diagnosis and therapy. Unfortunately, past and current attempts result in one of those infamous, widely decried “summary slides” displaying many arrows pointing this way and that, many subtended by question marks. Thus, the “simple algorithm” still remains to be revealed in the future.

But, at least, a few of the old arrows and question marks have been erased. For example, at the top of any algorithm should be the words “Prophylaxis for Acute Deep Venous Thrombosis.” Indeed, were these words widely appreciated and implemented, the rest of the algorithm could be quite small print. However, at the moment, this unfortunately not the case. So substantive issues of diagnosis and management, and many arrows, persist.

In terms of the diagnosis of acute venous thromboembolism, significant gains have been made. It is clear that clinical diagnosis is not adequate for ruling in (or out) deep venous thrombosis (DVT) or pulmonary embolism (PE). Objective tests are needed. In the case of DVT, the lower extremity deep veins are the “target” because 95% of PEs arise from these. Impedance plethysmography, ultrasonography, and contrast venography provide adequate but imperfect diagnostic approaches. New techniques are being explored: CT scans, MRI, angioscopy, radiolabeled compounds, etc. Their place in the diagnostic approach to DVT remains to be defined.

With respect to the diagnosis of acute PE, the current approach relies heavily upon perfusion/ventilation scans and pulmonary angiography. The former is sensitive but not specific; the latter is excellent but invasive. Again, new approaches are being explored. In some hands, chest CT scans with contrast have proven useful; early enthusiasm cannot substitute for solid, comparative investigations. These do not yet exist. Problems of access, technic, and interpretation persist and must be addressed before claims that this technic “replaces” contrast angiography are justified. The same is true of MRI, echocardiographic approaches, angioscopy, and other promising procedures.

In the realm of treatment, considerable progress has been made, but some elements of progress actually have introduced new uncertainties. The status of thrombolytic therapy remains unsettled and controversial. The potential of low molecular weight heparins, heparinoids, and antithrombin agents is under active exploration. These new agents may substantially alter future therapeutic approaches.

However, as these new developments represent a continuation in our evolutionary attempt to define a simple algorithm, revisiting old issues can be instructive. One old issue in PE diagnosis is the value of the ECG. In this issue of CHEST (see page 537), Ferrari and colleagues provide some new insights into this “old” test. Clearly, the ECG can neither make nor exclude the diagnosis of PE. But this study indicates that precordial T-wave inversion may assist in helping to define the severity of embolic obstruction. It should be noted that the report of Ferrari et al deals with an unusual population: a group of patients with a very high incidence of massive PE, who survived for at least 48 h before seeking treatment. How many patients may have had acute PE engrained on chronic PE is unknown. Nonetheless, the message is clear: in this patient group precordial T-wave inversion is frequent in those with extensive PE; and persistent T-wave inversion suggests that extensive PE persists. What this means in terms of long-term outcome of these patients is unknown. Is survival influenced? How many with persistent T-wave inversion will prove to have chronic thromboembolic pulmonary hypertension? Do the long-term outcomes of those patients who received thrombolytic therapy with earlier T-wave reversion differ from those treated with heparin alone? Perhaps follow-up of this interesting patient group will answer these questions.

As old questions are revisited, and new ones addressed, our approach to DVTs slowly evolves. Cautionary notes are in order during this evolution. “Early reports” tend to be the best. Studies done in sophisticated centers under tight investigatory controls may not translate well in general practice. However, one lesson learned will not change. Wider implementation of prophylaxis in patients at risk of acute venous thrombosis remains the central imperative in our attempts to reduce the morbidity and mortality tolls still exacted by DVT.

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There and Back Again
Lung Cancer Screening

Lung cancer is occurring in epidemic proportions both nationally and worldwide, and unfortunately will be the major cancer we will be contending with well into the 21st century. The mortality from lung cancer will exceed the combined mortality of breast, pancreatic and colorectal cancer.1 Survival will occur in a remnant. One of eight individuals initially diagnosed with lung cancer will survive 5
years. Yet the major cause of lung cancer is clearly known. Two percent of individuals who develop lung cancer are lifetime nonsmokers. In the United States an estimated 96,000 men and 73,000 women will develop lung cancer per year, yet not a single woman has been entered on a randomized prospective lung cancer screening trial.

In this issue of CHEST, Strauss and colleagues (see page 754) have reviewed lung cancer screening trials and have focused their attention on the Czechoslovakian randomized prospective trial and the Mayo Lung Project. Their analysis generates controversy in interpreting these two trials. Mortality and survival are not synonymous. Mortality is the number of deaths due to the disease, and mortality rates the number of deaths over a specific time period. Survival is the probability of living once the diagnosis has been made, and survival rates the percentage of individuals with a diagnosis of disease still alive after a specific period of time. Mortality rates and incidence rates are highly correlated, whereas survival rates are not. Cancer survival rates vary as a function of age, sex, race, social status, histology, location, stage, and treatment. Cancer survival can be influenced by improvement in treatment and early diagnosis. Screening trials that use survival as an end point are subject to bias, whereas mortality is not. Survival rates are subject to lead-time, length-time bias as well as overdiagnosis. Lead-time bias displaces the starting point proximal, but the natural history of disease remains unperturbed by intervention. Length-time bias moves the end point distally with selective detection of individuals with indolent disease who would have done well without intervention. Mortality in the entire cohort remains unchanged. Overdiagnosis is an extreme form of length-time bias. The disease course does not alter the expected survival compared to the normal population. The institution of treatment would be more harmful than helpful. An example of overdiagnosis is the early detection of low-volume and low-grade prostatic cancer by PSA, digital rectal examination, and transrectal ultrasound. Therefore, mortality, rather than survival, remains the final determinant of the effectiveness of screening trials. How, then, does one interpret a trial in which the incidence and mortality diverge?

Strauss and colleagues have critically reviewed the Mayo Lung Project and the Czechoslovakian randomized prospective lung cancer trials. Both trials demonstrated a survival advantage in periodic chest roentgenogram screening of male smokers over the age of 45. Both demonstrated an unexplained increased incidence of lung cancer in the screened group compared to the control group. Both trials did demonstrate an improved resection rate in the screened group. However, both trials failed to show a reduced mortality in the screened group. Strauss et al effectively dismissed lead-time bias, length-time bias, and overdiagnosis as the reason of the survival advantage in the screened group. The Czechoslovakian trial included a significant autopsy rate in both the screened and controlled group; and found no increase in “surprise” lung cancer incidence in the control group not previously detected autemorrem. This was also the finding of a much larger trial published by Wilde and the former German Democratic Republic. This essentially rules out underdiagnosis in the control group as a cause for the increased incidence in the study groups.

Comparing and contrasting studies can be helpful. Two previous large nonrandomized but prospective trials can be compared with the Czechoslovakian and the Mayo Lung Project. The trial by Wilde and the London study by Brett involved a large number of men screened by chest roentgenograms at 6-month intervals. The German trial control arm involved chest roentgenograms at approximately 18 months. The Czechoslovakian trial involved chest roentgenograms every 6 months for 3 years in a study group, whereas the Mayo Lung Project study group included chest roentgenograms every 4 months with sputum cytology at 4-month intervals vs chest roentgenograms at yearly intervals in approximately half of the controlled patients. Sputum cytologies were found by two additional trials to contribute little to screening.

The contamination of the Mayo Lung Project control group and the German control group would lessen the impact of screening on survival and perhaps mortality. Combining the Mayo trial with the Czech study and Wilde’s and Brett’s studies, however, would include 79,045 men who were screened, and a control group of 135,426 men. Comparing the studies demonstrates a remarkable finding. All four trials demonstrated an increased incidence of lung cancer in the screened population, an increased resection rate, and an improved survival in the screened population. However, all four trials failed to demonstrate a reduction in mortality. There was a 35% increase in lung cancer found in the screened groups. The survival in the controls was 15.6% at 5 years vs 29.6% in the screened group. The relative mortality rate was 1.1 when comparing screened to control cohorts.

What would be the cost of lung cancer screening? In the United States there are 104 million individuals over the age of 40 and 23.8% of these individuals smoke. The average cost of a chest roentgenogram is approximately $54, and if screening is done at 6-month intervals, then $267 million would be expended per year for screening purposes. If screening
adds a 15% additional survival advantage to 135,000 individuals per year who do develop non-small cell lung cancer, and assuming no gender differences in the screened population, then 20,250 additional lives would be saved. The cost would be approximately $131,850 per year per life saved. This would not include the cost of evaluating false-positive studies.

How can screening be improved? Patients with chronic obstructive lung disease who smoke have a greater than 3 times incidence in lung cancer compared with smokers without chronic obstructive lung disease. A family history of lung cancer in a person who smokes also increases the risk of developing lung cancer. Sputum cytology accompanied by lung cancer antigen immunohistochemical staining or molecular genetic analysis of RAS or p53 mutation may be more sensitive and specific in detecting early lung cancer. Phenotyping individuals for debrisoquine metabolism, CYP1A1 polymorphisms, or low levels of glutathione S transferases may predict lung cancer risks in individuals who do smoke.

Is it worth screening individuals who smoke with chest roentgenograms? If seen in terms of survival, the answer is yes. If seen in terms of mortality, the answer is no. The number of individuals who may benefit is not insignificant, but the cost of screening such a large population is quite high.

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REFERENCES

The Diagnosis of Hypersensitivity Pneumonitis

In this issue of CHEST (see page 813), Embil and colleagues from Winnipeg describe a possible new cause of hot tub lung, an example of hypersensitivity...