protein levels of IDO did not correlate well with message levels in hemangiomas as detected by the arrays. Of interest, IDO is known to catalyze tryptophan degradation and inhibit T-cell function, and is expressed by malignant tumors. The hypothesis was suggested that IDO may play a role in slowing T cell-mediated involution of hemangiomas by decreasing local levels of tryptophan. This hypothesis requires further investigation.

A second gene identified in proliferating hemangiomas compared to involuting hemangiomas and other vascular tissues was insulin-like growth factor 2 (IGF2). Real-time PCR (RT-PCR) showed increased IGF2 levels in proliferating hemangiomas, variable levels in plateau-phase hemangiomas, and very low levels in involuting hemangiomas. Furthermore, fresh hemangioma tissue treated with IGF2 showed dramatically increased sprouting. Expression arrays studying purified hemangioma-derived ECs compared to normal microvasculature ECs identified 10-fold higher expression of two other genes, angiopoietin 2 and FGF-13, which await further follow-up study.

Further functional assays are needed to follow-up on the candidates identified through the expression array method. Dr. Ritter reiterated the need to develop models for functionally testing potentially interesting candidate genes.

### **Pathology, Pathophysiology, and Molecular Insights: Discussion**

**Question:** If the perfect study could be designed, what would it be and would small biopsies be useful? If biopsies would be useful, then some work would need to be carried out to obtain IRB approval as biopsies are not generally indicated and most tissues are usually obtained from actual surgical resections.

**Answer:** Some in the field hypothesize that hemangiomas of infancy are caused by somatic mutations. It may be advisable to wait to pursue this line of study, that is, obtaining biopsies, until a more definite set of mutations is identified. In terms of microarrays, small amounts of tissue are useful. In the past, localized lobular lesions were most commonly analyzed. Other types, such as segmental, would be helpful to identify if we are dealing with multiple etiologies. We should consider looking at single

cells with microarrays to evaluate cells such as the epithelial endothelial cells.

Question: Do we know when leptin is expressed?

Answer: It is generally expressed late in mesenchymal cells, and it might be interesting to evaluate its potential role.

*Additional discussion:*

From the data CD133 was common, but this was difficult to reproduce in another laboratory. The reason was likely that there are no antibodies that are suitable on paraffin sections. However, there is a good protein level. The role of immunity in rejection of hemangiomas was brought up as a potential area of study, especially given the response of hemangioma to imiquimod. Circulating T cells are important in the neonate. Maybe these T cells can recognize the hemangioma of infancy as foreign.

The need for model systems was discussed. The role of IDO in hemangiomas of infancy and in tissue culture was discussed. The challenges of maintaining tissue culture were discussed, namely the difficulty in maintaining Glut-1. They will consider checking if IDO is maintained. A participant pointed out that injection of sentinel lymph nodes with GM-CSF prior to dissection has resulted in reversal of IDO in experimental data from UCSF. It was hypothesized that inhibitors of IDO might lead to reversing the “little red spot.”

A question was raised regarding a database of 300 mothers of children with hemangiomas from a patient support group representative. Seventy-eight percent of mothers reported a virus in the first trimester, usually either a sinus infection or a urinary tract infection. This led to a question as to whether an insult from an external source such as infection or antibiotic usage might play a role in pathogenesis. One discussant responded that there is recall bias in such a database, so it is difficult to infer causality.

**HEMANGIOMAS – CURRENT AND FUTURE EVALUATIONS, TREATMENTS, AND OUTCOMES**

Moderators: Francine Blei, M.D., Josee DuBois, M.D.

**Corticosteroid Therapy of Infantile Hemangiomas  
Amy Jo Nopper, M.D., Children’s Mercy Hospital,  
Kansas City, Missouri**

Indications for corticosteroid therapy include life- or function-threatening IH, especially those affecting vision or airway, those causing congestive heart failure, and those in anatomic locations with a high risk of permanent deformity (i.e., the nose or lip). Systemic corticosteroids may also be indicated for large or ulcerated hemangiomas.

The mechanism of action of corticosteroids is poorly understood. No prospective randomized controlled studies

have been performed to look at dosing or efficacy. Corticosteroids have several effects on the vasculature, including decreased angiogenesis, vasoconstriction, and decreased permeability. Hasan et al (12) studied the histologic and molecular changes in a proliferating hemangioma after steroid therapy and found increased numbers of mast cells, decreased transcriptional expression of cytokines, and enhanced transcription of mitochondrial cytochrome b gene.

The general recommendations for glucocorticoids are a starting dose of 2 to 5 mg/kg/day of prednisolone given in a single morning dose. The initial dose range is typically maintained for 4 to 12 weeks, followed by a gradual taper. Ranitidine and trimethoprim/sulfamethoxazole are used as concomitant therapy by some clinicians. Corticosteroid side effects include irritability, insomnia, behavioral changes, hypertension, gastric irritation, hyperglycemia, growth suppression, increased or decreased rate of weight gain, and adrenal suppression. In a study by Boon et al (13) evaluating 62 patients receiving systemic corticosteroid therapy for problematic IH, the following complications were seen: cushingoid facies (71%), personality change (21%), gastric irritation (21%), fungal infection (6%), and reversible myopathy (one patient). Diminished longitudinal growth was seen in 35% of the patients and diminished weight gain in 42% of the patients; however, catch-up growth occurred in most patients. In a study by George et al (14), 10 of 22 patients had a systolic blood pressure > 105 on at least three occasions during therapy.

Dr. Nopper reviewed studies showing that infants receiving systemic glucocorticoids are at risk for developing adrenal suppression. Unfortunately, no statistically significant variables have been identified to predict which patients are at risk. Infants with more pronounced growth suppression may be more likely to have adrenal suppression. Affected infants may be at a higher risk for hypoglycemia and adrenal crisis.

Additional potential adverse effects of glucocorticoid therapy include cataracts, glaucoma, osteoporosis, increased risk of infections (including *Pneumocystis carinii* pneumonia), hypertrophic cardiomyopathy, and neurologic complications.

Patients on systemic glucocorticoid therapy should be monitored for the development of potential side effects by looking at mood, sleep, blood pressure, weight, length, head circumference, developmental milestones, and adrenal function. Live vaccines should not be given to infants on systemic glucocorticoids. If they are exposed to varicella, varicella-zoster immune globulin and acyclovir should be considered.

Intralesional corticosteroids are best utilized for smaller, localized problematic lesions, rather than larger, segmental hemangiomas. Similar systemic side effects, particularly adrenal and growth suppression, may also occur in the set-

ting of intralesional corticosteroid injections. Special care should be taken when injecting periocular lesions.

### **Pharmacologic Treatment Options for Vascular Anomalies: Medical Therapies Other Than Corticosteroids**

**Denise Adams, M.D., Cincinnati Children's Hospital, Cincinnati, Ohio**

The approach to management of IH must take into account their size, location, presence of complications, age of the patient, and rate of growth (15). Indications for immediate treatment include interference with vital structures, possibility of permanent scarring, large facial hemangiomas, and ulcerated hemangiomas. Dr. Adams reviewed the use of interferon and vincristine in the treatment of hemangiomas. Interferon is an antiangiogenic agent that decreases endothelial cell proliferation by down-regulating bFGF. Numerous studies report the efficacy of interferon  $\alpha$ -2a and  $\alpha$ -2b (40–50% complete response with dosing 1–3 mU/m<sup>2</sup>/day). There is, however, a significant risk of neurotoxicity (spastic diplegia and developmental delay) in 10% to 30% of patients treated with interferon. Benzyl alcohol, used to reconstitute the most readily available commercial preparations, may be related to the neurotoxicity; but there have been reported cases of neurotoxicity with all preparations, even those without benzyl alcohol. There are some data that relate this neurotoxicity to age, with children less than 12 months having a higher risk. Other side effects include flu-like syndrome, anemia, neutropenia, thrombocytopenia, changes in liver enzymes, depression, and hypothyroidism. Because of these side effects, Dr. Adams suggests a neurologic examination (by a neurologist) at the start of therapy and every month, baseline, and then twice monthly blood counts and hepatic panels, thyroid function tests, and obtaining signed consent for the therapy. Interferon should be managed only by a physician with experience and considered only when other medical therapy has failed. The recommended dose is 1 mU/m<sup>2</sup>/day 5 days a week with a gradual increase to 2 to 3 mU/m<sup>2</sup>/day. Some studies have reported similar results with a 3 days per week schedule (M,W,F).

Vincristine is another option for patients who have failed or cannot tolerate other medical therapies. Vincristine interferes with mitotic spindle microtubules and induces apoptosis in tumor cells in vitro. The downsides of vincristine therapy include peripheral neuropathy, constipation, jaw pain, rare hematologic toxicity, syndrome of inappropriate secretion of antidiuretic hormone, and the need for a central line or PICC line for administration because it is a vesicant. Dr. Adams reviewed a retrospective study of patients treated with vincristine who had function- or life-threatening hemangiomas, side effects from steroids, inability to wean from steroids, or lack of

response to steroids. Vincristine was started at an average 8 months of age, and continued on average for 6 months. Nine of 10 patients responded and one had a partial response, with an average time to response of 3 weeks. Side effects in this study included constipation, neurotoxicity, alopecia, hyponatremia, and complications associated with the central venous catheter. Enjolras et al (16) found similar results in their study.

Dr. Adams concluded that vincristine is an effective treatment in complicated hemangiomas that do not respond to other therapies. Investigators are exploring new therapies that inhibit angiogenesis, oncogenes, and agents that modulate immune regulation. New agents include thalidomide, retinoids, bevacizumab, and other antiangiogenic agents.

### **Surgical Management of Hemangiomas**

**John B. Mulliken, M.D., Children's Hospital Boston, Boston, Massachusetts**

While most infantile hemangiomas can be watched and undergo natural regression, there is a subset of IH that benefit from surgical intervention. There are three questions to consider regarding surgical intervention:

- (1) *what* are the indications,
- (2) *when* should it be done (timing), and
- (3) *how* should it be done (technique).

In the proliferating phase, the indications for resection are: obstruction (airway or visual); deformation (corneal, retroauricular, cranial); recurrent bleeding; ulceration unresponsive to topical, intralesional, or systemic therapy; or postulceration scar revision. In the involuting phase, indications for resection are: resection is considered inevitable; size and appearance of the scar would be the same if resection is postponed; scar is easily concealed; and staged resection or reconstruction is considered necessary. An important additional consideration at this stage is that formation of facial image and memory occurs between ages 2.5 to 3 years.

In the involuted phase, indications for surgical intervention include damaged skin, abnormal contour (fibrofatty residuum), distortion or destruction of an important anatomic feature, and need for staged resection or reconstruction.

The traditional surgical technique is a lenticular excision with a linear closure. This technique is useful in the eyelid, lip, and neck regions. However, there are certain disadvantages of this technique that make it less suitable for certain anatomic sites, including the formation of dog ears, the length of the scar (longer than the greatest dimension of the lesion), central flattening (problematic if convex surface such as the cheek or forehead), and the

distortion of anatomic features at right angles to the excisional axis. An alternative technique that does not have these disadvantages is the circular excision with purse-string closure (17). This is now considered the first-line technique at any stage of the tumor's life cycle.

Nasal tip hemangiomas represent a unique subset needing surgical intervention more often than other anatomic sites. Nasal tip hemangiomas should be medically managed (i.e., intralesional steroid if small, systemic steroid if large) in infancy, with staged resection and alar apposition in early childhood. The most difficult case for surgical repair is fibrofatty residual tissue in the lower lip.

When treating hemangiomas, it is important to remember that surgeons are not sculptors working in only three dimensions. There is an important fourth dimension that needs to be respected: the tumor's regression and the child's growth, animation, and movement.

### **Laser and Other Destructive Modalities of Treatment** **Lawrence Eichenfield, M.D., San Diego Children's Hospital, San Diego, California**

The use of lasers in the treatment of IH is controversial. Superficial lesions may be responsive to pulsed dye laser, but response may depend on the biologic phase of the hemangioma. Limitations include focal scars, diffuse ulceration, pain associated with treatment, cost, and a limited impact on "deep" lesions. There are many variations in the use of lasers for the treatment of hemangiomas. Most studies have been with pulsed dye lasers at wavelengths of 585 to 595 nm and pulse durations of 450 to 1500  $\mu$ s. The cryogen spray or cooling handpiece can be very beneficial for decreasing pain and allowing higher fluences with a lower risk of scarring. The major questions in laser treatment include evaluating cosmetic outcome compared with natural involution and the impact on the color, volume, disfigurement, and scarring. Another question is evaluating the effect on the distinct biologic phases: proliferation, plateau, involution, and postinvolutional.

Dr. Eichenfield cited unpublished observations of his group, wherein the efficacy of pulsed dye laser alone and in conjunction with corticosteroids in the treatment of head and neck hemangiomas was examined, using a retrospective chart review and comparative slide assessment. Color, volume, and deformity were evaluated. The outcome showed significant improvement with superficial, plaque-type hemangiomas, but less improvement with thicker, tumor-like, or mixed superficial and deep lesions.

Batta et al (18) performed a randomized, controlled study of early pulsed dye laser treatment (versus observation only) of uncomplicated early hemangiomas, with a 1-year follow-up. They found no significant difference in the number of children with minimal residual signs or complete

clearance or whose parents considered the hemangioma to be a problem at 1 year. However, 30% of laser-treated patients versus 7% in the observation-only group were "completely clear" at 1 year. PDL-treated infants had a significantly higher rate of skin atrophy and hypopigmentation. Critiques of the study included lack of use of a cooling handpiece, the small spot size (5 mm), low fluences, and a small number of treatments in the laser group.

The main accepted uses for laser therapy are in the treatment of ulcerated IH and for postinvolution residua. There is debate regarding how long to wait to treat the postinvolution residua. A fair assessment of risks and benefits of lasers needs to be completed. There is the need for studies to control for parameters and concomitant therapies. Laser treatment of ulcerated hemangiomas is likely beneficial, but no controlled studies have been performed. There have been no studies comparing laser treatment with new medical therapies, such as becaplermin.

Other destructive modalities were briefly mentioned. Cryotherapy is popular in certain countries (particularly Germany and parts of South America). It is experience- and operator-dependent and scarring is a concern, but it has not been compared to other modalities of treatment or observation alone to objectively assess its efficacy.

### **Imaging of Hemangiomas: Where, When, Which, and Why?**

**Patricia E Burrows, M.D., Children's Hospital Boston, Boston, Massachusetts**

Doppler ultrasound and magnetic resonance imaging (MRI) are the two most efficient modalities for imaging hemangiomas. The choice of which modality to use depends on the clinical situation and the availability and expertise at each institution. Ultrasonography is useful for distinguishing a deep hemangioma from other entities, because it shows high flow vessels. Ultrasonography, however, is highly operator-dependent and may not be able to predict the extent of the lesion and presence of other anomalies. Magnetic resonance imaging is the study of choice when documentation of the extent of disease or associated anomalies is needed. Dr. Burrows recommends the following sequences:

- T1-weighted sequence without gadolinium
- T1-weighted sequence with fat saturation post gadolinium infusion
- Fluid-sensitive sequence with fat saturation
- Flow-sensitive sequence such as gradient recalled echo sequence or MRA

Computed tomography is inferior to MRI in imaging hemangiomas, but has the benefit of short scan times

without sedation. CT of hemangiomas should be done with and without IV contrast.

Dr. Burrows gave the following recommendations for when to image hemangiomas.

- 1 Large hemangiomas of the head and neck should be studied with MRI of the affected area, adjacent soft tissues, and the brain when they become problematic or require pharmacologic therapy. These hemangiomas should be imaged because of the risk of intracranial and airway involvement (beard distribution) and associated cerebral and cerebrovascular anomalies.
- 2 Cutaneous hemangiomas over the spine should be studied with ultrasound, then MRI with gadolinium (if abnormalities are present on ultrasound) as soon as they are recognized. These hemangiomas can be associated with intraspinal extension and dysraphic lesions (spinal dermoid, tethered cord, lipomyeloschisis).
- 3 Multiple (> 4) cutaneous hemangiomas should be screened with ultrasonography of the liver and brain when the skin lesions are enlarging or increasing in number. Patients with disseminated hemangiomatosis can have involvement of liver and brain. In cases of extensive, high flow, or enlarging lesions, MRI with and without gadolinium should be obtained.
- 4 Extensive perineal hemangiomas in the presence of urogenital or anal anomalies should be imaged as soon as possible with an MRI of the pelvis and spine because of the association with structural anogenitourinary anomalies.
- 5 Atypical presentations: Any presumed hemangioma in the presence of severe thrombocytopenia should be imaged with MRI with gadolinium because it is likely a Kaposiform hemangioendothelioma (KHE). High-flow lesions should be imaged with MRI/MRA or Doppler ultrasound because of the concern for RICH or AVM. A suspected hemangioma that presents after 6 months of age should be investigated with biopsy or excision because it may be a KHE, vascular tumor, or rhabdomyosarcoma.
- 6 Imaging is not necessary for cutaneous hemangiomas with typical clinical appearance and behavior that do not require therapy.

#### **Infantile Hemangiomas: Measuring the Burden of Disease**

**Sarah L. Chamlin, M.D., Children's Memorial Hospital, Chicago, Illinois**

Objective clinical outcome measures and subjective quality-of-life (QOL) instruments are lacking for IH. Such measures are needed to accurately quantify the burden of this disease on children and their families. Quality-of-life measures are needed because clinical measures and QOL are often not highly correlated. For example, the size and site

of hemangiomas are not well correlated with parental distress.

Standardized clinical data collection forms need to be developed. These forms should include lesion type (focal, segmental, indeterminate, multifocal), description (superficial, deep, or mixed), size, and stage (precursor, proliferating, plateau, involuting). Intraobserver reliability of a standardized form should be measured.

Although QOL is difficult to quantify, this multidimensional outcome can be measured. A QOL instrument for IH would measure the effects of disease on the child and parents. Issues for parents of children with hemangiomas include loss of control, anxiety, guilt, grief, sadness, concerns about disfigurement and self-esteem, and fear of strangers' reactions. The vulnerable child syndrome may occur in these families. Issues for the child may include low self esteem because of strangers' reaction and being different, bullying, and the vulnerable child syndrome.

The ideal QOL instrument would be disease specific and age specific with comprehensive content and established psychometric properties. Existing pediatric QOL measures do not accurately measure the effects of having a child with disfigurement. The process of developing a QOL instrument includes performing a literature review and a qualitative interview study to collect data needed to draft an instrument. The instrument is then pilot and field tested to evaluate the psychometric properties of reliability, validity, and responsiveness. A qualitative interview study of 25 parents of children with facial hemangiomas by Tanner et al (19) identified four common themes: parent emotion and adaptation, experiences with public reaction, parent-child interactions, and satisfaction/dissatisfaction with medical care. These themes can be used to draft a QOL instrument for parents of children with hemangiomas.

In conclusion, accurate QOL instruments and clinical data collection forms are needed to measure and compare treatment outcomes in patients with infantile hemangiomas.

#### **CURRENT AND FUTURE EVALUATIONS, TREATMENTS, AND OUTCOMES: DISCUSSION**

##### **Systemic Therapies**

Adrenal suppression was discussed. Questions included: what is a physiologic dose, what is normal, and when is the best time to test for adrenal suppression (during, at the end, or after treatment). Regarding effects on bone density, there are limitations because of the lack of data for normal bone densities in this age group.

Question: As vincristine has been around for a long time, is a known entity, and is relatively safe, why state that vincristine should be used with caution?

Answer: The proper dosing and side effects in very young infants are not well known. Prospective trials are

needed and there needs to be an increased awareness of the potential risks of vincristine. There was a discussion of hepatitis and motor delays seen with vincristine in an English study. A caution with this agent was advised because it is a known neurotoxic agent and there is very little known about its toxicities in premature infants. Prospective studies were discussed, because there is very little knowledge about the benefit of vincristine versus the known benefit of corticosteroids. Guidelines need to be established for the use of vincristine.

Question: Aggressive drugs seem to be neurotoxic, if prednisone fails, do you use vincristine or interferon first?

Answer: This depends on the hemangioma and the age of the patient. After a discussion of the side effects of each of these medications, the family should be allowed to help in making the ultimate decision.

Question: The data showing interferon related to spasticity are based on patients receiving interferon after corticosteroid therapy. How many children developed spasticity when being treated with interferon alone without prior corticosteroid therapy?

Answer: It is hard to assess this because most of the patients had received prior systemic corticosteroids.

Question: Has anyone heard about injecting bleomycin into hemangiomas? This was reported at the last ISSVA meeting?

Answer: In the discussion of this paper, it was unclear from the paper how many times bleomycin was injected. The risk of pulmonary fibrosis was discussed. Overall, it was concluded that bleomycin could not be recommended based on this small case series.

Comment: Intralesional injections of large lesions are difficult because the drug needs to be evenly distributed throughout the hemangioma. This is not a good method for large hemangiomas. There is a lack of consensus for when intralesional steroids are most useful. (See also therapies breakout session).

### **Surgery and Laser Discussion**

One of the problems with laser is that the laser and settings are often not specified in studies. Using laser might just be speeding up what would naturally occur over time.

Dr. Eichenfield warned against using laser as monotherapy, especially in complicated or large, plaque-like lesions that have a tendency to ulcerate. The use of systemic corticosteroids is important as a primary therapy to begin the involution process.

The difficulty in performing evidence-based medicine for lasers was discussed. But experiential evidence shows that laser can provide excellent pain control with localized ulcerated perineal hemangiomas, with cooling unit and proper settings. The difficulty in treating lumbosacral

hemangiomas was discussed. These tend to have recurrent ulcerations and may not be significantly helped by laser.

Dr. Rox Anderson (Massachusetts General Hospital, Harvard Medical School) commented on the dose–response curve in relation to laser settings. Increasing dose can give worse results. The pulsed dye laser was not initially designed to treat infantile hemangiomas, but rather port-wine stains. The best therapeutic response in hemangiomas likely occurs when there are small zones of endothelial injury leading to platelet adhesion, rather than vessel destruction. Dr. Anderson discussed potential modifications to the pulse dye laser to enhance its effectiveness in hemangiomas of infancy. He recommended prospective trials to maximize the benefit.

The optimal timing for surgical excision was discussed. Dr. Mulliken commented that this is difficult to describe, but in general, one can try to determine if the scar from surgery will be less than or equal to that which would be left from either ulceration or the hemangioma itself.

## **BREAKOUT SESSIONS**

**April 9, 2005**

**Pooks Hill Marriott**

On Saturday, April 9, participants of the workshop divided into three breakout sessions for more in-depth discussions of three subject areas: (i) basic science/translational research; (ii) systemic and other therapies; and (iii) endangering hemangiomas: risk stratification and management. The following represents summaries of these breakout sessions and conclusions/recommendations from them. Summaries were presented to all participants prior to the conclusion of the workshop.

### **BASIC SCIENCE/TRANSLATIONAL RESEARCH SESSION SUMMARY**

Moderators: Joyce Bischoff, Ph.D., Harvard Medical School, Boston, Massachusetts; Paula North, M.D., Ph.D., University of Arkansas, Arkansas; and Miikka Vikkula, M.D., Ph.D., Christian de Duve Institute and University of Louvain Medical School, Brussels, Belgium.

Recorders: Laurence Boon, M.D., Ph.D., St Luc University Hospital, Brussels, Belgium; and Sheila Fallon Friedlander, M.D., University of California, San Diego, California.

Dr. Bischoff from Children’s Hospital Boston and Harvard Medical School introduced the topics and format for the breakout session. The topics to be covered were: What is the origin of hemangioma? What triggers involution? Models for understanding hemangiomas. Mechanisms of drug effects.

To lead off the discussion of “the origin of hemangioma?” Dr. Edward Lammer from Children’s Hospital Oakland

Research Institute described several theories that have been formulated to explain the origin of hemangioma. He covered hypotheses such as placental embolization, migratory angioblasts, or germline or somatic mutations that would create a large segmental hemangioma or a small and localized one, depending on the timing of occurrence of the mutation. In another scenario, "rogue" cells could move into either a localized or segmental environment permissive for their growth and subsequently proliferate.

Dr. Eileen Boye from Harvard School of Dental Medicine then detailed the phenotypes of hemangioma-derived endothelial cells (HemEC). She and others have published studies showing that HemECs are clonal, whereas nonendothelial cells from the tumor are not clonal. HemECs show increased migration and proliferation in response to VEGF stimulation when compared to normal age-matched human microvascular endothelial cells. The most striking difference, however, is that endostatin, an inhibitor of angiogenesis *in vivo* and of endothelial migration *in vitro*, further increased VEGF-induced migration of HemECs.

The clonality findings and the functional abnormalities of HemEC when compared to normal human microvascular EC prompted Dr. Boye to hypothesize an intrinsic origin of hemangioma arising from somatic mutation in these EC. Moreover, several genetic polymorphisms have been identified on *VEGF*, *KDR*, and *FLT4* genes. However, as noted by Dr. Doug Marchuk from Duke University, these changes have not been found to alter signaling properties of these receptors. Since then, other polymorphisms have been found but still need further investigations in order to prove that they are causing the phenotype.

Another hypothesis put forth is that an extrinsic defect might be the cause of hemangioma. In this scenario, abnormalities in surrounding cells within or adjacent to the hemangioma (macrophages, fibroblasts, mesenchymal stem cells, adipocytes) or in cells recruited to the hemangioma tissue, such as monocytes, dendritic cells, EPC, MSC, and mast cells, would cause the aberrant proliferation of normal endothelial cells.

Still another hypothesis was discussed in which the HemEC could also be of placental origin. This is based on the discovery that the endothelial cells in hemangioma stain for several immunohistologic markers that are also expressed by placental endothelial cells. Further support for the placental origin hypothesis was given by Dr. Carmen Barnes from Children's Hospital Boston later in the breakout session.

Yet another possibility, consistent with aspects of all of the hypotheses discussed previously, would be that hemangioma could be a result of colonization by an immature precursor cell population. This concept is supported by the identification of EPC in proliferating hemangiomas and new data that these cells exhibit increased proliferation and delayed

differentiation to a mature endothelial phenotype. This topic was discussed in more detail later in the breakout session by Dr. Zia Khan from Children's Hospital Boston.

Dr. Boye also highlighted the importance of further research on the characterization of HemEC, the analysis of gene expression patterns using different conditions and different hemangioma subtypes, the use of three-dimensional *in vitro* explant assays, and the continuation of genetic studies. Dr. Paula North of the University of Arkansas also stressed the usefulness of comparing HemEC with EC isolated from pyogenic granulomas and other vascular tumors, as well as with other disorders having the same self-resolving behavior, such as Langerhans cell histiocytosis.

Dr. Carmen Barnes from Dr. Folkman's laboratory (Children's Hospital Boston and Harvard Medical School) showed experiments to further demonstrate the striking similarities between the gene expression profiles of hemangioma and placenta. This data provides additional support for the hypothesis that hemangiomas are derived from fetal placental progenitor cells during gestation. As Dr. North and colleagues have reported, hemangioma and placenta share several immunomarkers such as Glut-1, LeY, merosin, and FcγRII. Using Affymetrix gene array technology, Dr. Barnes and her colleagues compared the genome-wide expression profile of hemangioma with those of placenta, lung (which is highly vascularized), pulmonary tumors (abundance of proliferating EC), skin, scleroderma (which have injured vessels), skeletal muscle, and brain tissue. Of interest, she identified a very high similarity between the transcriptomes of placenta and hemangioma, which coclustered when analyzed by hierarchical and nonhierarchical clustering. The correlation between hemangioma and placenta was further increased when a set of endothelial-specific genes was compared. Furthermore, an additional set of placental-specific genes coexpressed by hemangioma was identified. These data provide strong support for commonality between placenta and hemangioma endothelium, and suggest a common origin.

Miikka Vikkula, M.D., Ph.D., Christian de Duve Institute and University of Louvain Medical School, Brussels, Belgium, introduced a second topic of the breakout session – "What triggers involution of infantile hemangiomas?" Dr. Paula North provided an overview of what has been reported in the literature and findings that are well accepted. First, the histology of involuting lesions has shown that Glut-1 immunostaining persists throughout the life cycle of hemangioma. Even though there is a substantial decrease in endothelium in involuting tumors, Glut-1-positive endothelium is still evident. Furthermore, endothelial cell dropout, apoptosis, and active fibrosis, but not dense desmoplasia, are seen in the involuting phase. In contrast, the hyaluron receptor LYVE-1 is detected by

immunohistochemistry in the proliferating phase but is lost in involuting lesions. The loss of LYVE-1 staining would lend support to the sense that there is evolution from an immature state to a more mature, albeit still abnormal, cellular state. Triggers and mechanisms for this process could include loss of stimulatory factors such as VEGF. Hot spots of ICAM-1 expression can be seen in early involuting phase hemangiomas. CD20-expressing B cells are present, but they are not found in large numbers except in ulcerated areas. In contrast, relatively large numbers of T cells are present throughout the lesions. Mast cells, which express CD83, but not ICAM-1 initially, are also present. Hence, immune mediators appear to be variably present within hemangiomas at different stages of involution.

One finding that warrants further investigation is the discovery of the enzyme indoleamine 2,3-dioxygenase (IDO) in the proliferating phase of hemangioma. Dr. Matthew Ritter and colleagues at the Scripps Research Institute in San Diego showed IDO mRNA was up-regulated in the proliferating phase but then down-regulated to lower levels as involution ensues. This enzyme degrades tryptophan, an amino acid critical for the function of T cells. It is found in placenta where it is thought to function to protect the fetus from rejection. Indoleamine 2,3-dioxygenase is expressed by macrophages and dendritic cells, but not by normal endothelial cells. It appears to be functionally expressed in hemangioma endothelial cells of any stage and could certainly play a role in initially protecting the hemangioma from rejection by starving T cells of tryptophan. One would therefore postulate that the enzyme would decrease as hemangioma involution or rejection takes place. Thus far, quantitative changes in IDO levels have not been noted in proliferating versus involuting lesions. Dr. North showed that strong IDO immunostaining is present in the endothelium of involuting as well as proliferative phase hemangiomas, but remarked that the overall tissue concentration of this enzyme drops in involuting lesions because of overall lesional capillary dropout. Thus the immune tolerance provided by IDO via tryptophan catabolism would be expected to wane during the involution process despite continued IDO expression by individual hemangioma endothelia, allowing tissue levels of tryptophan to rise and allow T-cell activation.

Dr. Ritter also discussed the possible role of myeloid cells in the hemangioma life cycle. He reviewed the myeloid cell lineage pattern, and noted the relationship of monocytes, macrophages, and immature dendritic cells. Proliferating hemangiomas harbor a large number of myeloid cells, and certain markers have been used to identify these cells. CD14 cells interdigitate around CD31 cells, and do not increase in the involuting phase. Colabeling of CD83 with endothelial cells has been noted, as well as colabeling of CD15 with endothelial cells. In addition, colabeling

of dendritic, myeloid, and CD14 markers has been noted. The hematopoietic cells are not proliferating; therefore they are unlikely to be the cells of origin. However, they could be stimulating proliferation via IGF2 production, or, conversely, be intimately involved in involution via immune mechanisms. Dr. Ritter speculated that hemangioma of infancy may represent a myeloid to endothelial transition state. Other clues as to the nature of hemangioma were discussed. There are differential enzyme functions of the fetal versus the maternal side of the placenta. The fetal side possesses enzymes that inactivate estrogen; cells from the fetal side may therefore be more or less hormonally sensitive.

Dr. Zia Khan, a postdoctoral fellow in Dr. Bischoff's laboratory at Children's Hospital Boston, spoke of the hypothesis that progenitor cells reside in hemangiomas and that these cells acquire a mutation that in turn leads to a defect in their ability to differentiate to mature endothelial cells. Hemangioma endothelial progenitor cells appear to respond in a robust and active fashion when incubated in the presence of the angiogenesis inhibitor endostatin. Endostatin increases adhesion, migration, and proliferation of hemangioma-derived endothelial progenitor cells as well as the HemEC, which are endothelial cells isolated from hemangiomas based on endothelial cell surface marker expression but without selection for expression of a progenitor cell marker. It is uncertain whether endostatin is involved in the pathophysiology of hemangiomas or merely represents a marker of abnormal cellular response. The robust and active response to endostatin by endothelial cells isolated from hemangioma tissue may decrease with involution and differentiation. Other thought-provoking characteristics of endostatin were discussed. Other characteristics of hemangioma EPCs include: they have a higher rate of serine phosphorylation; and they have increased NFkB and eNOS. Dr. Khan noted that the actions of endostatin may be mediated by integrins, and hemangioma-derived endothelial cells may up-regulate collagen XVIII, the precursor to endostatin.

All investigators lamented the lack of a good animal model for infantile hemangiomas. They noted that the fibrin gel system has problems; it is a lengthy model, and takes 3 to 4 weeks for capillary formation; the loss of Glut-1 staining in the endothelial cells seen in this model is also of concern. Many unsuccessful attempts to use severe combined immunodeficiency (SCID) models were discussed. Other models which have proven ineffective include in utero injections of placental or hemangioma cell suspensions into mouse embryos and placental implants into immunocompromized mice (both nude and SCID).

The final section of this breakout session addressed mechanisms of drug effects. Dr. Paula North provided an introduction to this topic. Dr. North discussed the use of imiquimod as a possible therapy for hemangiomas.

Topical application of imiquimod has been shown to induce regression of many tumors, and to inhibit vascular tumor growth in a murine hemangioendothelioma model. Martinez et al showed that application of this drug at 7 months of age led to resolution of the hemangioma lesion in 4 months. Imiquimod is thought to act through toll-like receptors 7 and 8. Innate immunity and natural killer-cell activity is increased, and cytokine stimulation has been documented. Breakdown and erosion of tissue is a possible risk of treatment and must be evaluated in further controlled clinical trials.

Dr. Ilona Frieden, University of California, San Francisco, discussed the use of Regranex® (beclapernin gel), which in a small case series has shown efficacy in the treatment of ulcerated hemangiomas. It is paradoxical that this medication works, as it is a pro-angiogenic agent (platelet-derived growth factor BB) and at least theoretically it might make hemangiomas grow, but this does not seem to be the case. This raises questions about whether the stimulation of angiogenesis is via a different pathway than hemangioma growth, and whether such an observation might have pathogenic implications. Further controlled studies will be extremely important in documenting the potential efficacy of this drug.

Other topics and issues addressed by the organizers of the breakout session included the following: It would be extremely useful to develop a standardized intake form and an IRB form for any clinical trials being conducted on hemangiomas. A tissue registry would be invaluable in providing centralized processing and storage of tissue. A junior faculty person identified as the "triage officer" for this bank would also be helpful. The overall atmosphere of the session was one of informal and active participation by nearly all attendees.

#### **Basic Science/Translational Research Workshop: Conclusions/Recommendations\*:**

- 1 More funding, from NIH and other sources, is urgently needed for research.
- 2 A tissue bank of IH specimens with clinical characteristics defined would greatly help research efforts.
- 3 A method for sharing failed experimental models of hemangiomas is recommended.
- 4 Increased study of segmental hemangioma tissue specimens to search for biologic similarities or differences to focal lesions, or both.

#### **TREATMENT SESSION SUMMARY**

Moderators: Denise Adams, M.D., Cincinnati Children's Hospital, Cincinnati, Ohio; Richard Azizkhan, M.D., Cincinnati Children's Hospital, Cincinnati, Ohio; Francine Blei, M.D., Hassenfield Children's Center for Cancer and

Blood Disorders, New York University, New York; Amy Nopper, M.D., Children's Mercy Hospital, Kansas City, Missouri.

Recorders: Sarah Chamlin, M.D., Children's Memorial Hospital, Chicago, Illinois; Maria C. Garzon, M.D., Columbia University, New York.

The treatment breakout session discussion was divided into two sections: a review/discussion of corticosteroid therapy for IHs and future directions. The session began with a discussion of corticosteroid therapy for the treatment of problematic IHs. Corticosteroids are the most accepted and commonly used treatment for problematic proliferating IHs. Several retrospective reviews and case series have been published in the medical literature but prospective data on corticosteroid therapy for problematic IHs is lacking. Dr. Amy Nopper from Children's Mercy Hospital in Kansas City reviewed the responses to an informal questionnaire that she developed and distributed to conference participants regarding the use of glucocorticoid therapy in the management of problematic IHs. (Tables 1 and 2). Forty-five physicians at the workshop, representing a variety of specialties, responded to the questionnaire. The indications for treatment varied but the majority of responders cited ocular complications or rapid growth with risk/presence of distortion of anatomic structures or organs as reasons for starting oral glucocorticoid treatment. The majority of respondents educated their patients verbally about the potential toxicities associated with oral glucocorticoid usage. Over half of the responders provided parents with educational handouts.

The majority of respondents to the questionnaire reported monitoring patients on oral corticosteroids closely for potential toxicity. Assessment of a wide variety of clinical indices were reported but varied among participants. In addition the majority reported administering ranitidine or another medication to prevent gastrointestinal side effects. Other less frequently administered concomitant medications included trimethoprim-sulfamethoxazole, calcium or vitamin D supplementation, and the Synagis vaccine. Individuals receiving intralesional corticosteroids seemed to be monitored less rigorously. Serious oral corticosteroid-related toxicities were infrequently observed by the respondents but included steroid myopathy, glaucoma, cataracts, cardiotoxicity, and life-threatening infections including varicella. Although recently reported in the medical literature, there were no cases of *P. carinii* pneumonia reported by the respondents among their patients.

Thirty-eight of the physicians who responded to the questionnaire treated or comanaged children who received intralesional corticosteroids for IHs. Approximately half of the responders reported selecting intralesional steroids rather than systemic steroids for small, localized lesions. There was no standard regimen for treatment with different

**TABLE 1** Systemic Corticosteroid (CS) Therapy in the Management of Problematic Infantile Hemangiomas

Clinical subspecialty (n = 45)	
Pediatric dermatology	30
Dermatology	4
Ophthalmology	3
Hematology/oncology	2
Pediatric surgery	3
Pediatric plastic surgery	2
Otolaryngology	1
Clinical experience: how many patients do you treat with CS per year?	
< 5 patients	4
5–9 patients	11
10–19 patients	13
20–29 patients	6
30–50 patients	6
> 50 patients	3
For which indications do you use systemic CS?*	
Ocular complications	42
Rapid growth with risk/presence of distortion of anatomic structure/organ	43
Ulceration	21
Cosmetic	22
Parental anxiety	5
Other: hepatic hemangioma, CHF, beard distribution	5
What form(s) of oral CS do you usually utilize?*	
Prednisone	10
Prednisolone	37
Other	0
How do you typically administer oral steroids?	
Alternate day	5
Single morning dose	38
Twice daily	12
At what dose do you usually begin oral CS therapy?	
< 1 mg/kg/day	0
1–2 mg/kg/day	2
2 mg/kg/day	9
2–3 mg/kg/day	13
3 mg/kg/day	11
3–4 mg/kg/day	4
4 mg/kg/day	4
Minimum starting dose of oral CS?	
1 mg/kg/day	8
2 mg/kg/day	26
3 mg/kg/day	9
Maximum dose of oral CS used?	
1 mg/kg/day	1
2 mg/kg/day	1
3 mg/kg/day	14
4 mg/kg/day	7
5 mg/kg/day	18
6 mg/kg/day	1
8 mg/kg/day	1
What is the average duration you continue initial starting dose?	
< 4 weeks	4
4–7 weeks	26
8–11 weeks	5
12–16 weeks	2
Other	3
Typical duration of oral steroid therapy including taper?	
2–3 months	5
3–4 months	3
4–5 months	7
5–6 months	11
6–8 months	9
8–10 months	2
10–12 months	2

\*More than one positive response possible.

preparations, dose intervals, and concentrations used by participants. The perceived advantages and disadvantages of intralesional corticosteroids compared to oral corticosteroids also varied among responders.

Topical steroids were used by over half of the responders to the questionnaire, with varying perceived clinical efficacy. Most reported using class 1 topical steroids for flat, small, superficial lesions. Only a few of the responders reported using pulsed dose intravenous glucocorticoids for infantile hemangiomas.

The discussion of the questionnaire responses highlighted the lack of standardized corticosteroid treatment protocols for oral and intralesional corticosteroids for infantile hemangiomas despite their wide acceptance as a first-line therapy for problematic lesions. Usage patterns and monitoring methods varied among physicians from different disciplines and among physicians within the same discipline. The need for future studies to develop guidelines for the optimal use of oral and intralesional corticosteroids and to assess for toxicity was emphasized. Areas for potential investigation were discussed, including adrenal suppression associated with oral and intralesional corticosteroid therapy and long-term sequelae (including neurotoxicity) associated with systemic corticosteroids.

Dr. Richard Azizkhan from Cincinnati Children's Hospital and Dr. Francine Blei from New York University presented a series of clinical cases of problematic IHs. The breakout group participants discussed treatment challenges. The discussion highlighted the facts that treatment strategies varied among participants and that it is difficult to predict the ultimate outcome associated with various treatment modalities. A multidisciplinary approach may be required to manage complex lesions.

Vincristine has emerged as a potential second-line therapy for treating problematic hemangiomas because of concerns about the neurotoxicity of interferon  $\alpha$ . Prospective data on the efficacy and side effects of vincristine therapy for complicated hemangiomas is lacking. Dr. Denise Adams from Cincinnati Children's Hospital led the discussion on a proposed prospective trial to assess the efficacy and the acute and late effects of vincristine in the treatment of complicated hemangiomas that have failed medical treatment or have significant side effects from the standard medical therapy, prednisone. The objective of the protocol also included assessment of the efficacy and the acute and late effects of prednisone therapy. Criteria for entry into the study would be infants with complicated hemangiomas requiring immediate systemic therapy. Initially, all patients would receive prednisolone therapy. If a patient was a nonresponder or experienced significant side effects from systemic corticosteroids, they would be switched to vincristine therapy. Another component of this study would be a pharmacokinetic study of vincristine in this patient population.

Recombinant platelet-derived growth factor (beclapernin gel, Regranex®) has been reported to be efficacious in the treatment of ulcerated infantile hemangiomas, but its mechanism of action and safety profile remain unclear. Dr. Rod Phillips from Australia brought a protocol to the work-shop proposing a randomized controlled study to assess the safety and efficacy of this agent for the treatment of ulcerated IHs. He will try to work with other interested centers that would like to participate in such a study.

In summary, this session reviewed many of the issues involved in the treatment of hemangiomas, including indications for treatment and various treatment approaches. The variation in practices was notable, emphasizing the need for future studies to develop better evidence-based guidelines for treatment. Prospective studies are being planned to investigate the efficacy and safety of vincristine for complicated hemangiomas and beclapernin gel for ulcerated hemangiomas.

### **Treatment of Hemangiomas: Conclusions and Recommendations\***

- 1 Future studies to develop guidelines for the optimal use of oral and intralesional corticosteroids and to assess for toxicity are needed.
- 2 Proposed areas of study included adrenal suppression associated with oral and intralesional corticosteroid therapy and long-term sequelae (including neurotoxicity) associated with systemic corticosteroids.
- 3 A study protocol addressing the efficacy and adverse effects of vincristine and prednisone in a prospective manner was discussed. Dr. Denise Adams will lead this effort.
- 4 A proposal to assess the safety and efficacy of recombinant platelet derived growth factor for the treatment of ulcerated infantile hemangiomas was discussed. Dr. Rod Phillips will help coordinate this effort.
- 5 Complicated hemangiomas require a multidisciplinary approach.

### **ENDANGERING HEMANGIOMAS SESSION SUMMARY**

Moderators: Odile Enjolras M.D., Lariboisière Hospital, Paris, France; Denise Metry M.D., Texas Children's Hospital, Baylor College of Medicine, Houston, Texas; Steven Fishman M.D., Children's Hospital Boston; Patricia Burrows M.D., Children's Hospital Boston.

Recorders: Eulalia Baselga M.D., Hospital de la Santa Creu I Sant Pau, Barcelona, Spain; Beth Drolet M.D., Medical College of Wisconsin.

Dr. Fishman gave a brief introduction and began the discussion with the question, "Which hemangiomas are potentially life-threatening?"

Hemangiomas in the following locations were considered to have the potential for life-threatening complications.

1. Liver hemangiomas
  - High output cardiac failure secondary to intrahepatic shunts
  - Diffuse liver hemangiomas associated with consumptive thyroid disease
2. Central nervous system (CNS) hemangiomas
  - The group agreed that these are very rare but that true infantile hemangiomas of the CNS do exist and can cause complications such as bleeding, mass effect, and sinus thrombosis. The idea of a registry was discussed
3. Gastrointestinal hemangioma
  - Hemorrhage
4. Airway hemangioma
  - Obstruction or compression of the airway

A short discussion ensued about which hemangiomas are distorting. Dr. Mulliken discussed the fact that nasal tip and lower lip hemangiomas are at high risk for disfigurement.

### **Large Facial Hemangiomas**

The evaluation of children with large facial hemangiomas was discussed. There was a lively discussion of what clinical clues (size, shape, and distribution) should warrant further evaluation in an infant with a large facial hemangioma for possible PHACE association. There was no definitive answer other than, "you know it when you see it." There was consensus that the screening evaluation should include:

1. MRI and possibly MRA of the head and neck at 3 months of age or at presentation if older than 3 months.
2. Consider MRA of the chest to evaluate for aortic arch anomalies; however, the feasibility of this is variable, depending on institutional policies on sedation and feasibility of the study (variable factors such as the size of the MRI coil).
3. Screening echocardiogram if MRA of the chest is not performed.
4. Eye examination.
5. There was a lengthy discussion regarding the need for repeat imaging in infants found to have cerebral vascular anomalies on the initial imaging. It was agreed that MRA should be done in any infant with new neurologic signs or symptoms. Although controversial, the majority of participants agreed that in infants with documented cerebral vascular anomalies, a repeat MRA was indicated every 3 months until 18 months, then yearly until 5 years of age.

### Lumbosacral Hemangiomas

Hemangiomas that overlie the lumbosacral region can be associated with occult spinal dysraphism, including tethered spinal cord. The positive predictive value for hemangiomas as a sign of spinal dysraphism is currently unknown. The group decided that the association was high enough to warrant screening of all infants with mid-line lumbosacral hemangiomas. There was a lengthy discussion about what screening tools should be used. A spinal ultrasound was felt to be sensitive by most radiologists in the room if done prior to 4 months of age. If the investigation was inconclusive or abnormalities were found, then a MRI of the spine should be performed. For infants who present after the age of 4 months a screening lumbosacral MRI should be done.

### Hepatic Hemangiomas

Our knowledge of liver hemangioma has changed considerably over the last few years because of the availability of new imaging procedures, and further insight into the histopathologic features of these lesions. Symptomatic liver hemangiomas are relatively uncommon, however, and the best way to further our knowledge of liver hemangiomas would be to gather as much information as possible from many centers. Such collaboration would help in further confirmation of a new classification of liver hemangiomas, in developing predictors of prognosis, and ultimately improving the care of patients with liver hemangiomas. Ideally, collected data, particularly imaging studies and liver biopsies (when available), would be reviewed by designated experts. In order to obtain similar information from different centers, an algorithm was proposed for evaluating liver hemangiomas.

The first question that was addressed during this segment of the breakout session was who should be screened for liver hemangiomas. It is known that children with multiple hemangiomas are at risk for visceral lesions but the definition of multiple or multifocal is an arbitrary one. In most centers, the standard of care is to obtain a screening abdominal ultrasound in asymptomatic children with five or more cutaneous hemangiomas. However, the incidence of liver hemangiomas in children with fewer lesions or even with a single cutaneous hemangioma is currently unknown. On the other hand, some participants felt that liver hemangiomas that are picked up by routine screening in asymptomatic infants are unlikely to need treatment, and therefore it is difficult to make recommendations. Although no consensus was reached regarding who should be screened, it would be useful to collect data from any particular patient who individually we decide to screen.

There was a consensus that liver hemangioma could at least provisionally be classified into three main categories: focal, multifocal, and diffuse. This classification is supported by imaging studies as well as by clinical observations. Focal and multifocal liver hemangiomas rarely are life threatening, as opposed to diffuse hemangiomas that often end up leading to liver transplantation or death. Focal hemangiomas represent for most authorities in the field, RICHs (rapidly involuting congenital hemangiomas), because they regress spontaneously during the first few months of life. However, this impression would need to be validated with biopsy specimen findings. Many of these focal hemangiomas may have large arteriovenous shunts and, in the past, they were often confused with arteriovenous malformations. Because of this AV shunting, focal hemangiomas may cause high-output heart failure, although it is a rare event. The consensus recommendation for focal hemangiomas when asymptomatic was to follow them up with repeated ultrasounds until regression to make sure that we are not dealing with other vascular tumors such as angioblastoma.

Multifocal hemangiomas are the most common type of liver hemangiomas and their natural history is similar to that of cutaneous hemangiomas of infancy. It was recommended to follow them until regression. They are often asymptomatic, although in some cases they may cause high-output heart failure. In those instances in which they are symptomatic, most attendees would choose corticosteroids as their first-line therapy. A few would consider vincristine. In cases that have no response to medical treatment, likely because of extensive AV shunting, embolization would be considered. No specific treatment protocol was proposed, but the importance of collecting data regarding the response to any form of treatment was emphasized.

The scenario is completely different for diffuse hemangiomas. Many of the patients with diffuse hemangioma do not have hemangiomas on the skin, or only a few do. Patients with diffuse liver hemangiomas often have an abdominal compartment syndrome because of a mass effect with vena cava compression. A second problem with diffuse liver hemangioma is that they often have associated hypothyroidism and need massive doses of replacement thyroid hormone. This requires involvement of a pediatric endocrinologist. The mortality in this subset of patients is extremely high.

Last, the possibility that noninvoluting congenital hemangiomas (NICH) may also exist in the liver was raised. No one in the session remembers having seen a NICH in the liver.

### Periocular Hemangiomas

Periocular hemangiomas, although not life threatening, are sight threatening and a major cause of morbidity. In

some instances there is obvious visual deprivation, strabismus, or evidence of mass effect to predict amblyopia. However, in many patients, amblyopia results from anisometropia or minimal eye malalignment that is not suspected by clinical inspection. The importance of predicting orbital involvement was discussed at length. Dr. Enjolras presented a series of cases where there was poor correlation between the cutaneous involvement and the orbital involvement. The question of routine imaging was addressed. Most attendees agreed that an MRI should be obtained whenever there is displacement of the eye globe or thickening of the eyelids.

There is need therefore for a consensus protocol on how to evaluate periocular hemangioma. A protocol for uniform evaluation and defining outcomes of periocular hemangiomas is being created and several physicians at the workshop, including Dr. Eulalia Baselga, Dr. Douglas Fredrick, and Dr. Lois Smith, met during the workshop to work on this. The details of the protocol, which is still in progress, were not presented in full.

Dr. Frederick, pediatric ophthalmologist at University of California, San Francisco, proposed the concept of randomizing children with periocular hemangiomas to either prophylactic occlusion of the unaffected eye for 1 to 2 hours a day, or occlusion only after anisometropia is detected.

#### **Endangering Hemangiomas: Conclusions/Recommendations\***

1. Large facial hemangiomas warrant screening evaluation for PHACES association. Studies to consider include:
  - MRI (and possibly MRA) of the head and neck at 3 months of age or at presentation if older than 3 months
  - MRA of the chest to evaluate for aortic arch anomalies (ability to obtain this may be institution dependent).
  - Screening echocardiogram if MRA of the chest not completed
  - Eye examination
  - MRA of the brain in infants with new neurologic signs; repeat MRA in infants with cerebral vascular anomalies every 3 months until 18 months, then yearly until 5 years of age
2. Lumbosacral hemangiomas should be investigated by imaging centers. Many centers recommend spinal ultrasound if the patient is less than 4 months of age with older patients being screened with MRI, whereas some radiologists recommend MR imaging at all ages when there is a concern of spinal cord anomalies.
3. Focal and multifocal liver hemangiomas rarely are life threatening, as opposed to diffuse hemangiomas,

which have an extremely high degree of morbidity and risk of mortality. Focal and multifocal hemangiomas, when asymptomatic, should be followed by serial ultrasound until evidence of regression. When they are symptomatic, corticosteroids are first-line therapy.

4. Diffuse liver hemangiomas are often associated with profound hypothyroidism that needs aggressive replacement therapy and involvement of a pediatric endocrinologist. These hemangiomas require aggressive pharmacologic therapy and consideration of liver transplant because of their poorer prognosis.
5. Periocular hemangiomas that result in displacement of the globe or thickening of the eyelids warrant an MRI. Future protocols to evaluate periocular hemangiomas are planned.

\*This workshop was not a consensus conference. The conclusions and recommendations in these proceedings are not meant to be construed as official guidelines of care.

#### **ACKNOWLEDGMENTS**

This workshop was supported by R13 grant AR052663-01 with funds from the National Institute of Arthritis, Musculoskeletal, and Skin Diseases (NIAMS) and the Office of Rare Diseases, as well as private donations. We acknowledge the help of Alan Moshell, M.D., Skin Disease Branch Chief, NIAMS, for strategic and logistical support in planning of the workshop.

#### **REFERENCES**

1. Slaton JW, Perrotte P, Inoue K, et al. Interferon- $\alpha$ -mediated down-regulation of angiogenesis-related genes and therapy of bladder cancer are dependent on optimization of biological dose and schedule. *Clin Cancer Res* 1999;5:2726-2734.
2. Cheung DS, Warman ML, Mulliken JB. Hemangioma in twins. *Ann Plast Surg* 1997 March;38:269-274.
3. Metz BJ, Rubenstein MC, Levy ML, et al. Response of ulcerated perineal hemangiomas of infancy to becaplermin gel, a recombinant human platelet-derived growth factor. *Arch Dermatol* 2004;140:867-870.
4. Kassirjian A, Zurakowski D, Dubois J, et al. Infantile hepatic hemangiomas: clinical and imaging findings and their correlation with therapy. *Am J Roentgenol* 2004;182:785-795.
5. Kassirjian A, Dubois J, Burrows PE. Angiographic classification of hepatic hemangiomas in infants. *Radiology* 2002;222:693-698.
6. Boye E, Yu Y, Paranya G, et al. Clonality and altered behavior of endothelial cells from hemangiomas. *J Clin Invest* 2001;107:745-752.
7. Walter JW, North PE, Waner M, et al. Somatic mutation of vascular endothelial growth factor receptors in juvenile hemangioma. *Genes Chromosomes Cancer* 2002;33:295-303.

8. North PE, Waner M, Mizeracki A, et al. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. *Hum Pathol* 2000;31:11–22.
9. North PE, Waner M, Mizeracki A, et al. A unique microvascular phenotype shared by juvenile hemangiomas and human placenta. *Arch Dermatol* 2001;137:559–570.
10. Dadras SS, North PE, Bertocini J, et al. Infantile hemangiomas are arrested in an early developmental vascular differentiation state. *Mod Pathol* 2004;17:1068–1079.
11. Yu Y, Flint AF, Mulliken JB, et al. Endothelial progenitor cells in infantile hemangioma. *Blood* 2004;103:1373–1375.
12. Hasan Q, Tan ST, Gush J, et al. Steroid therapy of a proliferating hemangioma: histochemical and molecular changes. *Pediatrics* 2000;105:117–120.
13. Boon LM, MacDonald DM, Mulliken JB. Complications of systemic corticosteroid therapy for problematic hemangioma. *Plast Reconstr Surg* 1999;104:1616–1623.
14. George ME, Sharma V, Jacobson J, et al. Adverse effects of systemic glucocorticosteroid therapy in infants with hemangiomas. *Arch Dermatol* 2004;140:963–969.
15. Frieden IJ, Eichenfield LF, Esterly NB, et al. Guidelines of care for hemangiomas of infancy. American Academy of Dermatology Guidelines/Outcomes Committee. *J Am Acad Dermatol* 1997;37:631–637.
16. Enjolras O, Breviere GM, Roger G, et al. Vincristine treatment for function- and life-threatening infantile hemangioma. *Arch Pediatr* 2004;11:99–107.
17. Mulliken JB, Rogers GF, Marler JJ. Circular excision of hemangioma and purse-string closure: the smallest possible scar. *Plast Reconstr Surg* 2002;109:1544–1554.
18. Batta K, Goodyear HM, Moss C, et al. Randomized controlled study of early pulsed dye laser treatment of uncomplicated childhood hemangiomas: results of a 1-year analysis. *Lancet* 2002;360:521–527.
19. Tanner JL, Dechert MP, Frieden IJ. Growing up with a facial hemangioma: parent and child coping and adaptation. *Pediatrics* 1998;101:446–452.
20. Martinez MI, Sandiez-Carpintero I, North PE, Mihm MC Jr. Infantile hemangioma: clinical resolution with 5% imiquimod cream. *Arch Dermatol* 2002;138:881–884.

#### APPENDIX A *Hemangioma Investigator Group Sites and Members*

---

University of California, San Francisco  
 Ilona Frieden and Anita Haggstrom  
 Medical College of Wisconsin  
 Beth Drolet and Nancy Esterly  
 Columbia University  
 Maria Garzon and Kim Morel  
 Baylor College of Medicine  
 Denise Metry  
 Childrens' Memorial Hospital/Northwestern University  
 Sarah Chamlin and Anthony Mancini  
 Mercy Childrens' Hospital/University of Missouri-Kansas City  
 Amy Nopper, Kim Horii, and Brandon Newell  
 Cincinnati Children's Hospital  
 Anne Lucky  
 Hospital de la Santa Creu I Sant Pau, Barcelona, Spain  
 Eulalia Baselga

---

#### APPENDIX B *Organizing Committee*

---

Ilona J. Frieden, M.D., University of California, San Francisco, principal investigator  
 Anita N. Haggstrom, M.D., Washington DC, co-principal investigator  
 Beth A. Drolet, M.D., Medical College of Wisconsin, co-principal investigator  
 Francine Blei, M.D., Pediatric Hematology-Oncology, Hassenfield Children's Center for Cancer and Blood Disorders, New York University  
 Steven J. Fishman, M.D., Pediatric Surgery, Boston Children's Hospital  
 John B. Mulliken, M.D., Pediatric Plastic and Reconstructive Surgery, Boston Children's Hospital  
 Paula E. North, M.D., Ph.D., Pediatric Pathology, University of Arkansas  
 Miikka Vakkula, M.D., Ph.D., Human Molecular Genetics, Christian de Duve Institute and University of Louvain Medical School, Brussels

---

GLOSSARY OF ABBREVIATIONS

- AVM – arterial–venous malformation  
AV-shunt – arteriovenous shunt  
bFGF – basic fibroblast growth factor  
CHF – congestive heart failure  
CNS – central nervous system  
CS – corticosteroid  
CVS – chorionic villus sampling  
EC – endothelial cells  
eNOS – endothelial nitric oxide synthase  
EPC – endothelial progenitor cells  
FACS – fluorescence-activated cell sorting  
FcγR – constant fragment of IgG receptor  
FGF – fibroblast growth factor  
FDA – Food and Drug Administration  
FLT4 – FMS-related tyrosine kinase 4  
GABRE – gamma-aminobutyric acid A receptor, ε  
GEDI – gene expression dynamic inspector  
GLUT-1 – glutamine transferase 1  
HemEC – hemangioma-derived endothelial cells  
HIG – hemangioma investigator group  
ICAM – intercellular adhesion molecule  
IDO – indoleamine 2,3-dioxygenase  
IFN – interferon  
IGF2 – insulin-like growth factor 2  
IH – infantile hemangiomas  
KDR – kinase-insert domain receptor (also known as VEGF-receptor 2)  
LeY – Lewis antigen Y  
LYVE-1 – lymphatic vessel marker  
MRA – magnetic resonance angiography  
MRI – magnetic resonance imaging  
MSC – mesenchymal stem cells  
NIH – National Institutes of Health  
NFκB – nuclear factor kappa B  
NICH – noninvoluting congenital hemangioma  
NVSS – National Vital Statistics  
PDL – pulsed dye laser  
PHACE association – an acronym for the association of posterior fossa defects, hemangiomas, arterial anomalies, cardiac defects and coarctation of the aorta, and eye anomalies.  
PHACE(S) – same acronym as above with “S” signifying associated sternal clefting and/or supraumbilical raphe  
PV-shunt – portovenous shunt  
QOL – quality of life  
RICH – rapidly involuting congenital hemangioma  
RT-PCR – real-time polymerase chain reaction  
SCID – severe combined immunodeficiency  
SNP – single nucleotide polymorphism  
VEGF – vascular endothelial growth factor