The study of any disease requires a pragmatic, unequivocal definition of the disorder, such that one is able to distinguish those with and those without the condition. Unfortunately, asthma defies definition. The symptoms of asthma, i.e., cough, wheeze, and dyspnea, are nonspecific. Airway hyperreactivity, although characteristic of asthma, is neither sufficient nor specific for diagnosis. For clinical purposes, a diagnosis of asthma is based on an impression gained by medical history, physical examination, chest radiography, and physiologic testing. When large numbers of subjects are studied, the diagnosis of asthma must be based on more limited data, such as responses to questionnaires. One cannot be certain, therefore, that subjects identified as asthmatic in epidemiologic surveys, correspond to those defined by clinical criteria. In a previous issue of CHEST, Kivity et al. reported asthma prevalence in Israeli military recruits. In Israel, all of the Jewish population is subject to recruitment into the armed forces, and all undergo a medical examination before induction. The investigators therefore had access to nearly the entire population of young Jewish adults. In addition, these subjects were then available for follow-up observations. The methods of this epidemiologic study are unusual in that the diagnosis of asthma was established by usual clinical criteria. In those individuals who provided a history suggestive of asthma, the diagnosis was confirmed by a detailed interview, a physical examination, and spirometry. In those without airway obstruction, a test of airway reactivity was also performed. The investigators documented a cumulative prevalence of asthma of 6%, with a 22% increase for a period of 3 years. Although this increase in prevalence may represent only a meaningless statistical blip, the finding is consistent with other studies in Israel and elsewhere where prevalence was examined over longer periods of time. Since an accompanying increase in incidence could not be shown, the authors hypothesized that the increased number of new cases might have arisen during childhood. Any number of factors may be responsible for this phenomenon including changes in breast-feeding, alterations in both indoor and outdoor environments, and exposure to certain allergens such as dust mites. These hypotheses are testable by appropriate cohort studies.

Advances in our understanding and treatment of any disease result from an interaction of multiple lines of investigation. Cellular research led to new insights into asthma pathogenesis, while pharmaceutical research led to the marketing of improved bronchodilators. However, epidemiologic investigations revealed that these advances did not translate into improved asthma care, and thus, spurred the recent reassessment of asthma treatment. It is now the task of epidemiologists to document whether the shift in emphasis from use of bronchodilators to that of anti-inflammatory agents will result in a decrease in asthma morbidity and mortality. We await their findings with interest and concern.

Arthur S. Banner, MD, FCCP
Manchester, New Hampshire

References
1 Buist AS, Vollmer WM. Reflections on the rise in asthma morbidity and mortality. JAMA 1990; 264:1719-20
4 Woolcock AJ. Worldwide differences in asthma prevalence and mortality: Why is asthma mortality so low in the USA? Chest 1986; 90(suppl):405-48
10 Weiss KB, Gergen PJ, Wagner DK. Breathing better or wheezing worse? the changing epidemiology of asthma morbidity and mortality. Am Rev Public Health 1993; 14:491-513

The International Cooperative Pulmonary Embolism Registry

The contemporary prognosis of pulmonary embolism (PE) is poorly understood, despite recent advances in diagnostic, therapeutic, and prophylactic modalities. We have very limited information on current rates of mortality and recurrent PE. Furthermore, we do not yet have available a well-validated system for risk stratification of patients with PE. The largest (n=160) PE trial (thrombolysis vs heparin alone) was undertaken a generation ago, before more streamlined, contemporary methods of thrombolysis were established. While the second largest PE treatment trial was more recent and included 101 patients from 13 American centers, these patients were normotensive at the time of initial presentation and do not reflect the entire spectrum of individuals treated for PE.

Prior reported rates of mortality (Fig 1, top) and
To plan future clinical trials of PE treatment, an accurate assessment of the rates of death and recurrent PE must be undertaken. Only in this way can accurate sample sizes be estimated.

Prior trials probably do not reflect current event rates because of the evolution of novel treatment strategies. For example, patients with PE now receive more intensive and rapid anticoagulation than previously, with heparin dosing often guided by formal protocols. There is also a lower threshold for using thrombolysis, particularly in normotensive patients with right ventricular dysfunction. A trend is emerging in which thrombolysis is employed in patients with PE whose conditions are diagnosed noninvasively, thus decreasing the rate of bleeding complications, particularly hematomas, that occur at the site of femoral vein catheterization for pulmonary angiography. Finally, embolectomy, often undertaken in the catheterization laboratory, is enjoying a renaissance, because results are improving as techniques are refined.

Although the progress of the past decade is commendable, our knowledge of PE lags far behind our understanding of myocardial infarction (MI). Whereas several hundred thousand patients have been recruited into MI clinical trials, only hundreds of patients with PE have been similarly evaluated. There are multiple data banks with information on MI diagnosis, treatment, and prognosis, but no equivalent resource exists for patients with PE.

The problem, of course, is that recognized PE occurs far less often than MI. This makes single-center studies and even cooperative trials within a single country quite difficult to carry out. Therefore, international collaboration is useful for organizing meaningful studies of sufficient sample size.

Trans-Atlantic collaboration in PE clinical research has two precedents. First, the Bolus Alteplase Pulmonary Embolism (BAPE) group recruited 90 patients with PE in the United States, Italy, and Canada for a randomized controlled trial of reduced-bolus tissue plasminogen activator (TPA) vs continuous-infusion 2-h TPA. Second, a group of French clinical researchers adopted a parallel protocol to that of the BAPE group, which subsequently permitted pooling of the results of both trials.

A landmark International Cooperative PE Registry (ICOPER), sponsored by Boehringer Ingelheim, is now being initiated. This Registry embodies the principle of international collaboration and will recruit 1,000 patients with PE within 2 years. Centers from Italy and the United States will form the core investigative group, and additional European centers may also participate. The principal objective is to collect and analyze prospective data on a broad clinical spectrum of patients with PE, ranging from small PE to cardiogenic shock. The secondary objective is to intensify PE detection, at least among the participating institutions. The Registry will include all patients who are treated for PE, irrespective of diagnostic workup or treatment modality.

The Registry will not dictate but, instead, will reflect actual clinical practice. Each physician will be at liberty to establish the diagnosis of PE in any way that he or she chooses. At participating centers, all patients diagnosed as having PE will be included, regardless of how the diagnosis is established. Also, the Registry will not exclude patients who are treated for asymptomatic PE that is discovered incidentally on lung scanning (which might be performed, for example, in patients with deep vein thrombosis). The Registry will also include those patients in whom occult PE is discovered at autopsy if the PE is judged by the examining pathologist to have contributed to the patient's death. Case Report Forms will include information on prophylaxis (if any) prior to PE, diagnostic workup, treatment, and outcome. Electronic data collection and networking will be used within Italy and, eventually, most data collection will be carried out with a paperless system.

As the coordinators of ICOPER, we are enthusiastic about the utility and benefits of the Registry. ICOPER will permit us to describe the contemporary
risk factors, diagnostic workup, treatment, and outcome of patients with PE. Descriptive and exploratory analyses of the data will permit us to generate hypotheses that may well improve our understanding of the disease as well as patient care. Importantly, the Registry will permit us to plan future clinical trials in which patients at high risk for PE are targeted for aggressive intervention.

Samuel Z. Goldhaber, MD, FCCP
Boston
Luigi Visani, MD
Milan

REFERENCES