Hemangiomas and Vascular Malformations in Infants and Children: A Classification Based on Endothelial Characteristics

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> ... Those difficulties which have hitherto amused philosophers, and blocked up the way to knowledge, are entirely owing to ourselves. That we have first raised a dust and then complain we cannot see.
>
> *George Berkeley (1685–1753)*[1]

The management of cutaneous vascular lesions is hampered by a bewildering nomenclature that has evolved from ignorance of pathophysiology. Textbook classifications offer an array of admixed histologic and descriptive terms. *Hemangioma* has been used as a generic word to describe a variety of vascular lesions with different etiologies and natural histories. The most common tumor of infancy, known as "strawberry," "capillary," "juvenile," or "cellular" hemangioma, predictably undergoes involution. Yet, port-wine stains, which never regress, also are classified as capillary hemangiomas.[5,6] Unfortunately, the histologic term *cavernous* has been used clinically to describe vascular lesions that involute[7] and rarely involute.[8] Lesions of lymphatic origin, called *lymphangiomas*, grow commensurately with the child, sometimes enlarge,[9] or may improve with time or even disappear.[10-12] Hybrid terms, such as *capillary-cavernous hemangioma* and *lymphangiohemangioma*, permeate the literature and further add to the confusion. *Hamartia* (Greek, *hamartia*, "to sin") is defined as any developmental defect. Albrecht introduced *hamartoma* to describe proliferative lesions of developmental origin, such as neurofibromatosis and hepatic vascular lesions.[13] However, *hamartoma* is too comprehensive a term—it could be applied to any lesion that histologically shows a proliferation of cells normally present in a tissue. Contemporary terminology of vascular lesions is enough to befuddle pathologist and clinician alike.

HISTORICAL PERSPECTIVE

It has been argued whether vascular lesions are developmental malformations or types of neoplasia. Dupuytren called them "erectile tumors."[14] Other nineteenth century expressions, such as "naevus maternus" and "stigma metrocelis," indicted the mother. Vascular lesions were thought to be "produced by the longing of the mother for particular things, or her aversion to them; hence these marks resemble mulberries, strawberries, grapes, pines, bacon, etc."[15] Virchow considered these lesions to be vascular tumors and classified them based on channel architecture as *angioma simplex, angioma cavernosum*, and *angioma racemosum*.[16] He believed that one type could transform into another by either cellular proliferation or vessel dilation. Wegner, after studying with Virchow at the Berlin Pathological Institute, proposed a similar histomorphologic classification of lymphatic swellings that is still used today: *lymphangioma simplex, cavernosum*, and *cystoides*.[17] Wegner believed that these lesions resulted from either lymphatic inflammation and dilation, malfor-

TABLE I

Classification of Vascular Lesions in Infants and Children

Hemangiomas	Malformations
Proliferating phase	Capillary
Involuting phase	Venous
	Arterial
	Lymphatic
	Fistulae

TABLE II

Cellular and Clinical Features of Pediatric Vascular Lesions

Hemangiomas (n = 26)	Malformations (n = 23)
Endothelial cell proliferation	Normal endothelial cell cycle
Forty percent present at birth usually as a small red mark	Ninety percent recognized at birth
Rapid postnatal growth and slow involution	Grow commensurately with child
Female: male, 5:1	Female: male, 1:1

mation, or endothelial proliferation.

With an increased appreciation of cardiovascular embryology, it was suggested that vascular lesions originated from persistent angioblastic tissue that normally reorganized and regressed.[18-20] Thus "angiomas" could be either capillary, venous, or arterial with or without fistulae, depending on the stage at which morphogenesis was disturbed.[21]

The histopathologic classifications of Stout and Lattes include a variety of lesions, both congenital and acquired, under the title of "angiomato-

ses."[22] These authors called the proliferative lesion of infants "benign hemangioendothelioma" and reserved Mallory's term,[23] "hemangioendothelioma," for malignant neoplasia.[24]

This prospective investigation was undertaken to define the cellular features of cutaneous vascular lesions in infants and children in relation to history and clinical course. Surgical specimens were analyzed by selected histochemical, autoradiographic, and electron microscopic techniques. This study presents a simplified classification of pediatric vascular lesions that clarifies clinical diagnosis and therapeutic approaches.

MATERIALS AND METHODS

Forty-nine fresh operative specimens were obtained from a variety of cutaneous vascular lesions in 35 females and 14 males. Patient age range was from 2 months to 16 years (mean = 6.9 years). Sixty percent of the lesions were from the head and neck region; the rest were from the extremities or trunk.

Formaldehyde-fixed specimens were embedded in paraffin, sectioned to 4 μm, and stained by H&E, reticulin, van Gieson, periodic acid-Schiff (PAS), and Masson trichrome techniques. As markers of endothelial maturation, alkaline phosphatase activity (Sigma Technical Bulletin No. 85) was determined, and in some specimens, factor VIII antigen was localized with a fixed peroxidase method.[25] In order to demonstrate DNA synthesis by the tissues, we performed radioautography after 18 hours of incubation at 37°C of 2-mm^3 pieces with 4 μCi/ml [^{3}H]thymidine in Me-

FIG. 1. (*Left*) Newborn child. (*Right*) Five months later, hemangiomatous proliferation involves the face and neck, necessitating tracheostomy and systemic steroid administration.
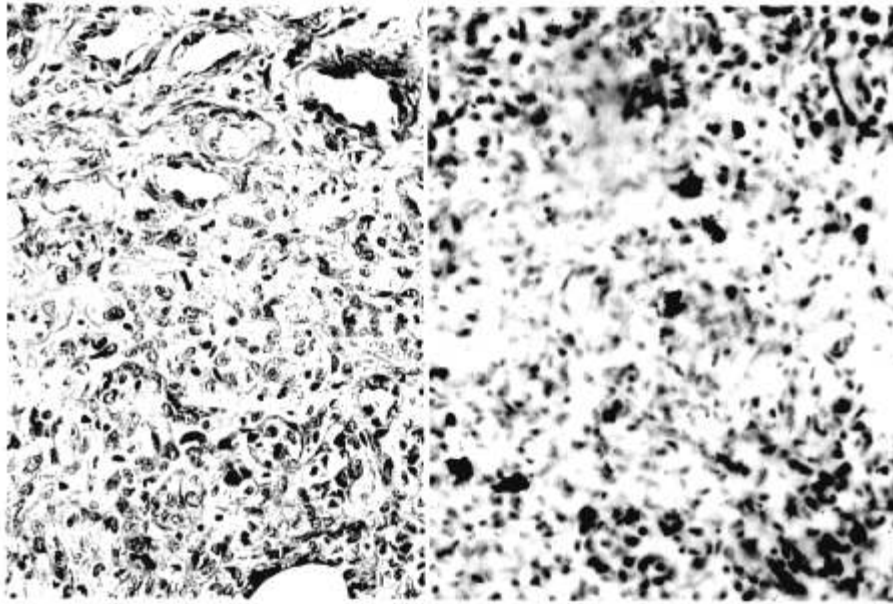
Fig. 2. (*Left*) Proliferative hemangioma showing endothelial hyperplasia, with and without lumen formation (H&E, 1000×). (*Right*) Autoradiograph of an early proliferative hemangioma. Grains represent endothelial cell DNA synthesis (720×).

dium 199 (Grand Island Biologicals Inc.). Fragments of tissue also were prepared for electron microscopy by fixation in 2.6% glutaraldehyde in 0.1 M cacodylate buffer followed by buffered 2% osmic acid. Specimens were embedded in Epon 812. Thick sections were cut on an LKB ultramicrotome, stained with toluidine blue, and examined by light microscopy. Thin sections were stained with uranyl acetate and lead citrate and

examined in a JEOL-JEM-100S electron microscope. The slides were interpreted and grouped without knowledge of the patient's identity or history. The clinical histories were later reviewed and correlated with the cellular features.

RESULTS

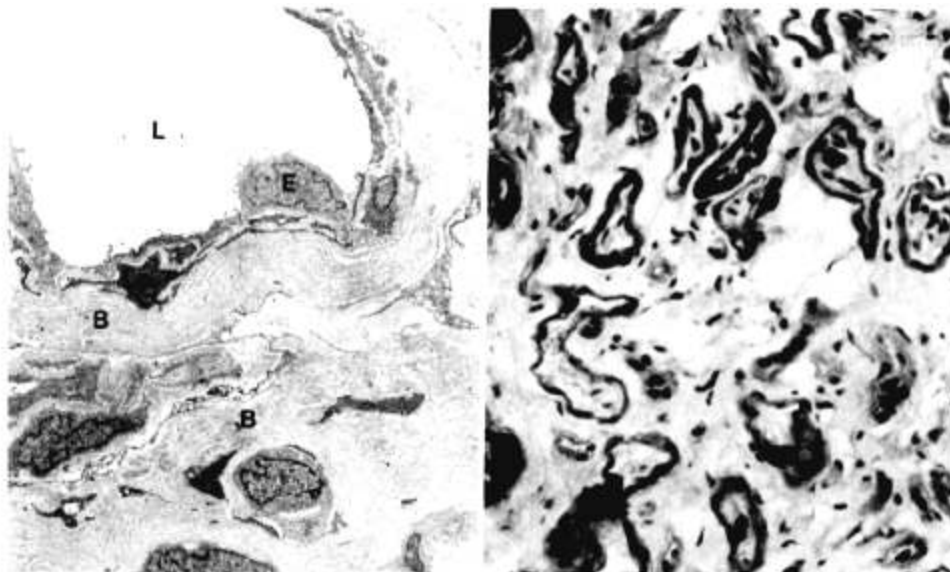These cellular studies revealed two major types of vascular lesions (Tables I and II): (1) those

Fig. 3. (*Left*) Electron micrograph of a 2-year-old hemangioma showing multilamination of the basement membrane (*B*), endothelial cell (*E*), lumen (*L*), and pericyte (*P*) (2000×). (*Right*) Thickened basement membranes in the same lesion seen with PAS stain (980×).

exhibiting a history of rapid neonatal growth and slow involution were characterized by hypercellularity during the proliferating phase and fibrosis and diminished cellularity during the involuting phase (*hemangiomas*); and (2) those present at birth which grew commensurately with the child were characterized by a normal rate of endothelial cell turnover (*malformations*).

Hemangiomas

These lesions were present at birth in 40 percent of the patients in this series ($n = 22$ females; $n = 4$ males), usually only as a small red mark. They characteristically grew rapidly for 6 to 8 months (Fig. 1) and regressed to a variable extent. Specimens were studied from both the proliferating and involuting phases.

Proliferating phase. Fourteen lesions were distinguished by increased endothelial cell activity with the formation of syncytial masses with and without lumens (Fig. 2, *left*). Alkaline phosphatase was localized throughout the areas of hypercellularity, as well as in mature vessels. Factor VIII antigen was present in endothelial cells of the hemangioma and in cells of normal adjacent vessels in specimens from patients as early as 2 months of age.

Autoradiograms showed labeling of endothelium both in the presence and absence of vascular lumens (Fig. 2, *right*). Of 12 specimens prepared, 9 were interpretable; endothelial cells were labeled at an index of 27 ± 12 per high power field (HPF) in early proliferative lesions (<1 year, $n = 5$) and 9 ± 3 per HPF in late proliferative lesions (>1 year, $n = 4$).

Electron microscopic characterization will be described in detail elsewhere. In brief, there were multiple laminas of basement membranes underlying the endothelium in hemangiomas (Fig. 3, *left*). This thickening also was evident on light microscopy by PAS stain (Fig. 3, *right*). There was an active rough endoplasmic reticulum and microtubular bodies of Weibel and Palade[26] within the endothelial cytoplasm.

Involuting phase. Twelve specimens showed diminished cellularity with islands of fatty deposits intermingled with fibrous tissue (Fig. 4, *left*). There were prominent vascular channels lined by plump endothelium; these channels were devoid of smooth-muscle coating.

Involuted lesions demonstrated no [³H]thymidine incorporation ($n = 6$). Hemangiomas that failed to undergo complete regression showed foci of endothelial proliferation coexistent with areas of fibrofatty infiltration (Fig. 4, *right*).

Vascular Malformations

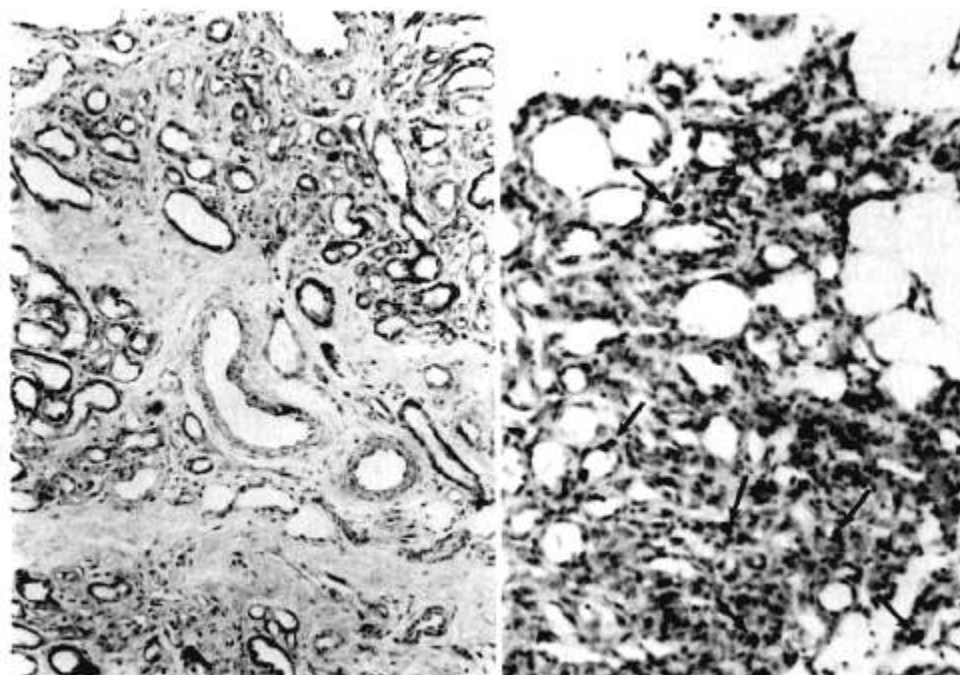Twenty-three lesions (from 13 females and 10 males) grew commensurately with the child, none

Fig. 4. (*Left*) Hemangioma in the involuting phase showing fibrofatty infiltration and diminished cellularity (trichrome stain, 300×). (*Right*) Hemangioma with foci of [³H]thymidine incorporation (*arrows*) coexistent with fibrofatty infiltration (640×).

regressed, and several expanded with onset of puberty. Ninety percent of these had been recognized at birth. Most of these lesions were predominantly venous in type, six were lymphatic, and two were port-wine stains.

The specimens were not hypercellular, but rather were composed of vascular channels lined by flat "mature" endothelium (Fig. 5). Normal reticulin networks surrounded the vessels. Alkaline phosphatase and factor VIII antigen were localized to the endothelium of the abnormal channels.

The endothelial lining in the vascular malformation group, including the lymphatic lesions and port-wine stains, was not proliferative on the basis of $[^3H]$thymidine radioautography ($n = 15$) (Fig. 6).

Electron microscopy showed typical Weibel-Palade bodies and smooth endoplasmic reticulum within endothelium overlying single-layered basement membrane (Fig. 7).

DISCUSSION

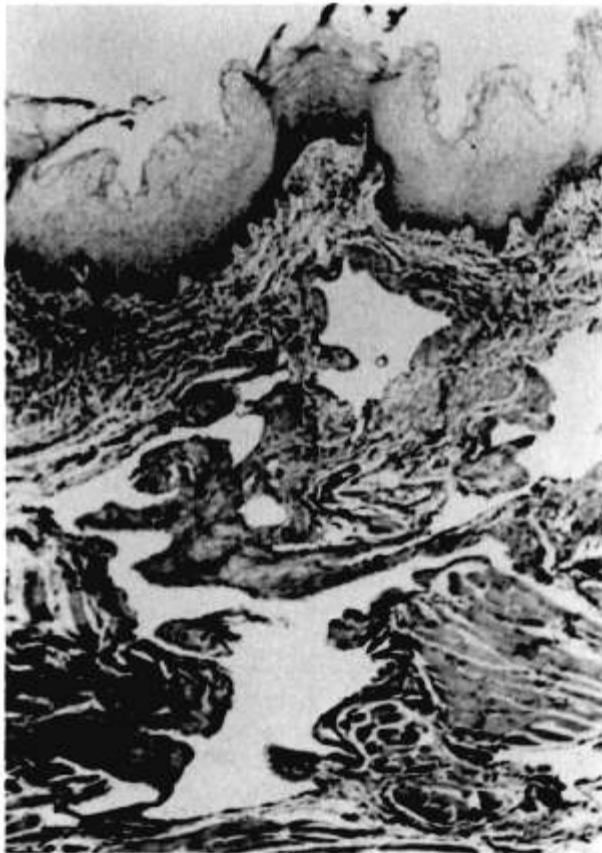From this analysis of cellular features, childhood vascular lesions could be classified as either

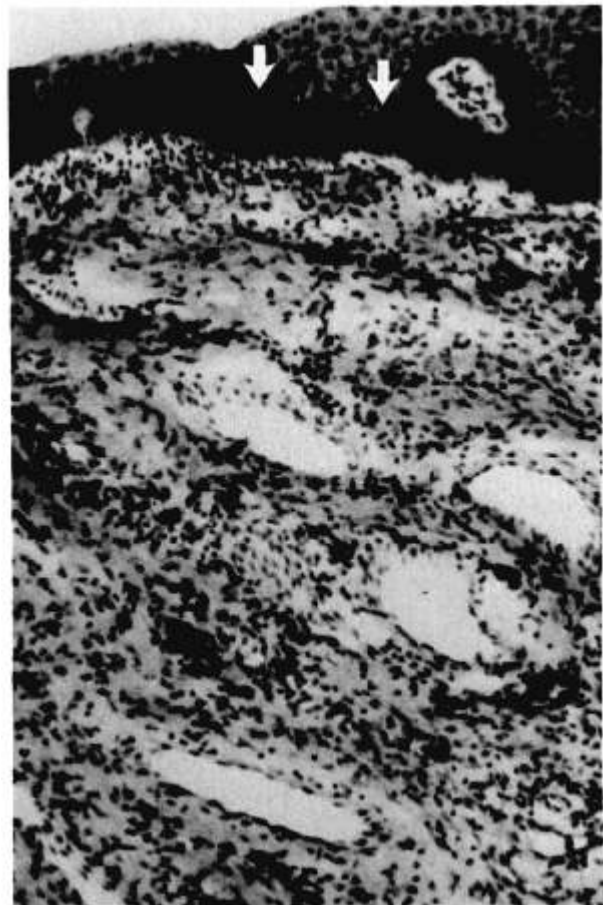FIG. 6. Autoradiograph of a port-wine stain showing incorporation of $[^3H]$thymidine (*arrows*) in epidermis but not in abnormal vascular channels in dermis (400×).

FIG. 5. Vascular channels of a venous malformation of the neck (H&E, 350×).

FIG. 7. Electron micrograph of venous malformation of the hand in a 3-year-old child showing basement membrane (*B*), endothelial cell (*E*), and lumen (*L*) (3600×).

hemangiomas or *malformations*. The suffix *-oma*, from the Greek *ōnkōs*, meaning "a mass or swelling," should be restricted to lesions that exhibit cellular proliferation. Thus we propose that the term *hemangioma* be limited to those lesions that show increased mitotic activity. These are the most common tumors of infancy. They make their appearance during the late fetal or early neonatal life, grow rapidly, and usually undergo regression. Studies to demonstrate whether or not the endothelium in such lesions is embryonal in type showed the cells to be differentiated enough to contain Weibel-Palade bodies, factor VIII antigen, and alkaline phosphatase. The multilaminated basement membrane in hemangiomas[27] may be the result of cellular proliferation and death, as suggested for similar ultrastructural vascular alterations in diabetes.[28]

Vascular lesions that grow *pari passu* with the child, fail to regress, and show normal endothelial mitotic activity should be called *malformations*

(Fig. 8). They may have any combination of capillary, venous, arterial, and lymphatic components, with or without fistulae. The colorful claret or port-wine stain belongs to the malformation category and consists of venule-like channels located within the dermis (Fig. 9). Although from a cellular standpoint, vascular malformations are stable, clinically they can be devastating, particularly when there is arteriovenous shunting.[29] Most investigators agree that congenital lymphatic lesions are true malformations with a normal cell replication cycle;[30,31] only Goetsch presented contrary findings.[32] The term *lymphangioma* should be reserved for a hypercellular tumor that can be documented to be of lymphatic provenance. The hybrid terms *lymphangiohemangioma* or *hemangiolymphangioma* should not be used to describe congenital vascular anomalies. These words imply a potential for growth by cell proliferation (Fig. 10). Our studies confirm the view that such lesions are combined deformities of blood and lymphatic vessels.[17] The shrinking of lymphatic malformations should be called *resolution*, or *deflation*, rather than involution until the mechanism is elucidated. Because lymphatic

FIG. 8. A 7-year-old boy with venous malformation of the neck that expanded with Valsalva maneuver. Histology is shown in Figure 5.

FIG. 9. Port-wine stain involving the skin innervated by all three divisions of the trigeminal nerve. Autoradiograph of this type of malformation is seen in Figure 6.

Fig. 10. Lymphatic malformation of the forehead and orbit in a 2-year-old girl. Since infancy the child's diagnosis has been "lymphangiohemangioma."

Fig. 11. A 3-month-old child with a deep, rapidly growing hemangioma of the right supratrochlear region first noted at 3 weeks of age. Autoradiograph of this lesion is shown in Figure 2 (*right*).

channels develop in association with the venous plexus,[33,34] venolymphatic shunts may play a role in the natural history of lymphatic anomalies.

A classification is justifiable only if it has diagnostic applicability, helps in planning therapy, and guides studies of pathogenesis. Vascular lesions are perceived differently on the basis of this simplified, cell-oriented terminology. Not all hemangiomas look like strawberries. Hemangiomas may grow deep in subcutaneous tissue and muscle and not involve the papillary dermis (Fig. 11). The characteristic bright red color of a hemangioma is a reflection of subepidermal endothelial penetration. Lesions that clinically appear to be "mixed," with "capillary" (superficial) "cavernous" (deep) components (Figs. 12 and 13), present a uniform histologic picture. Much of the confusion lies in the fact that with the aid of a microscope, mature or late involuting phase hemangiomas can look "cavernous." The term *cavernous* should be restricted to the histologic description of large channel (venous or lymphatic) malformations, or perhaps the term should be discarded altogether.

Sophisticated laboratory techniques are not necessary to assign a lesion to either of the two major categories, hemangioma or malformation.

The diagnosis can usually be made by an accurate history and physical examination. Hemangiomas should be approached as problems of increased endothelial proliferation. Malformations, however, are structural abnormalities, errors of vascular morphogenesis, the enlargement of which can occur with changes in pressure and flow, ectasia, collateral formation, shunting, and hormonal modulation. Therapy of vascular malformations should be on a rheologic basis.

This classification does not exclude the possibility of lesions that appear to be combinations of neoplasia and malformation. For example, endothelial proliferation may establish a vascular network within a hemangioma that could mimic a malformation or function as a physiologic shunt.[35-37] Perhaps, flow or pressure triggers endothelial cell growth within anomalous vessels, i.e., a reactivation of dormant angiopoietic cells.[38] Yet, to date, evidence for stimulation of endothelial proliferation by hemodynamic factors has not been convincing. Folkman and co-workers have demonstrated, in fact, that capillary endothelial proliferation[39] and migration,[40] as well as lumen

FIG. 12. Proliferative hemangioma in a 2-year-old child; it was not present at birth. In the past, these lesions were called "mixed" or "capillary-cavernous" hemangiomas. Histology of this lesion is shown in Figure 2 *(left)*.

FIG. 13. A 2-year-old girl with a large, deep hemangioma, showing central regression of the superficial element. Autoradiograph of this lesion is shown in Figure 4 *(right)*.

formation,[41] can occur ex vivo in the absence of blood flow.

SUMMARY

Forty-nine specimens from a variety of vascular lesions were analyzed for cellular characteristics. Two major categories of lesions emerged from this investigation: *hemangiomas* and *vascular malformations*. This classification and its implications are justified by several considerations. Hemangiomas in the proliferating phase ($n = 14$) were distinguished by (1) endothelial hyperplasia with incorporation of [^{3}H]thymidine, (2) multilaminated basement membrane formation beneath the endothelium, and (3) clinical history of rapid growth during early infancy. Hemangiomas in the involuting phase ($n = 12$) exhibited (1) histologic fibrosis and fat deposition, (2) low to absent [^{3}H]thymidine labeling of endothelial cells, and (3) rapid growth and subsequent regression. The endothelium in hemangiomas had many characteristics of differentiation: Weibel-Palade bodies, alkaline phosphatase, and factor VIII production.

Vascular malformations ($n = 23$) demonstrated no tritiated thymidine incorporation and normal ultrastructural characteristics. These lesions were usually noted at birth, grew proportionately with the child, and consisted of abnormal, often combined, capillary, arterial, venous, and lymphatic vascular elements.

This cell-oriented analysis provides a simple yet comprehensive classification of vascular lesions of infancy and childhood and serves as a guide for diagnosis, management, and further research.

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