Collaborative Science and the American Thoracic Society

Cooperation in Harmony with Conflict of Interest

Maurice Hilleman was the archetype for a translational scientist. He was the key contributor to the discovery and development of vaccines against measles and mumps. For his achievements, he was awarded the National Medal of Science and was recognized by scientists worldwide. Acceptance within both industry and academic environments was a key to his success (1). Beyond medicine, similarly successful collaborative efforts across academia, government, and industry benefit us daily, including, for example, dramatic advances in communication and electronic technology. Recent advances in the treatment of lymphangioleiomyomatosis, based on research conducted by American Thoracic Society (ATS) members and supported by the ATS, provide another example of the value of such collaborative efforts among academic, industry, and government scientists.

These stories highlight the benefit of collaboration and open dialogue to the advances in biomedical research. A significant body of scholarship emphasizes the benefit of diverse teams to problem solving (2). However, there are also situations in which relationships between institutions, for example, industry and either academia or professional societies, have resulted in serious concerns about conflicts of interest and have threatened to undermine public trust in biomedical research.

To optimize medical advances in a time of shrinking resources, these differing perspectives must be reconciled. Although the ATS has instituted transparent processes to address conflicts of interest, the recent focus on such conflicts has had the unintended consequence of creating barriers to initiatives fostering collaborative efforts across academia, government, and industry.

To take full advantage of the potential of these collaborative efforts, a midcourse correction will be necessary. By addressing this challenge, we hope to further the mission of the ATS "to improve health worldwide by advancing research, clinical care and public health in respiratory disease, critical illness and sleep disorders," while ensuring that perceived conflicts of interest are appropriately identified and managed, promoting ethical conduct as well as public confidence and trust.

WHY IS IT IMPORTANT TO ACHIEVE THIS GOAL DESPITE SIGNIFICANT CHALLENGES RAISED BY CONFLICTS OF INTEREST?

Recent advances in our knowledge of biology have been breathtaking. As new knowledge accrues, however, we realize that identifying biologic pathways in health and disease and new therapeutic targets becomes increasingly complex. This fact makes interdisciplinary (biology, chemistry, genetics, clinical pharmacology, epidemiology, health services, and behavioral and social sciences) and interinstitutional (academia, government, and industry) collaboration and information sharing essential to the translation of scientific advances into improved health and healthcare. We all benefit when scientists from different backgrounds, possessing diverse skills, experiences, and perspectives work collaboratively to promote this translational effort (3).

WHY IS THIS DIALOGUE NECESSARY AND TIMELY?

There are unfortunate examples of conflicted relationships between industry and clinicians as well as industry and clinical scientists. In some instances, industry marketing has resulted in overprescribing of expensive drugs rather than less costly alternatives. Drugs have been marketed for unapproved uses. Lack of transparency with important scientific data has been reported. Media reports of physicians making significant sums lecturing on behalf of industry have served to further undermine already shaky public confidence. Although industry practices have changed to address these problems, these examples have led justifiably to a heightened public awareness of the potential for harm from conflicted relationships.

In this environment, some have criticized all relationships between industry and both academia and professional societies. Even straightforward collaborative dialogue between industry and nonindustry scientists is interpreted as inconsistent with the interests of truth and transparency. These relationships are seen as posing an inherently irreconcilable conflict of interest, implying a "zero tolerance" for these interactions. This expansive application of conflict-of-interest principles has had unforeseen consequences, including the creation of barriers to important collaborative efforts.

This is a worrisome development. Historically, interactions among academic, government, and industry scientists, as well as clinicians, have always been critical to the therapeutic discovery process. Without these interactions, the development and implementation of innovative therapies addressing unmet health needs is hindered significantly. Industry consults with outside scientists and clinicians to validate innovative ideas for therapeutic needs as well as to test new therapies and develop ways to ensure that effective therapies reach those who need them. Similarly, industry may provide the resources and scientific experience to develop new drugs, devices, and therapeutic approaches.

Given the emerging focus on team science, collaborative efforts should accelerate. Such collaborative efforts are needed to overcome the difficulties in deciphering biological pathways in health and illness, as well as to identify, develop, and implement novel therapeutic approaches addressing unmet public health needs (Figure 1). These challenges have triggered a renewed interest in collaborative efforts, including translational research, development and regulatory science, novel methods of drug discovery and development, and implementation science (4). But this is only the culmination of trends that have long been underway. Governments have recognized the practical need to facilitate collaborative translational efforts in the public interest. For example, Congress enacted the Bayh-Dole Act, enabling universities and government-based researchers to benefit from federal grants by patenting discoveries and facilitating engagement with pharmaceutical scientists doing similar work in discovery and development. This approach is reflected in federal policy such as the Cooperative Research and Development Agreement (CRADA) (5) that aims

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to foster cooperative arrangements. In CRADA, the potential for conflict of interest is recognized and appropriately managed. Recently, the National Institutes of Health has highlighted the importance of academic, government, and industry scientists working together through initiatives such as Therapies for Rare and Neglected Diseases (6). In the European Union, the government-led Innovative Medicines Initiative fosters collaborative scientific efforts on important precompetitive development issues (7). Other efforts in the United States include the Small Business Innovative Research program, which permits the government to support innovative small businesses, and the Foundation for the National Institutes of Health, which helps to support collaborative, translational initiatives (8). It is important to ensure that new collaborative models to address unmet public health needs are supported and strengthened.

WHAT STANCE SHOULD THE ATS ADOPT?

Our view is that the ATS must keep foremost in mind the fulfillment of its mission—improving public health worldwide. Deciphering the pathobiology of diseases like asthma, COPD, idiopathic pulmonary fibrosis, lung cancer, sleep disorders, critical illness, and many others will require considerable skill in translational science and establishing systems of care to deliver those advances to the bedside and into communities. Exclusion of any important stakeholders will inevitably slow progress. We must ensure that the ATS scientific and organizational culture and operational procedures enable rather than obstruct open dialogue and collaboration.

A collaborative effort begins with common goals and shared principles. Regardless of work setting, biomedical scientists share two fundamental principles. They must adhere to a common set of research ethics based on truth, transparency, integrity, and education of future generations of scientists (9). Developing trust among all stakeholders requires that all scientists abide by these rules. A second guiding principle is achieving the goal of improving the health of all individuals (10). Other organizations have supported these principles actively (11).

We must not, however, be naive. Multiple and competing conflicts of interest are inevitable when people and institutions work collaboratively (12). Personal desires for health, fame, power, financial security, and the concurrent interests of our home institutions are also important. By adopting the Council of Medical Subspecialty Societies code a year ago, the ATS decided against excluding industry relationships completely. Industry scientists are important members of the ATS and should participate in all society activities, with the exception of service in key leadership positions or on its clinical guideline committees where the risk of perceived conflicts of interest may outweigh the benefits of participation. Although managing these multiple competing interests is challenging, with the requirement for disclosure and transparency as only the first step, these challenges are unique neither to the ATS nor to this current scientific environment (13).

We believe it is important for the ATS to rededicate itself to fostering a scientific culture that values inclusiveness—a scientific "community of excellence" (14). We must accomplish these goals with the highest ethical standards, holding interests of patients and the public as paramount. Industry scientists should be encouraged to participate in scientific activities of the Society, including presentation of recent work, active involvement in the ATS International Conference and other scientific meetings, and service on committees and in assemblies. The entire ATS, including leadership and our diverse membership, should be committed to honoring and promoting these principles, including developing and facilitating effective mechanisms for their implementation. We need to continue to improve our ability to identify and address potential conflicts of interest, effectively. These relationships will continue to evolve as the nature of team and translational science evolves. To the extent that we meet these objectives, the ATS will be recognized as a leader among professional societies by demonstrating the advantages of diverse and collaborative scientific relationships. By adapting these goals, the ATS will be a stronger organization, in a better position to benefit our patients and communities and allowing all of us the opportunity to follow in Dr. Hilleman's admirable translational footsteps.

Figure 1. Harmony through transparent, directed collaboration.

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Extubation and the Myth of "Minimal Ventilator Settings"

Few interventions are more appreciated by a critically ill patient than the removal of an endotracheal tube. Extubation eliminates a major source of discomfort, eases communication, and expedites the path to recovery (1). Nonetheless, as many as 20% of patients require reinsertion of the endotracheal tube, although this is usually accomplished without complications (2). In a small proportion of patients, however, the need for rapid reintubation is lethal in its consequences.

I have been recently consulted about a number of patients who had been breathing comfortably at a low level of pressure support and positive end-expiratory pressure (PEEP) before extubation but, after extubation, developed immediate respiratory compromise followed by cardiorespiratory arrest and irreversible hypoxic brain injury. Analysis of these cases has motivated me to write this commentary.

The vast majority of patients can be successfully weaned from mechanical ventilation irrespective of whether this is executed by intermittent mandatory ventilation, pressure support, or T-tube trials. Randomized controlled trials have revealed differences in the relative speed with which weaning is accomplished by these techniques (3, 4), but the trials do not provide guidance on extubation—especially of the vulnerable patient. Some physicians find it convenient to extubate a patient once he or she can breathe comfortably on a pressure support of about 7 cm H_2O and PEEP 5 cm H_2O. Other physicians do not extubate patients until they are able to breathe on a T-tube circuit (without continuous positive airway pressure [CPAP]) for 30 to 60 minutes. From the perspective of extubation, the difference in endpoints appears unimportant because most patients reaching either target will tolerate tube removal.

But here's the rub. The challenge of clinical medicine is not about taking care of the great majority of patients who do well irrespective of the methods employed by their physicians. Instead, the goal is to take feasible steps that have a high likelihood of circumventing a catastrophe in a small number of instances.

At the point of extubation, a clinician needs to ask him or herself two questions: (*1*) will the patient be able to sustain spontaneous ventilation following tube removal? and (*2*) will the patient be able to protect his or her airway after extubation? My focus is solely on the first question. A patient's ability to successfully sustain spontaneous ventilation after extubation will depend on the mechanical load on the respiratory system secondary to resistance, elastance, and intrinsic PEEP, and how well a patient's respiratory muscles can cope with the imposed load (5). If there is any reason to fear that a patient might experience respiratory difficulties following extubation, it is incumbent on a physician to try and replicate the conditions that the patient will face after extubation—but to do so before removal of the endotracheal tube.

Some physicians claim that application of pressure support of 5 to 10 cm H_2O simply overcomes the resistance engendered by an endotracheal tube (6). Thus, if a patient is able to sustain ventilation at this ventilator setting, he or she should be able to breathe without difficulty following extubation. This claim ignores the inflammation and edema that develops in the upper airways after an endotracheal tube has been in place for a day or more. On removal of the tube, the mucosal swelling produces an increase in upper airway resistance. Straus and colleagues (7) demonstrated experimentally that the respiratory work dissipated against the supraglottic airway after extubation is almost identical to the work dissipated against an endotracheal tube before extubation. Thus, applying any level of pressure support causes physicians to underestimate the respiratory resistance a patient will encounter after extubation. The addition of a small amount of pressure support produces surprisingly large reductions in inspiratory work in ventilated patients: 5 cm H_2O decreases inspiratory work by 31 to 38%, and 10 cm H_2O decreases work by 46 to 60% (8, 9). Nonetheless, most—but not all—patients can tolerate a 30 to 60% increase in inspiratory load at the point of extubation.

Some clinicians believe that insertion of an endotracheal tube leads to the loss of "physiologic PEEP," which is thought to result from intermittent narrowing of the vocal cords (10). The concept of physiologic PEEP, however, is a myth. Lung volume at end-expiration generally approximates the relaxation volume of the respiratory system, which is determined by the static balance between the opposing elastic recoil of the lung and chest wall (11, 12). Accordingly, static recoil pressure of the respiratory system is zero at end-expiration in a healthy adult. The addition of 5 cm H_2O of PEEP can decrease work of breathing by as much as 40% in ventilated patients (9). PEEP also produces a substantial increase in cardiac output in patients with left-ventricular failure (13). In patients with heart or lung disease, the elimination of PEEP at the moment of extubation can lead to rapid cardiopulmonary decompensation. As when assessing patients on low levels of pressure support, observing a patient breathe on CPAP 5 cm H_2O hampers the ability of a physician to predict the patient's capacity to handle an increase in cardiorespiratory load following extubation.