This ancient Chinese teaching would surely dampen the hubris of any clinician who has just made a difficult, serious diagnosis. But it is no time for complacency, as illustrated by deep venous thrombosis (DVT), “a wolf in sheep’s clothing.”\(^1\) Even without its insidious complication, the post-thrombotic syndrome (PTS). Despite enormous advances in recent years in the diagnosis and treatment of DVT,\(^2\) much less progress has been made in the understanding and management of PTS. Some of this shortfall stems from variations in PTS case definition, especially in earlier studies. Estimates of the incidence and prevalence of PTS have accordingly spanned a wide range. In the preheparin era, Bauer\(^3\) documented a relentless deterioration of patients with DVT, 80% of whom eventually acquired ulceration, \textit{i.e.}, severe PTS, 15 years after their initial thrombosis. Even in studies over the past 20 years, the prevalence of PTS ranged from 21 to 88%\(^4–6\) depending on the basis for diagnosis, the presence of underlying medical conditions, and the treatment employed. Recently, more uniform, reproducible classifications like that of Villalta et al\(^7\) lent more order to this area of investigation. That scale scores five symptoms (pain, cramping, limb heaviness, pruritus, paresthesias) and six signs (edema, induration, pigmentation, venous ectasia, redness, calf tenderness). By grading each element from 0 to 3 in severity, a combined score is developed. Even here, the categories of mild/moderate (score of 5 to 14) vs severe (\(\geq 15\), or stasis ulceration) create a somewhat awkward delineation. Use of the scale of Villalta et al\(^7\) has yet to be reported as a means of monitoring patients after DVT. Nor are there validated physiologic measures to predict which patients are destined to acquire PTS. Though limited by the lack of “gold standard” criteria for diagnosis, physicians in 2003 can give patients with DVT a global estimate that even with optimal therapy, approximately one third of them go on to acquire PTS.\(^4–6\) Could such somber information lead patients to follow treatment advice more fully? Does it spur us clinicians to do a better job in following guidelines for primary prevention of DVT?\(^8\)

Progress in preventing PTS is hindered by the lack of current attention to the syndrome in some quarters. It is barely mentioned in major textbooks of cardiovascular medicine.\(^9–12\) It was addressed briefly in an update of long-term treatment of venous thromboembolism.\(^13\) A Cochrane review\(^14\) comparing home vs inpatient treatment of DVT found that none of the trials considered the incidence of PTS. Nor has PTS been analyzed as a late result, after studies in which home-based treatment of DVT with low-molecular-weight heparin compared favorably with hospital treatment using unfractionated heparin.\(^15–17\) One current resource on medical disability\(^18\) painted DVT with a sunny prognosis, saying “complete recovery occurs within a relatively short period of time,” except in 3% of patients who have serious complications. Recurrence rates of DVT were estimated at 3 to 15%/yr,\(^18\) but PTS got barely a nod.

The study of PTS is further hampered by the lack of identified risk factors in DVT patients—other than recurrence, and perhaps body mass index > 22 in young women\(^19\)—which make them more likely to acquire this complication.\(^20,21\) The 30-year-old study of Corrigan and Kakkar\(^22\) and its follow-up investigations\(^23,24\) are relevant in this regard. They showed that pedal venous pressure (PVP) dropped briskly with exercise, from 50 to 20 cm H2O, in both normal legs and in legs of patients after DVT, whose deep veins remained blocked but whose perforating veins were still competent (valves intact). PVP fell much less with exercise in those patients after DVT in whom both the deep and perforating veins were incompetent. These latter patients also showed a faster return of PVP to baseline after exercise, and slower exercise clearance of subcutaneously injected sodium-24. These authors reasoned that early identification of PTS-prone patients might enable its prevention. Although the surgical treatment approach they espoused has not been very successful, the concept of early identification of those at risk remains important, if we are to test, prospectively, interventions to block the development of PTS. Their diagnostic use of exercise-induced changes in PVP and foot volumetry\(^25–24\) did not gain lasting attention, perhaps because they failed to provide follow-up information on the patients whose exercise responses seemed such a gloomy portent. Other noninvasive techniques\(^25\) might succeed in identify-


Getting a Leg Up on the Postthrombotic Syndrome

If you save someone’s life, you are responsible for them forever.

This ancient Chinese teaching would surely dampen the hubris of any clinician who has just made a difficult, serious diagnosis. But it is no time for complacency, as illustrated by deep venous thrombosis (DVT), “a wolf in sheep’s clothing.”\(^1\) Even without its insidious complication, the post-thrombotic syndrome (PTS). Despite enormous advances in recent years in the diagnosis and treatment of DVT,\(^2\) much less progress has been made in the understanding and management of PTS. Some of this shortfall stems from variations in PTS case definition, especially in earlier studies. Estimates of the incidence and prevalence of PTS have accordingly spanned a wide range. In the preheparin era, Bauer\(^3\) documented a relentless deterioration of patients with DVT, 80% of whom eventually acquired ulceration, \textit{i.e.}, severe PTS, 15 years after their initial thrombosis. Even in studies over the past 20 years, the prevalence of PTS ranged from 21 to 88%\(^4–6\) depending on the basis for diagnosis, the presence of underlying medical conditions, and the treatment employed. Recently, more uniform, reproducible classifications like that of Villalta et al\(^7\) lent more order to this area of investigation. That scale scores five symptoms (pain, cramping, limb heaviness, pruritus, paresthesias) and six signs (edema, induration, pigmentation, venous ectasia, redness, calf tenderness). By grading each element from 0 to 3 in severity, a combined score is developed. Even here, the categories of mild/moderate (score of 5 to 14) vs severe (\(\geq 15\), or stasis ulceration) create a somewhat awkward delineation. Use of the scale of Villalta et al\(^7\) has yet to be reported as a means of monitoring patients after DVT. Nor are there validated physiologic measures to predict which patients are destined to acquire PTS. Though limited by the lack of “gold standard” criteria for diagnosis, physicians in 2003 can give patients with DVT a global estimate that even with optimal therapy, approximately one third of them go on to acquire PTS.\(^4–6\) Could such somber information lead patients to follow treatment advice more fully? Does it spur us clinicians to do a better job in following guidelines for primary prevention of DVT?\(^8\)

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ing patients heading for PTS, signaling the need for extra care to try and head it off.

Analyses4–6,20,21 indicate that most of the eventual cases of PTS declare themselves within the first 2 years after acute DVT. One retrospective review26 found the onset occurred 10 to 20 years after the initial event, perhaps related to recognized (16% of series) or occult DVT recurrences. But the weight of evidence indicates that PTS should not be overlooked as a near-term outcome; it is at once a nasty complication and an appealing research target. The need to take it into account is underscored by the costs that PTS exacts, both in the currencies of chronic pain and lost human resources, and the coin of the realm.5,26–29

To physicians caring for patients after acute DVT, the emergence of PTS brings a dark cloud to an already misty clinical horizon. These clinicians may indeed have had initial satisfaction over making the diagnosis of DVT (with or without pulmonary embolism) in a subtle case, especially when there were none of the usual risk factors, such as trauma, pregnancy, malignancy and its treatment, thrombophilic states, prolonged immobilization, oral contraceptives, or major cardiopulmonary diseases. They then may have been diligent in arranging for meticulous anticoagulation of appropriate intensity and duration, while steering clear of hemorrhagic or other complications. What insidious pathogenesis were they missing?21,5 Only a few prospective studies have addressed this question, but some clues have emerged. For example, Haenen et al30 studied 70 legs with DVT in 67 patients over 24 months by duplex ultrasound and strain-gauge plethysmography, demonstrating that 99% of deep vein occlusions underwent partial resolution after 3 months. They also found, however, that many legs affected with DVT later engage in a dynamic dance, with clot regression and clot propagation vying for ascendency. Resolution was shown to occur in 36% of legs, while propagation dominated the venous drainage picture in 27%, especially in older patients and those with proximal lesions. High levels of venous outflow resistance at 1 month and 12 months of follow-up were associated with a high risk of developing PTS symptoms, as was a high thrombosis score in proximal veins at months. Residual abnormalities by duplex ultrasound in ipsilateral popliteal and tibial veins have been also been associated with PTS in a retrospective series.

Other prospective studies have tried to illuminate this process, but differences in diagnostic criteria and therapy limit consensus.3,20,21,30,32 Venous valves share center stage with thrombus dynamics in the drama. When healthy, they tolerate pressures up to 400 mm Hg acutely, but their upstream cusps are often where the original thrombosis arises in DVT. As acute thrombosis progresses, occlusion and obstruction to the normal centripetal flow develops, culminating in venous hypertension. Whether endothelial damage is a cause or effect of this hypertension is unclear, as is its contribution to the pathogenesis of PTS. Re-canalization is often irregular and may cause further valve damage. Valves eventually become incompetent in both the deep and communicating (perforating) veins. The brisk, sustained fall in venous pressure that normally accompanies exercise no longer occurs. Abnormal capillaries develop in the skin and soft tissues over the distal leg and their permeability to erythrocytes and fibrin leads to hemosiderin deposition as the errant red cells lyse and release their contents. Edema results both from hydrostatic forces and osmotic ones related to protein breakdown, and perhaps mediator release as well. Venous stasis also leads to tissue hypoxia that eventually causes dermal necrosis and ulcer formation. The denuded areas of soft tissue become easy prey for bacterial infection.

How to prevent PTS? One risks “proselytizing the converted” by mentioning the need for primary prevention of DVT, given the series of consensus conferences on the matter in CHEST.2 But while both unfractionated and low-molecular-weight heparin are very effective prophylaxis, they are actually prescribed to only one third of patients at high risk for DVT.8 Is “traveler’s thrombosis” enough of a threat to persons at high risk for DVT to treat them preemptively? Cesarone et al33 thought so, and found that one dose of low-molecular-weight heparin apparently protected 82 air travelers from DVT (0.6% vs 4.5%, p < 0.002, in 82 control subjects). Prevention of DVT recurrence is also crucial if we are to minimize PTS. Although meticulous anticoagulation is no talisman against PTS, at least one retrospective study26 indicted inadequate warfarin therapy for its late development. A randomized controlled trial31 strongly supports the use of carefully fitted elastic stockings, for even though DVT recurrence was not prevented by them, they did reduce PTS. Even with elastic stockings, however, 31% of patients still acquire some degree of PTS.

Can thrombolytic therapy of DVT prevent PTS? One might expect so, by minimizing early valvular damage. Indeed, a meta-analysis34 of studies comparing heparin vs streptokinase in DVT found that lytic therapy was followed by a significantly lower rate of PTS (odds ratio, 0.32; 95% confidence interval, 0.12 to 0.86), but major bleeding occurred more often in the streptokinase recipients (odds ratio, 3.78; confidence interval, 1.26 to 11.32). The methodologic limitations of existing reports led others35 to conclude that thrombolysis cannot be recom-

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mended, given its current risk-to-benefit function. The possible benefit of exercise in preventing PTS has not been systematically studied, perhaps for fear that it might cause a new DVT or pulmonary embolus. However, evidence has been provided that early walking exercise does not increase these events. When combined with compressive bandages or stockings, exercise achieved faster resolution of pain and swelling than did bed rest.

In this issue of CHEST (see page 399), Kahn et al lay important additional groundwork for the possible use of exercise in treating established PTS. They show that a single session of treadmill exercise was well tolerated by a group of middle-aged patients with PTS. Leg symptoms did not worsen, and active flexibility of the calf muscles of the PTS-affected leg improved significantly after exercise. Both findings occurred in spite of a greater increase in postexercise volume of the affected leg, as measured by water displacement. As Heywood’s proverb reminds us, however, “One swallow maketh not summer.” Kahn et al need no such reminding. They call for controlled trials of structured exercise in patients with PTS, as discussed below.

Should such trials be conducted while patients are wearing compression stockings, so as to offset the hydraulic loading of distal tissues that would otherwise occur? An abstract from the laboratory of Kahn et al suggests this precaution is not needed, though no hemodynamic measurements were mentioned in the abstract. Their current study came up with some other surprises. First, there was no difference between patients after DVT with PTS vs those without it, in habitual daily activity, perhaps because those with more severe PTS opted not to participate in the study. There was also no difference between PTS and non-PTS patients in maximal exercise heart rate, treadmill speed, or duration. These findings suggest it is reasonable to test the hypothesis that exercise may be beneficial to patients with PTS. Although Bernardi and Prandoni already suggested that regular exercise might be beneficial to patients with established PTS, the articles they refer to make little or no mention of this modality. Nor could one find published studies of risks or benefits of structured exercise therapy in patients with PTS.

Once PTS is diagnosed, what therapy is useful? Continued prevention of DVT recurrence by effective thromboprophylaxis and use of graduated elastic stockings is needed. Elevation of the extremity during rest is recommended. Home use of intermittent compression is advocated for patients with severe symptoms. A randomized control trial of horse chestnut seed extract found it as effective as compression stockings in reducing leg edema in patients with chronic venous insufficiency. The latter study does not warrant the use of such medication instead of compression stockings, but combination therapy may be useful if the finding is confirmed.

For severe cases, eg., ulcers, the Unna boot has been helpful for over a century. Hydrophilic dressings were preferred by patients in one study, but were not as effective as the more cumbersome boot. A clutch of small trials have shown promise, such as the use of aspirin, oxpentifylline, prostaglandin E1, and heparan sulfate. Their place in treating advanced PTS remains to be determined. Given the lifelong issues facing clinicians who feel bound by the Chinese maxim, well-done therapeutic trials are likely to be welcome, including the use of exercise.

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References

Is It Difficult To Diagnose Sarcoidosis?

Some diseases are inherently more difficult to diagnose with certainty than others. Most diseases are easier to diagnose when the clinical presentation fits the paradigm that we learn as a function of our training and experience. The opposite is also true—if the presentation is atypical, the diagnosis becomes much more difficult. One such example is a pulmonary embolus that complicates severe chronic obstructive lung disease, particularly if the patient is being supported by mechanical ventilation. Pulmonary physicians are likely to be a little