abach-Merritt syndrome with prednisone and epsilon-aminocaproic acid. Ped Hematol Oncol 1991; 8:329–334.
11. Ricketts RR, Stryker S, Raffensperger JG. Ventral fasciotomy in the management of hepatic hemangioendothelioma. J Pediatr Surg 1982; 17:187–188.
12. Orchard PJ, Smith, CM III, Woods WG, et al. Treatment of haemangioendotheliomas with alpha interferon. Lancet 1989; 2: 565–567.
13. White CW, Sondheimer HM, Crouch EC, et al. Treatment of pulmonary hemangiomatosis with recombinant interferon alpha-2a. N Engl J Med 1989; 320:1197–1200.
14. Spiller JC, Sharma V, Woods GM, et al. Diffuse neonatal hemangiomatosis treated successfully with interferon alpha-2a. J Am Acad Dermatol 1992; 27:102–104.
15. Hatley RM, Sabio H, Howell CG, et al. Successful management of an infant with a giant hemangioma of the retroperitoneum and Kasabach-Merritt Syndrome with alpha-interferon. J Pediatr Surg 1993; 28:1356–1359.
16. Folkman J, Klagsbrun M. Angiogenic factors. Science 1987; 235: 442–447.
17. Folkman J. Successful treatment of an angiogenic disease. N Engl J Med 1989; 320:1211–1212.
18. White CW. Treatment of hemangiomatosis with recombinant interferon alpha. Sem Hematol 1990; 27:15–22.
19. Folkman J, Ingber DE. Angiostatic steroids: method of discovery and mechanism of action. Ann Surg 1987; 206:374–383.
20. Kasabach HH, Merritt KK. Capillary hemangioma with extensive purpura: report of a case. Am J Dis Child 1940; 59:1063–1070.
21. Stahl RL, Henderson M, Hooks MA, et al. Therapy of the Kasabach-Merritt syndrome with cryoprecipitate plus intra-arterial thrombin and aminocaproic acid. Am J Hematol 1991; 36:272–274.
22. Sato Y, Frey EE, Wicklund B, et al. Embolization therapy in the management of infantile hemangioma with Kasabach-Merritt syndrome. Pediatr Radiol 1987; 17:503–504.
23. Ozsoylu S, Irken G, Gurgey A. High dose intravenous methylprednisolone for Kasabach-Merritt Syndrome. Eur J Pediatr 1989; 148: 403–405.
24. Ezekowitz A, Mulliken J, Folkman J. Interferon alpha therapy of haemangiomas in newborns and infants. Br J Haematol 1991; 79 (suppl 1):67–68.
25. Sloan GM, Reinisch JF, Nichter LS, et al. Intralesional corticosteroid therapy for infantile hemangiomas. Plast Reconstr Surg 1989; 83:459–466.
26. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med 1971; 285:1182–1186.
27. Brouty-Boyé D, Zetter BR. Inhibition of cell motility by interferon. Science 1980; 208:516–518.
28. Friesel R, Komoriya A, Maciag T. Inhibition of endothelial cell proliferation by gamma-interferon. J Cell Biol 1987; 104:689–696.
29. Sidky YA, Borden EC. Inhibition of angiogenesis by interferons: effects on tumor-and lymphocyte-induced vascular responses. Cancer Res 1987; 47:5155–5161.
30. Baron S, Tyring SK, Fleischmann, WR Jr, et al. The interferons: mechanisms of action and clinical applications. JAMA 1991; 266: 1375–1383.
31. Tolaymat A, Leventhal B, Sakarcan A, et al. Systemic lupus erythematosus in a child receiving long-term interferon therapy. J Pediatr 1992; 120:429–432.

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-

tion and the medications, if you will, that are coming from Judah Folkman's lab almost on a monthly basis are really quite exciting. The implications of these findings for treatment of all kinds of disorders, particularly neoplasms, are very exciting. But where will we go with hemangioma? Alpha interferon is the first of what will probably be several agents. And do you know of anything else on the horizon?

DR. H. BIEMANN OTHERSON, JR. (Charleston, South Carolina): I think Dr. Ricketts and his co-authors were wise in pooling their cases, because no one institution has any real number of these patients. We've had two, and I think a number of other places have had similar amounts of these very challenging patients. Hopefully, there will be a national registry and a protocol that we can use to gain some meaningful statistics. We've used it on two patients. One of them with an hepatic hemangiomatoses as an infant, and the second one had hemangioendothelioma, which was surrounding the trachea, extended up into the neck and down into the chest. In contrast to what Dr. Ricketts reported in his manuscript where he had a fairly rapid response, we noticed a very slow response to the interferon. In fact, the hepatic hemangiomatosis patient went into cardiac failure and was put on a ventilator. Finally, the patient got better. The other patient had a laminectomy, for invasion of the spinal cord with this tumor. So all of this brings me to my question. And that is, with such a slow response and with the fact that these tumors will undergo spontaneous involution anyway in a period of 8 to 12 to 9 to 15 months or so, how can you separate the therapeutic response to this very slow-acting drug from spontaneous involution?

DR. BENJAMIN F. RUSH (Newark, New Jersey): When I was in Lexington in the 1960s, we ran into a couple of patients with huge hemangiomas and published a little tract on the treatment of these with 5Fu given intra-arterially, which worked pretty well. The problem is, that many of these lesions don't have a single arterial source. In addition, 5-FU given intra-arterially can have some pretty morbid results. So the technique never spread very widely. That paper came out about 1965. I was just talking to Alex Haller during the break, and I recall that he had his name on a paper which did spread the word that prednisone or cortisone would help these lesions. He reminded me that it was Dr. Avery, of their pediatric department who was the senior author on that paper but did confess to having been a participant. I've lost track of what had happened to the treatment of these lesions, since I don't treat them myself any longer. The rationale for angiogenesis which has just been expressed this morning was very interesting.

However, the original concept was that there was a retention of multi-potential primitive mesenchymal tissue that was involved in this. And I suspect that may still be true. In other words, simply having angiogenic factors expressed doesn't explain why a lesion happens in one particular place. So I presume that this must be because of some previous deposited tissue which has the potential of expressing itself. I have to agree with Dr. Otherson that the time range in which many of these lesions are recovering is actually the time period over which many of us have seen lesions of similar size regress spontaneously. Perhaps a prospective study comparing this technique with steroids and no treatment would be worthwhile.

DR. RICHARD R. RICKETTS (Closing Discussion): I will try to answer your questions to the best of my ability, although the actual mechanism of how interferon works in these lesions is not totally understood at this point. As far as the dosage, whether it would be safe to increase the dosage or not, there has been reported complications with high dosage of this drug, such as sloughing and such as initiation of cardiovascular compromise in some of these patients. Long-term dosage can result in complicated problems such as SLE, nephritis and hemolytic anemias. So that therapy probably ought to be limited to a good response of, say, 50% reduction of the lesion or more. In our particular patients we gave the drug for a mean of about 6 months, and by that time, most of the lesions had regressed quite dramatically. As far as selection with respect to age, it does seem, in our patients and in the others reported, that the younger patients do respond better. But, of course, the first patient that was ever tried on this drug was a 12-year-old, and he did respond. I think it would be something that you could try to use in older patients, but I wouldn't expect the dramatic response that the infants show. As far as the effect of the drug itself, as I said, the mechanism of action is not totally understood. It does seem to increase prostacycline release. It seems that this drug dramatically reverses Kasabach-Merritt syndrome; whereas, it takes a much longer time for the lesion to regress. As far as speculating on the future, this drug is not yet FDA approved for this use, and, hopefully, with studies like this and other ones, it will become approved in the future. It is a weak anti-angiogenic agent in comparison to some of the others that Dr. Folkman has studied, and it probably is not going to have any applicability to tumor angiogenesis. Dr. Otherson, yes, these are difficult patients. I'm going to refer them all to you since yours seem to be even worse than the ones we've had. We use this drug only in patients where other therapy has failed or that we would expect complications from the other therapy to be more than those associated with alpha interferon. There is and has been no prospective study comparing this drug with steroids or any other method of therapy. In some of these patients it would be hard to randomize them to receive alpha interferon versus steroids, particularly those with the Kasabach-Merritt syndrome because of such dramatic response that has been reported by all people who have used this drug for hemangiomas. In a study on steroids for very large and so-called alarming hemangiomas, one author found that there was a definite positive response rate of 30%, a definite negative response rate of 30%, and about 40% of the patients they couldn't really tell whether the steroids made any difference or not, or whether this was the natural history of the disease. And I guess that same thing can be said for alpha interferon. Perhaps the regression does occur over a time period corresponding to the

natural history of the lesion, although the response the does seem to be so dramatic that it's hard to believe that natural history alone accounts for it. Dr. Rush, I appreciate your comments with respect to the national study and the Boston study. All of those patients in the Boston study had received prednisone and had failed that therapy before they were put on alpha interferon, and then they had a response. So although it wasn't a controlled study, they did use conservative therapy first.