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Interferon–Alpha-2a for the Treatment of Complex Hemangiomas of Infancy and Childhood

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Objective

The authors describe the use of interferon—alpha-2a (IFN—α-2a) in the treatment of complex hemangiomas and review the role of interferon (IFN) in this example of an angiogenic disease.

Summary Background Data

Hemangiomas are the most frequent tumors of infants and children. They grow rapidly for 6 to 8 months and then resolve over a period of years. Approximately 5% produce life-, sight-, or limb-threatening complications, with mortality rates between 20% and 50%. Aggressive therapy with steroids, arterial ligation or embolization, or surgery has been used in these situations with variable results and high morbidity. Recently, IFN—α was found to be effective treatment in these complex hemangiomas.

Methods

Four infants and one child were treated with IFN—α-2a at an initial subcutaneous dose of 1 million units/m^2/day and a sustained dose of 3 million units/m^2/day for 5 to 11 months. Appropriate laboratory values were monitored and adverse reactions and ultimate response to therapy were recorded.

Results

Two patients experienced minor complications that were managed easily. Three patients had total or near-total regression of the hemangioma, one had partial (50%) regression, and one had stabilization but no regression after an average of 7.1 months of IFN therapy.

Conclusion

Interferon—α inhibits angiogenesis and endothelial cell migration and proliferation *in vitro*. The patients in this study add to the growing number who have benefited from IFN therapy. As such, IFN—α should be considered as a first-line agent in treating complex hemangiomas of infants and children.

Hemangiomas are the most frequent tumors of infants and children,[1,2] occurring in approximately 0.54/1000 live births.[3] Their natural history is that of rapid growth until 6 to 8 months of age, stabilization, and involution beginning in the second year of life. Ninety per cent resolve by the time the patient is 10 years old.[4] Complex or alarming hemangiomas[5] are those which do not follow this normal course, but grow to threaten the patient's life,

vital organs, or limbs by obstructing, compressing, or destroying structures[6] or by resulting in high-output cardiac failure, consumptive coagulopathy, bleeding, or infection.[4,6,7] These hemangiomas are associated with a 20% to 50% mortality rate[4,6,8] unless they are managed aggressively with high-dose steroids,[2,9,10] arterial ligation (or embolization), or surgical resection.[3] Some infants are refractory to even these forms of therapy,[6,11,12] or the therapy itself may prove to be life-threatening or mutilating.[6] Interferon—α has been found to be an effective treatment in these select infants.[6,8,12–15] We describe four infants and one child who were treated successfully for complex hemangiomas with IFN—α-2a and examine the mechanism of action of interferon (IFN) in this disease.

METHODS

After obtaining institutional review board permission and informed parental consent, four infants and one child, aged 4 weeks to 28 months, were treated with IFN—α-2a (Roferon, Hoffmann—La Roche, Nutley, NJ) for complex hemangiomas. There were three boys and two girls, three whites and two blacks. Only two patients had received prior therapy for the hemangioma—compression in one and prednisone plus blood product replacement therapy and antifibrinolytic agents for treatment of Kasabach-Merritt syndrome in the other. The indication for use of IFN—α was a threat to life in two patients (apnea, Kasabach-Merritt syndrome), a threat to limb or organ in two patients (left eye, left arm), and rectal bleeding in one patient. Interferon—α-2a was administered subcutaneously beginning at a dose of 1 million units/m^2/day for the first week and advancing up to 3 million units/m^2/day over a 1-week period. Therapy was continued for 5 to 11 months (one patient is still on therapy after 11 months), according to the response of the lesion. Complete blood counts, serum chemistries, and coagulation profiles were obtained at least monthly and more frequently if indicated. At the completion of therapy, the IFN dosage was tapered over a 1- to 2-week period and then discontinued. Additional courses of therapy were not required.

A synopsis of the patients is presented in Table 1. The individual case summaries follow.

Patient 1

A 4-week-old black boy presented with a huge cavernous hemangioma involving the right flank, chest wall, and retroperitoneum with displacement of the right kidney and inferior vena cava to the left and upward (Fig. 1). He developed Kasabach-Merritt syndrome, which is characterized by thrombocytopenia (platelets < 10,000/m^3), hypofibrinogenemia (56 mg/dL; normal = 200–400), and anemia (Hgb 7.8 g/dL). Treatment with prednisone (5 mg/kg/day), tranexamic acid, and blood product replacement failed to correct the coagulopathy. Interferon therapy commenced and no further blood product administration was required. The coagulopathy was corrected rapidly, after which the lesion began to diminish in size, as determined by serial magnetic resonance imaging (MRI) examinations. After 9 months of therapy the lesion had regressed completely, and IFN therapy was stopped. The patient has had no recurrence and is developing normally 18 months since completion of therapy.

Patient 2

A 7-week-old black girl presented with a large hemangioma involving the left temporal and ophthalmic region of her face associated with ptosis of her left eye, closure of her left eyelid, and extension into the left parapharyngeal spaces, as determined by MRI (Fig. 2). Her coagulation profile was normal. She was treated with IFN because of threat to her left eye. There has been partial regression of her hemangioma after 11 months (ongoing) of therapy. Her ptosis has resolved, and the eye and eyelid are fully functional.

Patient 3

A 4-month-old white boy presented with a circumferential perianal hemangioma extending into his right buttock and anal canal, which was rapidly enlarging and was associated with rectal bleeding (Fig. 3). The coagulation profile was normal; no blood transfusions were required. Surgical resection would have necessitated a colostomy; therefore, we elected to treat him with IFN. Therapy was discontinued for 1 week for mild granulocytopenia. He was treated for 5 months and the lesion responded completely. There has been no recurrence 6 months after cessation of therapy.

Patient 4

A 6-month-old white boy presented with a rapidly enlarging hemangioma involving the left arm circumferentially from the elbow to the dorsum of the hand, which was associated with bleeding and ulceration (Fig. 4). Compression therapy was tried without success. The coagulation profile was normal, but an MRI showed extension of the hemangioma into the forearm musculature. Interferon—α was administered for 6 months, during which there was near total regression of the lesion. There has been no recurrence 6 months after completion of therapy.

Patient 5

A 28-month-old white girl presented with airway obstruction from a progressively enlarging hemangioma involving her right tonsillar pillar, soft palate, false vocal cord, tongue, and nasopharynx (Fig. 5). Treatment with

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Table 1. SUMMARY OF PATIENTS

No.	Age/Sex/Race	Location of Lesion	Prior Therapy	Indication for Interferon Alpha	Duration	Result
1	4 wks./M/ black	Retroperitoneum, flank	Prednisone Tranexamic acid Blood products	Kasabach-Merritt	9 mos.	Complete regression
2	7 wks./F/black	Face, pharynx, periorbital region	None	Organ (eye) threatening	11 mos.	Partial (50%) regression
3	4 mos./M/white	Perianal, anal canal	None	Bleeding	5 mos.	Complete regression
4	6 mos./M/white	Extremity (circumferential)	Compression	Limb (arm) threatening	6 mos.	95% regression
5	28 mo./F/white	Pharynx, soft palate, false vocal cord	None	Apnea	6 mos.	Stabilization

IFN—α for 6 months resulted in cessation of growth of the lesion (stabilization), but no regression. Mild fever, which was easily controlled with acetaminophen, occurred during therapy. She required a tracheostomy. After the lesion had stabilized, it was ablated with three KTP laser treatments.

RESULTS

Three patients had total or near total regression, one had partial regression, and one had stabilization of the hemangioma in response to IFN—α-2a therapy for a mean of 7.4 months (range 5–11 months). In one patient, severe consumptive coagulopathy (Kasabach-Merritt syndrome) resolved immediately on initiation of IFN therapy. Two patients experienced minor complications of therapy—fever and granulocytopenia—which were reversed easily by acetaminophen or cessation of therapy for 1 week, respectively. All patients have grown and developed normally. There have been no recurrences after a mean follow-up of 9 1/4 months (range 6–18 months) after cessation of therapy.

DISCUSSION

Vascular lesions in infants and children are classified as vascular malformations or hemangiomas. The former are hamartomas composed of mature vascular endothelial cells that do not proliferate or involute, but grow commensurate with the child. They always are present, although not always apparent, at birth.[4] The incidence is equal in boys and girls. The endothelial cell turnover rate is normal. No mast cells are present. Examples of vascular malformations include the port wine stain, salmon patch, arteriovenous malformations, venous malformations, and lymphangiomas.[4] These do not respond to IFN,[4,6,15] and thus, will not be considered further in this report.

Hemangiomas, on the other hand, are neoplasms composed of rapidly proliferating vascular endothelium, pericytes, fibroblasts, and mast cells that grow out of proportion to the child during infancy, stabilize, and then involute in a process characterized by fibrosis and diminished cellularity.[4] There is a tenfold increase in the number of mast cells when compared to the surrounding tissue. This may have significance in considering hemangiomas as an example of an "angiogenic disease"[16,17] because the mast cells may produce an angiogenic factor (perhaps heparin or a heparin fragment) that induces or promotes the formation of new blood vessels.[4,18,19]

Hemangiomas are subclassified into the following three varieties: 1) capillary or "strawberry", involving only the dermis; 2) mixed capillary/cavernous, involving the dermis and subcutaneous tissues; and 3) cavernous, involving the panniculus and deeper structures.[4] The natural history is similar for all three varieties, although the deeper hemangiomas may regress more slowly and may be associated more with complications.[4]

Hemangiomas have a 3:1 to 5:1 female predominance.[4,8] They rarely are present at birth, except perhaps as a small pinpoint lesion, a blanched spot, or a localized telangiectasia.[2,4,8] Shortly after birth, they begin to enlarge rapidly for a period of 6 to 18 months. Then there is a period of slow but inevitable regression for the next 5 to 10 years, at a rate of about 10% per year, such that 50% have regressed by 5 years, 75% by 7 years, and 90% by 10 years.[4,8] Approximately 10% do not resolve completely,[4] and approximately 3% to 5% become extremely large, involve vital organs, or produce life-threatening complications, resulting in a 20% to 50% mortality if not treated aggressively.[3,6,8,12] Complications associated with hemangiomas include ulceration, infection, hemorrhage, Kasabach-Merritt syndrome, disfigurement, occlusion or compression of vital structures or orifices, high-output cardiac failure, infection, and altered drug pharmacology.[2–4,11,15]

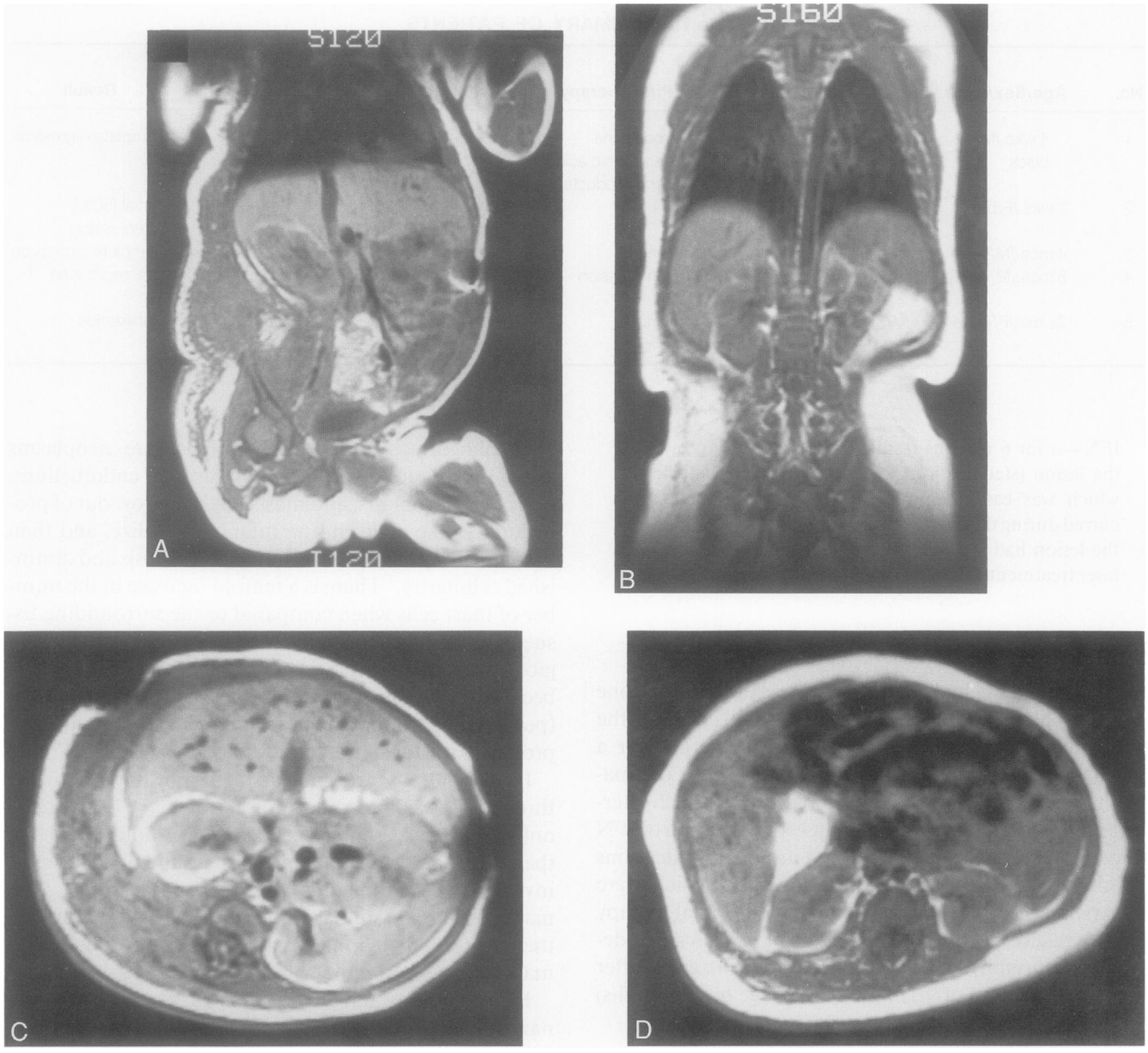

Figure 1. Magnetic resonance imaging of patient 1 showing large retroperitoneal hemangioma with displacement of the right kidney and inferior vena cava upward and to the left. (A) Coronal view, before therapy; (B) coronal view, after therapy; (C) axial view, before therapy; (D) axial view, after therapy.

Kasabach-Merritt syndrome[20] results from platelet trapping within the hemangioma leading to a localized consumptive coagulopathy.[4,10,21] It is characterized by anemia, thrombocytopenia, prolonged prothrombin and partial thromboplastic times, low fibrinogen levels, and elevated levels of fibrin split products.[4] Traditional treatment for this complication included blood product replacement therapy, use of antifibrinolytic agents, high-dose prednisone, compression or embolization, and surgery.[4,10,12,21-23] Even with such aggressive therapy, the mortality rate for Kasabach-Merritt syndrome has been 30% to 40%.[8] Recently, IFN—α has been used successfully to treat this complication of hemangiomas.[8,12,15,24] A favorable response is noted almost immediately,[8,15] although the size of the lesion remains unchanged initially. Our first patient illustrates this phenomenon.

The vast majority of hemangiomas can be treated with reassurance and observation because the natural history is that of spontaneous regression. Although recommended in the past,[1] radiation therapy is no longer used because of the risks of skeletal deformity and malignant potential.[2-4,9]

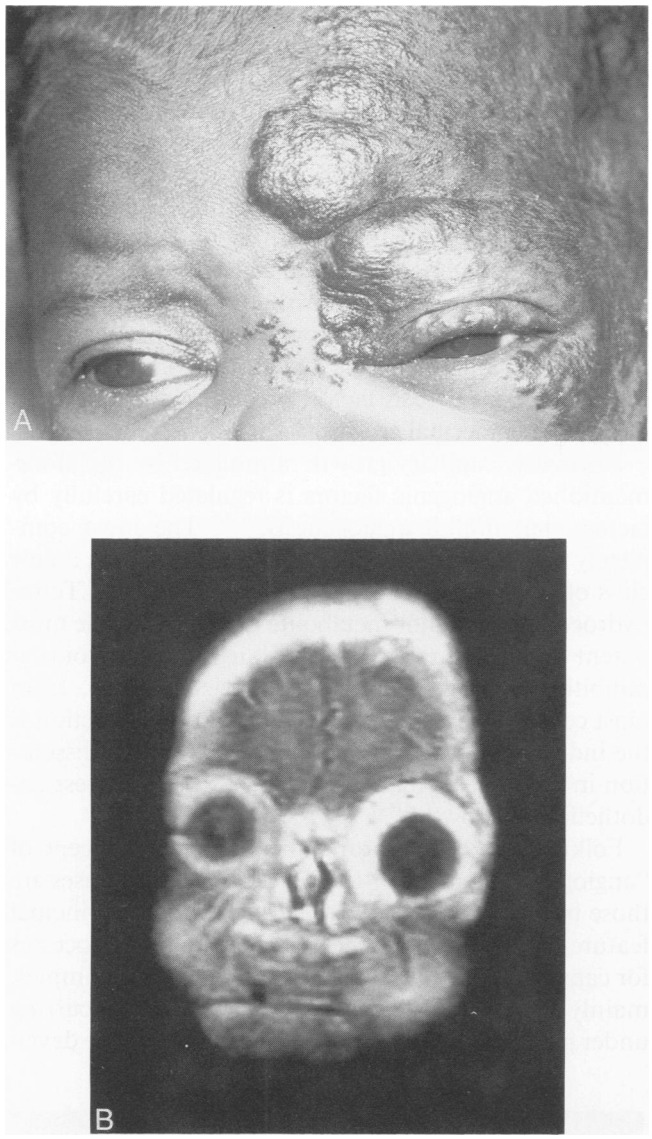

Figure 2. (A) Hemangioma involving the ophthalmic and temporal region of the face of patient 2. (B) Magnetic resonance imaging demonstrating extensive periorbital involvement of the hemangioma.

Treatment with steroids, systemic or intralesional,[25] at a dose from 2 to 10 mg/kg/day, for a period of weeks to months has been recommended for complex or alarming hemangiomas.[2,5,9,10] However, the response rate has been variable, and complications have been common. Weber et al. treated 11 children with prednisone, 3 to 8 mg/kg/day; only 2 (18%) were cured, and there was clear failure of therapy in 4 (36%). Five of the 11 patients (45%) developed hypertension.[3] Enjolras et al. treated 25 children with alarming hemangiomas, none of whom had Kasabach-Merritt syndrome. There was an excellent response to steroids in 30%, no response in 30%, and a slow, doubtful response (e.g., perhaps representing the natural history) in 40%. They found no clinical factors that predicted a response or a lack of response to steroid therapy.[5] The mechanism of action of steroids is unclear. They may increase the vascular sensitivity to circulating vasoconstrictors;[2] the immature vascular tissue of a hemangioma may be sensitive to the anti-anabolic effects of steroids;[9] or the steroids or their breakdown product may function as angiostatic steroids and inhibit angiogenesis by mechanisms yet to be discovered.[17,19]

Surgical therapy (resection or arterial ligation) for hemangiomas may be indicated for obstruction of the visual axis or luminal structures; uncontrolled ulceration, bleeding, infection, or coagulopathy; arteriovenous shunts with heart failure; small lesions in which excision would not lead to a significant cosmetic deformity; or for questionable histology.[3,11] Weber et al. reported a cure in 15 of 16 patients treated surgically (94%), although there were serious associated complications, such as skin loss, wound infection, nerve paralysis, and significant blood loss.[3] Surgery often is performed in stages and only as a last resort when other therapies have failed.[3,7]

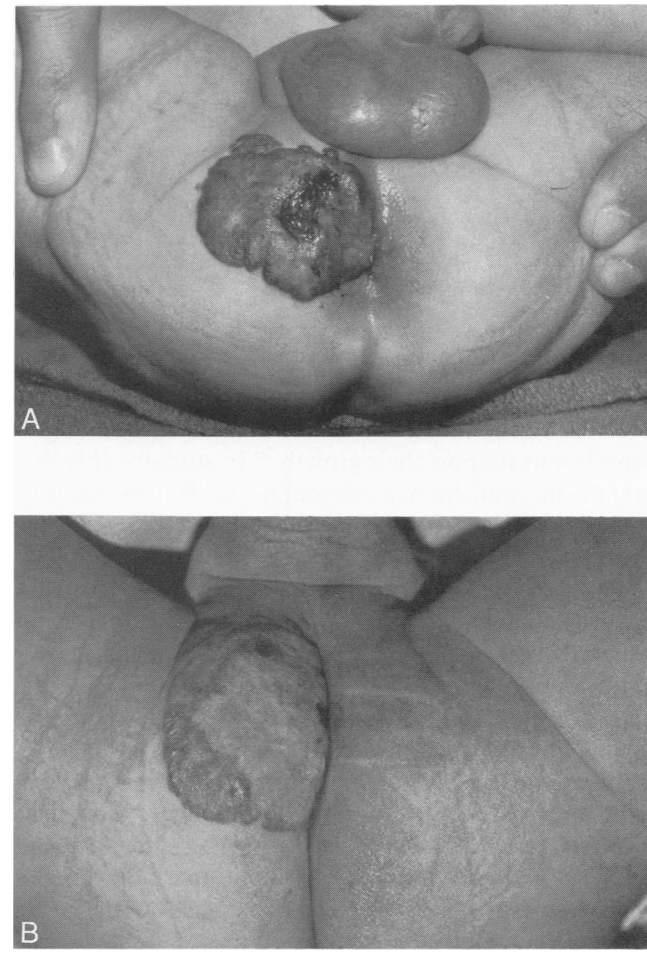

Figure 3. Perianal hemangioma of patient 3. (A) Before therapy; (B) during therapy with IFN—α-2a.

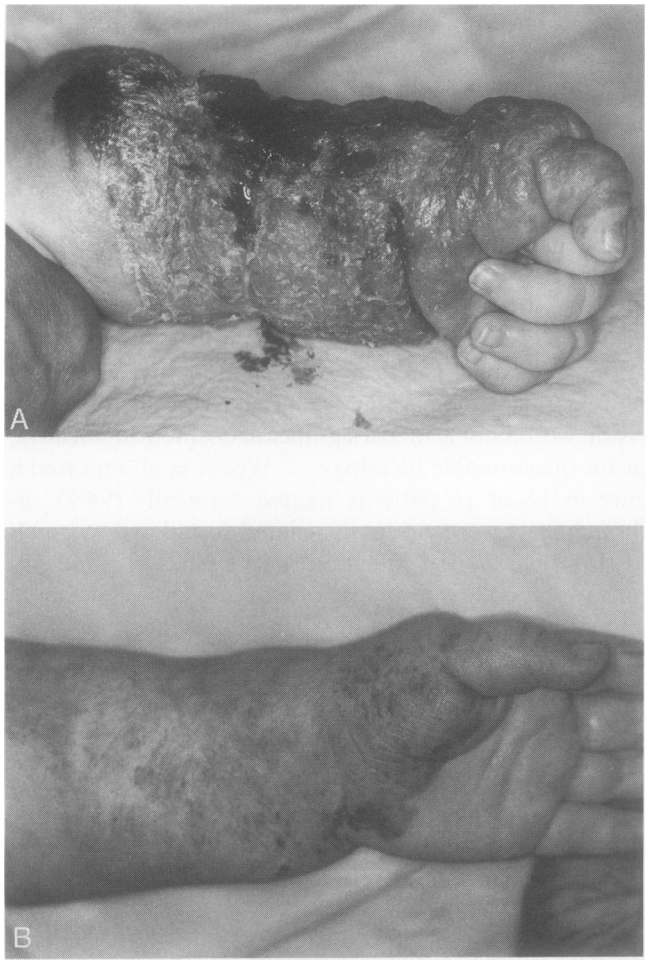

Figure 4. Circumferential hemangioma of arm of patient 4. (A) Before therapy; (B) after completion of therapy with IFN—α-2a.

In 1971, Folkman proposed that the growth of tumors depends on the formation of new blood vessels—angiogenesis—to support their growth.[26] In studying this theory, the mechanism of angiogenesis, the factors that promote angiogenesis, and some factors that inhibit angiogenesis have been found.

The components of angiogenesis include degradation of the basement membrane of the parent venule (from which the new capillary originates), endothelial cell migration, endothelial cell proliferation or multiplication,[16] and endothelial cell differentiation.[4] Several angiogenic factors have been identified, some of which act directly by stimulating migration or proliferation of the endothelial cells. Others act indirectly by mobilizing host cells (such as macrophages) and activating them to release endothelial growth factors.[16,18] To date, the major angiogenic factors studied include basic fibroblast growth factor (FGF), angiogenin, platelet-derived endothelial cell growth factor (PD-ECGF), and transforming growth factors (TGF) α and β.[16–18] Fibroblast growth factor acts directly on the endothelial cell to stimulate proliferation and migration. It is probably the primary angiogenic factor responsible for growth of hemangiomas.[4] The mechanism of action of angiogenin is not known. Platelet-derived-ECGF stimulates proliferation and is chemotactic to endothelial cells. Transforming growth factor-α stimulates endothelial cell proliferation, similar to FGF and PD-ECGF. Transforming growth factor-β is not mitogenic or chemotactic for endothelial cells, but acts indirectly to induce capillary growth by mobilizing macrophages, which then release growth factors, or by mechanisms still unknown.[16,17] Other angiogenic factors include tumor necrosis factor, prostaglandin PGE_1 and PGE_2, and epidermal growth factor.[4,16]

Normally, capillary growth stimulated by the aforementioned angiogenic factors is regulated carefully by factors that inhibit angiogenesis.[16–18] The most completely studied inhibitors of angiogenesis include a new class of compounds called angiostatic steroids.[19] Tetrahydrocortisol, a major metabolite of cortisol, is the most potent of the naturally occurring angiostatic steroids at inhibiting heparin-stimulated angiogenesis (i.e., from mast cells in hemangiomas). Its mechanism of action is the induction of capillary basement membrane dissolution in growing capillaries.[19] Pericytes also suppress endothelial cell growth.[16,17]

Folkman and Klagsbrun introduced the concept of "angiogenic diseases" in 1987.[16] Angiogenic diseases are those in which abnormal capillary growth is a principal feature or those in which the normal regulatory processes for capillary growth fail.[17,18] There are several examples, mainly in women, of excess capillary growth occurring under physiological conditions. These include the devel-

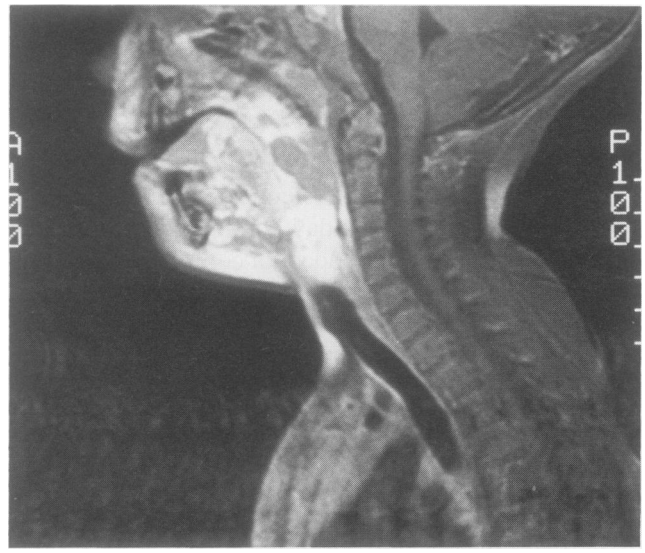

Figure 5. Magnetic resonance imaging of patient 5 showing extensive hemangioma of pharynx, soft palate, and false vocal cord.

opment of the placenta, ovulation, the short time after menstruation, and wound repair in men and women.[18,19] Pathological examples of unabated capillary growth include diabetic retinopathy, retrolental fibroplasia, neovascular glaucoma, psoriasis, and hemangiomas.[17–19] (Interestingly, hemangiomas occur more frequently in women.)

The discovery that IFN could be useful in treating hemangiomas was initiated in 1980 when Brouty-Boye and Zetter reported that IFN inhibited capillary endothelial cell migration *in vitro*.[27] In 1987, Friesel et al. reported that IFN-τ inhibited endothelial cell proliferation *in vitro*.[28] Sidkey and Borden, also in 1987, reported that IFN inhibited tumor-induced angiogenesis *in vivo* in a murine model.[29] In 1989, two independent investigators obtained regression of life-threatening hemangiomas in children with the use of IFN.[12,13] In the first report, White et al. obtained regression of pulmonary hemangiomatosis in a 12-year-old boy treated with IFN—α-2a. The patient's exertional dyspnea and clubbing resolved and the pulmonary function tests and pulmonary angiogram normalized.[13] In that same year, Orchard et al. reported dramatic response to IFN—α-2b in two infants, one with uncontrollable Kasabach-Merritt syndrome and one with a large facial hemangioma.[12] In 1990, a clinical trial for the treatment of life- or sight-threatening hemangiomas with IFN—α-2a was initiated at the Boston Children's Hospital. Ezekowitz et al. reported their results in 1992.[8] There were 20 patients (16 girls, 4 boys), 3 weeks to 2 years of age, entered into the trial. Four had Kasabach-Merritt syndrome; ten had head, neck, or airway lesions; three had periorbital lesions; and three had lesions in other locations. Overall, there was a 50% or more regression of the hemangioma within 7.8 months of therapy in 18 of 20 patients; there was one death from Kasabach-Merritt syndrome.

The mechanism of action of IFN is not understood fully. Interferon does inhibit endothelial cell migration and proliferation *in vitro* and angiogenesis *in vivo*,[27–29] and thus, acts directly as an angiogenesis inhibitor.[17] It also may act indirectly by inhibiting the angiogenic stimulus itself; by inhibiting the effects of specific growth factors on the proliferation of endothelial cells, smooth muscle cells, or fibroblasts; by decreasing the production of collagen; or by enhancing the production or release of endothelial cell prostacyclin.[6,14,18] Interferon may have its beneficial effects in the Kasabach-Merritt syndrome by decreasing platelet adherence and trapping by the endothelial cell surface.[6]

Side effects of short-term IFN therapy (6–12 months) include mild fever, malaise, leukopenia, and elevation of liver transaminases. An occasional patient with a massive hemangioma may experience transient hemodynamic changes when IFN therapy is initiated. These side effects are reversible by stopping therapy for a short period.[18,30] Long-term therapy can be associated with acute interstitial nephritis with nephrotic syndrome and several autoimmune diseases such as systemic lupus erythematosus, autoimmune hemolytic anemia, thyroiditis, and thyrotoxicosis.[31]

From the results of recent studies and from the results noted in our patients, IFN—α-2a seems to be indicated for the treatment of hemangiomas in patients with life-or sight-threatening lesions; in those with life-threatening complications, especially the Kasabach-Merritt syndrome; or in those with major disfigurement or disability or in which there is a threat of amputation. The side effects of IFN therapy (fever, leukopenia, elevated liver enzymes) are few, mild, and reversible in the recommended dosage of 3 million units/m^2/day. Growth of the child is not decreased; in fact, it may be improved by the avoidance of high-dose steroids.[6] Because the benefits of therapy far outweigh the complications, and because of the dramatic response seen in our patients and in those reported in the literature, we would recommend that IFN—α-2a be considered as the first-line agent in the treatment of complex hemangiomas of infants and children.

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Discussion

DR. BRADLEY M. RODGERS (Charlottesville, Virginia): This is a very important paper, I think. Clearly, the use of interferon is going to introduce a new era in treatment of hemangiomas, at least, interferon or similar type substances. There are many members of this society who have given us significant information about the pathophysiology about hemangiomas, and I remember well my first Southern meeting in 1975, here at the Homestead. Dr. Edgerton presented his vast experience with hemangiomas and pointed out the very dramatic response of many of these lesions to steroids. I think we are now into a new era of treatment. Everybody that's dealt with these tumors understands that they are capricious in their nature, and it's hard with any small group of hemangiomas to really know whether the drug that you're giving or the intervention that you are providing is having a significant impact on the pathophysiology. Obviously, it's going to take a large number of patients before most of us are absolutely convinced of the dramatic effects of alpha interferon. And, yet, those that are using it are clearly impressed. And I think some of the cases that Rick showed today are fairly dramatic in the effect of this drug on these tumors. I have three questions I'd like to address to Rick. One is the question of dosage. Most people have centered on the dosage of 3 million units per m^2 per day as a single dose, and I wonder if you could give us some insight as to how that dose was arrived at, and is it possible to increase that dose? Some of your lesions, for instance, and others have shown only partial regression. And if 3 million is good, is 6 million better in those patients? The other question is how long to give this drug. Your patients received the drug for 6 to 9 months. Others have chosen 11 to 14 months. Is there any indicator as to when you should stop the drug, and can it be started again if the lesion tends to increase in size after stopping it? There seem to be few complications of the medication, but can you talk about some of the more severe complications and how you handle those in these patients? The next question relates to the selection of patients. You have been careful to point out that this medication only works in those patients with diseases of angiogenesis, and sometimes, it's a little hard to define, to differentiate between lymphangiomas and hemangiomas. But the other question is the age of the patients. Can alpha interferon have a significant effect on some of the older patients that many of us have in our practice with relatively established and quiescent and yet very deforming hemangiomas? And in that respect, is it significant that your 2½-year-old child showed only a stoppage of the progression, if you will, not really a resolution of the tumor? Does it work less successfully in the older patients compared to the very young patients? The last question I had is what's the real effect of this drug? It has to be more than just inhibition of angiogenesis. And you pointed out in your discussion the very rapid effect on platelet trapping that's seen with this medication. That's clearly not an angiogenesis effect. The thing that impressed me about your first case is that you started with a very bulky hemangioma and within a period of several months ended up with virtually nothing. This is different from the usual involution or natural involution of these hemangiomas that end up with a piece of fibrous tissue or relatively a cellular tissue. In this case you end up with nothing. How does this work? This is not just stopping capillary proliferation. Somehow there must be more going on. The last thing I'd ask is if you would speculate as to where we're going to go with this. This is obviously just the tip of the iceberg. And the informa-