ORIGINAL ARTICLES

From the American Venous Forum

Presidential address to the 1998 American Venous Forum: Where are we now? Where are we going? Inching forward

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One of the primary goals of the American Venous Forum is education. The forum should bring the latest information in the field to the medical community interested in acute and chronic venous disease. The success of this effort is best measured by the scientific content of the annual meetings and the dissemination of information that follows. Is this effort successful? Does the educational effort achieve its goal of improving the care of patients and health care delivery? Does the information reach the right audience? These are important questions. Although no one argues about the mission, I am, at times, uncertain about the forum's effectiveness in changing the way we think and how we carry out our business. Those of us in academic life are fortunate to be challenged every day of our lives by students, residents, and fellows. However, even here one senses considerable resistance to change. Habits are very difficult to break, and new concepts are often difficult to accept.

EDUCATIONAL FAILURE

Where have we failed? I mean this in a collective sense, because it is not just the members of this organization or other organizations who are fully responsible for our lack of progress in key areas. There is little doubt that a failure to detect a problem that costs a life represents the worst possible outcome. One only need look at our society to determine how such failures are handled at the present time. The death of even one patient from something that could have been prevented is taken very seriously. In the case of acute deep vein thrombosis (DVT), we have collectively failed to correct a concept that has cost untold lives. This relates to the use of Homans' sign as a screening test in patients suspected of having DVT. Since the publication by Haeger, it has been well accepted that the bedside diagnosis of acute DVT is very imprecise.[1] It is well known that Homans' sign is worthless, and indeed dangerous, yet, for reasons that are mysterious to me, every medical student, resident, fellow, and physician in the entire world appears to know about this sign and roughly how to use it at the bedside. It continues to be used even today. Can it be stamped out?

What did Homans have to do with this physical finding? In 1944, in a medical progress review in the *New England Journal of Medicine*, he reviewed the diagnostic aspect of DVT in some depth.[2] It is a bit ironic that he was aware of the seminal work on venography by Gunnar Bauer, but dismissed the method as being "rather untrustworthy."[3] Homans notes in his review that the dorsiflexion sign (as he described it) was positive in 42% of patients with acute DVT. However, because he did not use venography, the diagnoses had to be made on clinical grounds alone. He noted that the use of his name to identify this sign was not popularized by him, but by Allen and his associates, who in 1943 wrote, "Homans' sign is a term used in our clinic."[4] Dr. John Homans himself preferred to refer to it as the "dorsiflexion sign."[2] It is interesting to speculate what might have happened if the test had not had his name attached. Why his name remains so

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much a part of a physician's vocabulary will remain a mystery, but we all must continue to decry the test's application.

When I was asked to contribute the chapter on peripheral vascular disease in Harrison's *Principles of Internal Medicine*, I left the term "Homans' sign" out. I refused to perpetuate its use or even its mention. It is a pity that Homans' name was attached to such a worthless finding, because he made so many contributions to our knowledge in this field.

EDUCATIONAL SUCCESS

Although Homans' sign continues to be used widely, the recognition that something else is needed is appreciated by all who work in acute venous disease. It is clear that a major success story in my lifetime is the insistence on using objective testing to make the diagnosis of acute DVT. Credit has to be given to Gunnar Bauer, who in 1940 really defined the role of venography and how it should be used.[3] Yet, as noted above, American surgeons were slow to accept this test as being definitive. It is ironic that in 1957 Bauer himself stated that it was no longer necessary to use venography if one would simply pay attention to the physical findings. He said, "I may seem to have dwelt unduly long on a description of these symptoms, but I am firmly convinced that if a combination of several or many of the general and local signs are recorded, one can be reasonably certain that early thrombosis is present; it is no longer necessary to rely on phlebography to establish the diagnosis. This method was of great value as long as the whole problem was still in the course of investigation, but it is quite superfluous nowadays. The diagnosis can be made by means of routine clinical methods."[5] This is, of course, not true, and none of us would now use clinical symptoms and signs as the gold standard.

Although Bauer no longer thought that the test he popularized was needed, venography did become the gold standard here and abroad. However, it was beset by problems, not the least of which was the discomfort it produced. With injections into veins on the dorsum of the foot, the iliac veins were not seen well in 20% of cases, and the deep femoral vein was seen only 50% of the time. In addition, the myriad of veins in the calf presented problems, even for the experienced. It was common to use a stereo viewer in an attempt to unravel what was and wasn't there. In addition, this examination was one that many radiologists were not comfortable doing. However, the method was used extensively as the final arbiter in the diagnosis and localization of venous thrombi from the level of the calf to the iliac veins.

My own interest in diagnostic methods goes back to 1968, when we first started applying continuous wave Doppler to the study of the venous system and comparing it with venography.[6] In experienced hands, this worked well for the major deep veins, but it was indirect and subjective, with the diagnosis depending on a single observer. Plethysmography came along at about the same time and quickly proved to be useful for screening purposes.[7-10] It—particularly the impedance method—became widely used throughout the world, until ultrasonic duplex scanning began to be applied to this area.[11,12] Very quickly, both venography and the indirect methods largely disappeared from the scene. The indirect tests established the diagnosis based on physiologic changes, not anatomic findings. This is in contrast to venography, which demonstrated the exact sites of occlusion. Interestingly, the method most widely tested against venography was the impedance testing method. In fact, it was clear that a positive/negative test could reliably determine for the physician which form of therapy should be carried out. The test was insensitive to calf vein thrombosis, but this did not appear to be relevant in the subsequent development of pulmonary embolism if the test was negative. It is safe to say that the calf veins were totally ignored in this phase of study of the venous system. It was concluded, perhaps inconclusively so, that the calf veins are not important as contributors to the overall spectrum of pulmonary embolism. However, this remains an open question, and it is likely that more information will become available in the next few years to settle this issue.

The availability and application of ultrasonic duplex scanning changed the entire landscape, because we now had a noninvasive imaging and Doppler method that could be used from the level of the calf to the iliac veins and inferior vena cava. Duplex scanning was initially applied only to the carotid artery, but, with improvements in the technology, all the major veins of the upper and lower extremities became available for study. The earliest systems were "black and white," which somewhat limited their application, particularly to the veins of the calf. However, with the availability of color, this has changed. The use of color not only speeds up the examination, but also makes vessel identification quicker and more certain. Very quickly, venography disappeared from the scene, with its use becoming almost of historical interest only. Scanning has had an enormous impact on clinical practice, but it has created another set of problems. For example, because the method is simple, noninvasive, and

quick to perform, it is overused. At our institution, the positive yield is in the range of 10% only. Is this too low? Given the vagaries of the history and physical examination and the consequences of making the wrong diagnosis, I would have to say no. I see no readily available alternatives at the moment. There is ongoing interest in the use of a screening blood test, such as D-dimer, but this has not proven to be a suitable screening test in limiting the need for imaging. However, with time and more experience, one can predict that this is likely to occur. Even given the low positive rate, I doubt seriously that anyone would want us to return to the bedside diagnosis or venography as the alternative. I have no answer to this dilemma, but I am pleased that physicians are, for the first time, taking full advantage of a new technology to make a correct diagnosis and institute proper therapy. Our patients have benefitted immensely from this practice. Perhaps the availability of a very sensitive and specific blood test that can be done and reported within a few hours may limit the number of negative scans that are reported.

RESEARCH

During my professional career, physicians have constantly referred to Virchow's triad when trying to explain the basis for the development of DVT. In its simplest terms, it provides the broad definition of what is needed for thrombosis to occur.[13] The 3 major parts are stasis, intimal injury, and hypercoagulability. These intuitively make a lot of sense, but when we attempt to define in quantitative terms each element of the triad, we get into trouble. Let's deal with each of these elements and elaborate on the problems involved.

Stasis. I have never met a physician who did not appear to have an intuitive understanding of what stasis means. However, when asked to explain or quantify what is meant by this word, they get into trouble. Slowing of blood flow is what stasis means, but how, when, and where? One needs to look at the sites where thrombi occur to come to grips with this concept. From studies with I-125 labeled fibrinogen, it is known that the origins of thrombi appear to be most commonly in the sinuses of the soleus muscle and the sinuses of the venous valves.[14] If one lies quietly and examines the residence time of contrast agents, it appears that the dye does tend to linger longer here than at other sites. This would appear to confirm the thesis that stasis must play some role, and the thesis is further suggested by the relationship between the development of DVT and the "quiet" patient on the operating table or the somnolent patient on a long-distance flight. However, there are still no quantifiable data on how long this residence time must be for the process to become initiated in conjunction with activation of the coagulation cascade.

Intimal injury. Because we know that healthy endothelium does not support or encourage the development of thrombi, something must take place at this level to promote the development of thrombosis. Short of direct trauma to the vein wall with frank intimal disruption, it has been very difficult to identify problems with the endothelium that help initiate this process. We don't have methods available to study the endothelium directly. In addition, we don't have access to the area before or at the time of the thrombosis to assess what transpired. One intriguing experimental finding was that of Stewart, who demonstrated the separation of the intercellular connections permitting the attraction of leukocytes to the area and the beginning of thrombosis.[15] Interestingly, this would occur in response to injury at a site remote from where the thrombosis occurred. Does this answer the second dilemma with regard to Virchow's triad?

Hypercoagulability. It is obvious that when DVT occurs it is rarely a systemic phenomenon, but is usually confined to a specific venous segment. However, with the recent emphasis on the role of genetic factors along with identifiable markers, we have for the first time culprits to which we can attribute at least some of the cases that we see clinically. However, this is obviously not a major contributor, as evidenced by the large number of people with the disorder who never develop DVT and the much larger number of people who will have only 1 episode in their lifetime associated with the situations commonly recognized as playing a role. For example, the recurrence rate for DVT in patients with established disease is in the range of 10%, and this is most often associated with a traumatic event that was often minor.

THE ROLE OF INFLAMMATION

Traditionally, the process associated with DVT has been referred to as thrombophlebitis. In clinical practice, this would appear to be a misnomer, because the only form of venous thrombosis that has the classical clinical features of inflammation involves the superficial veins. I don't believe there is an association or similarity between involvement of the superficial and deep venous system. In fact, inflammation that produces the classical clinical signs of

infection is unusual when the deep venous system is involved. This is why many investigators, including myself, prefer the term thrombosis without the attached qualifier.

However, Wakefield and his colleagues have provided us with some interesting insights and clues as to the role of an inflammatory response in the pathogenesis of DVT.[16] The views expressed by these authors can be summarized to some degree by the stages in this process described by Stewart[15] and can be summarized as follows:

1. Thrombosis that is the major stimulus for inflammation occurs at sites of cellular separation.
2. Continued activation of the platelets and neutrophils at the site of the thrombosis will generate procoagulant and inflammatory mediators that further amplify the initial process.
3. In the third stage, coagulation proceeds more rapidly, and the thrombus grows in size.
4. Continued layering of white cells and platelets occurs as the thrombus enlarges.

In this consideration of events, there are complex factors at each stage that either promote the process or halt it in its tracks. As noted by Wakefield, an inflammatory response might well down-regulate thrombomodulin and increase C4b binding protein, decreasing the free protein S availability for protein C cofactor activity, and thus diminishing its ability to act as an effective natural anticoagulant.[16] Most of us working in this field have downplayed the role of inflammation in the development of DVT. However, based on the work of Wakefield, we may have to rethink this process, because his early data using MRI suggests that it may be important at the clinical level as well. If inflammation with infiltration of the venous wall does occur, it leads to another critically important question, which is, what is the relationship of inflammation to the long-term damage to the wall and the venous valves? It is well known that there are 2 processes that lead to the long-term sequelae of the post-thrombotic syndrome, which is chronic venous obstruction either alone or in combination with loss of venous valve function.[17-19] The 2 competing processes that are going on simultaneously when DVT occurs are continued thrombosis and lysis. It appears that the long-term outcome will depend on which of these 2 processes is dominant. In addition, we have shown that inadequate levels of anticoagulation are common both during the acute and chronic phase of therapy. When this occurs, ongoing thrombosis can occur, leading to further venous damage. These studies further emphasize the need for better and more controllable levels of anticoagulation.

INTRINSIC THROMBOLYSIS

If the studies done in our laboratory are correct, the outcome after an episode of DVT can be explained in large part by the extent to which spontaneous thrombolysis occurs and by its relationship to the preservation of patency and valve function.[18,19] It should have been suspected before the readily available imaging techniques were developed that this had to be occurring. In 1981, Browse recognized that there was very little relationship between the extent of the thrombosis at the time of its detection and long-term outcome.[20] Our long-term study published in 1983, which used indirect testing, showed that up to 40% of patients with an episode of DVT would never have a complaint in the long-term.[21] This could have only 1 of 2 possible explanations. The first is that chronic venous obstruction and the lack of sufficient collaterals could explain who developed the post-thrombotic syndrome. Likewise, if a patient was totally symptom-free, this might be explained by the more efficient collateral development. Another explanation that seems more plausible now is that spontaneous thrombolysis can occur and be most effective in restoring venous patency and preserving valve function. This has been suggested by some of our data taken during long-term follow-up studies.

If thrombolysis is important, can we identify who will benefit from it and who will not? This problem is being addressed by Northeast et al[22] and others, and it is, in my view, one of the more exciting areas for research in the next several years.

THERAPY

It would appear from the programs of this society that we are just interested in the wrecks that follow the acute process. This is, in my view, a terrible mistake, because I believe strongly that we must play a role in defining the role of therapy during the acute phase and its effect on long-term venous function. How then can we contribute? Many members of this society have been pioneers in the study of venous function and physiology, defining how and why patients with DVT get into trouble. How is this understood by our colleagues interested in thrombosis and "thromboembolism"? I think this can be summarized by the response of Levine to a letter I submitted to the *New England Journal of Medicine* having to do with the use of low-molecular weight heparin for outpatient therapy for DVT.[23] I was concerned that failure to consider suitable candidates for catheter-directed thrombolysis might prevent some patients from benefitting from therapy that might

result in preservation of the lumen and valve function. Levine's response to my letter was[23,24]: "The most clinically relevant outcome measures—recurrent deep-vein thrombosis, pulmonary embolism, and bleeding—were used in the trial. The extent of recanalization, the status of the venous valves, or the extent of residual venous obstruction may be of physiologic interest, but they are not important clinical outcomes."

This is, to me, an unbelievable response in 1997. How could Levine not understand that the changes that are observed in the deep venous system are critical to outcome? I believe this is caused by another problem that those of us who work in this field must come to recognize. It is very important for us to publish some of our best work in high quality nonsurgical journals. It is very clear that we read their literature more often then they do ours. In fact, I would be surprised if even the best of the surgical journals are read by our nonsurgical colleagues. I believe this is a real problem.

TREATMENT ALGORITHMS

Deep vein thrombosis is one entity that is treated by nearly all specialties in medicine. This is because, until the present time, the treatment has appeared to be standard, with very little confusion as to how it should be done. The protocol was straightforward, with the giving of heparin followed by Coumadin for a period of 6 months. The only significant change in this approach was the adoption of the International Reference Standard (INR) as a better method of standardizing and controlling the level of Coumadin therapy.

However, several things have begun to occur that are changing our approach to the problem. The first is the recognition that conventional therapy may be inadequate given the high recurrence rate and the appearance of low-molecular weight heparin. These new heparin preparations have the promise of making the early phase of anticoagulation more certain and predictable in outcome. In addition, the promise that therapy can now be done on an outpatient basis is particularly significant. In addition, the duration of anticoagulation therapy is open to question as well.

How can we, as a group, affect therapy both in the acute and chronic phase? The first and most obvious way is to promote good educational efforts for our colleagues, who look to us for direction. This can be accomplished through workshops and tutorials, and, most importantly, with the promotion of good clinical trials looking at outcome. These can be randomized trials or vigorously controlled case-control studies.

We must also be able to promote the study of newer forms of therapy, whether they are surgical or nonsurgical. For example, continued work on venous valve surgery, the perfection of the technique, and the development of the "perfect" valve must be continued. Similarly, the resurrection of the perforator interruption methods must proceed to determine if this new approach will produce lasting benefit without the high incidence of wound breakdown.

PREVENTION

Although one might think that all the work that needs to be done *is* done, this is not the case. We have new drugs, such as the low-molecular weight heparins, that are going to play an important role, and we should participate in their evaluation.[25,26] However, unless *we* undertake an evaluation of their effects on the deep veins and their valves, it will not be done. Likewise, the role of compression therapy by either stockings alone or pneumatic devices continues to excite a lot of interest from both a clinical and research standpoint.

LYMPHEDEMA

Perhaps one of the most perplexing and difficult problems seen is lymphedema, which can occur from a variety of causes. This entity is frequently confused with the edema seen in chronic venous insufficiency, although the distinction is rather simple from a clinical standpoint. The greatest challenge is in its therapy, which most physicians know very little about. It is not simply a matter of giving a diuretic and prescribing elastic support hose. More hospitals are developing lymphedema centers that are attracting large numbers of patients who simply do not have a home. The management of lymphedema is complex and life-long, and it is critical if the patients are to lead a relatively healthy life. We should begin dialogue among ourselves about this interesting area of circulation.

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