Laboratory research and the practicing vascular surgeon: An oxymoron?

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I have been asked to address the question of whether the subject of laboratory research and the practicing vascular surgeon is an oxymoron. Can one, in this day and age, be both a laboratory researcher and a practicing vascular surgeon, or are these activities mutually exclusive? Should we even try to do both, or should we as vascular surgeons abandon laboratory research?

The word oxymoron is derived from the Greek oxyys meaning sharp and moros, meaning stupid or foolish and signifies a combination of contradictory or incongruous words. Numerous well-known oxymorons exist, including living dead, military intelligence, and benevolent dictatorship. Some would say that a word meaning both sharp and foolish is a perfect description of a surgeon or of the field of surgery. How about surgical research? And how about laboratory research and clinical vascular surgery? Are they contradictory and incongruous activities? Certainly the minority of practicing vascular surgeons do laboratory research, but should they do both be abandoned?

Historically, laboratory research has been essential in the development of surgery as we know it today. Without surgical laboratory research, much of the explosive advances in biomedical research would not have been possible. Laboratory research by surgeons was essential in developing an understanding of shock, fluid resuscitation, and nutrition. The laboratory development by surgeons of techniques of vascular anastomosis, cardiopulmonary bypass, and organ transplantation have exposed new horizons and opened vast new areas of knowledge in physiology, biology, and immunology. Laboratory research in vascular surgery has been critical to our understanding of circulatory physiology, blood coagulation, vascular grafting, biomaterials, ischemia, and reperfusion.

However, laboratory research in the 1990s will continue to become more sophisticated and complex and will be increasingly focused on cell biology and molecular genetics. Remarkable advances have been made in these areas, and with the decreased availability of research funding, these may be the only areas of readily available research funding in the future. Cell biology and molecular genetics are in an explosive growth phase and are poorly understood by most surgeons. Scientists working in these areas must be actively involved and fully committed to be competitive. The cost and technologic commitments required are enormous. This field is as foreign to most surgeons as the operating room is to basic scientists. But should we allow the new developments to pass us by, or should we encompass them into vascular surgery?

Many vascular surgeons feel that they should involve themselves with clinical research only, leaving laboratory research to PhDs. Unfortunately, what passes for clinical research in vascular surgery is all too often simply experience reporting. Although clinical reports with comparisons of different treatment methods, reports of new procedures and approaches, and evaluations of outcomes are important for our clinical practices, they do little to advance fundamental new knowledge. Even well-controlled, prospective clinical trials add little to our understanding of vascular biology or disease mechanisms. These require controlled laboratory experiments and hypothesis testing. Vascular surgeons must not abandon laboratory research and the generation of new knowledge if vascular surgery is to persist as a scientific discipline in the future.

But can practicing vascular surgeons contribute meaningfully to laboratory research in the 1990s? I feel that they can, because their knowledge and understanding of clinical vascular disease allows them to pose meaningful questions and hypotheses for testing. They will, however, need to include the new tools and concepts of the 1990s in their thinking. The techniques of gene sequencing and splicing, messen-
ger ribonucleic acid (mRNA) hybridization, the polymerase chain reaction, and in situ hybridization are bewildering and complex. Yet the techniques of molecular biology, no matter how sophisticated, are not science in themselves. They are simply tools that can be applied to test hypotheses. Practicing vascular surgeons can develop an understanding of vascular biology and begin posing clinically relevant questions at more basic levels. They will usually need to develop collaborative efforts with basic scientists to be able to apply state of the art techniques to scientific questions. Basic scientists who are skilled and expert in modern techniques of molecular biology may lack the perspective to apply them to significant clinical problems and welcome contacts with clinicians. Clinical vascular surgeons can bridge this gap, provide clinical correlation and perspective, and provide animal models to test hypotheses.

Several types of collaborative arrangements with basic scientists are possible. These include hiring a PhD to develop molecular capabilities in one’s own laboratory or establishing a coequal collaborative arrangement with independent basic scientists. I prefer the coequal collaboration because the basic scientist must not be simply a “postdoc” who carries out sophisticated assays for the surgeon. He must be able to compete on his own against his peers for funding. Promotion, growth, and development of basic scientists in clinical departments is sometimes inhibited by lack of acceptance of these scientists by their peers in basic science departments. Collaboration with such scientists requires a real commitment by the vascular surgeon, patience, diligence, mutual respect, and good communication. One should not be confused into thinking that achieving the capability of performing high-technology molecular biology assays is the end in itself. We must apply the scientific method that depends on hypothesis testing, experimental design, proper use of controls, quantitative assessment of the results, and proper statistical analysis.

Most practicing vascular surgeons have a number of explanations and justifications that prevent them from becoming involved with laboratory research. These include (1) being too busy in the operating room, (2) not having enough time, (3) not knowing the new laboratory techniques, (4) being more interested in outcome and surgical results than in disease mechanisms, and (5) not having funding for laboratory research. These are all valid arguments, and they become even more valid as a vascular surgeon matures and his practice grows. His busy clinical practice is gratifying, but preoccupation with only this aspect of vascular surgery by all clinical vascular surgeons will ultimately have negative repercussions on the specialty of vascular surgery.

Vascular surgery is a scientific discipline and a recognized specialty of medicine; it is not a trade. Each specialty must carry with it a scientific body of knowledge, not merely surgical techniques. Vascular surgery research has a rich heritage and has been important in developing a new and unique body of knowledge. Clinical vascular surgeons contributed importantly to understanding the pathophysiologic characteristics of vascular disease and developed objective, noninvasive quantitative methods of evaluating the vascular system in man. They have been important in developing our understanding of circulatory physiology and vascular biology. However, to remain a scientific discipline, vascular surgery must maintain its commitment to developing new information and must maintain a significant role in the science of the vascular system. Vascular surgeons have historically had the greatest experience in and understanding of the clinical manifestations of peripheral vascular disease and have the most direct access to obtaining normal and diseased blood vessels in the operating room. They are in an ideal position to link the new scientific capabilities of studying vascular biology to the unsolved problems of human vascular disease.

Thus laboratory research and clinical vascular surgery is not an oxymoron. Laboratory research has been well integrated in vascular surgery in the past, and it must remain so in the future. However, we must recognize that laboratory research is changing and changing dramatically. We must take steps to keep pace with the rapid changes. We must train our residents and fellows to understand vascular biology and train a portion to be surgeon-scientists. Clinical vascular surgery is also changing. Explosive new developments in vascular surgery intervention, nonsurgical techniques, and risk factor control have generated a renewed interest in peripheral vascular disease. The National Institutes of Health will soon be funding research and training programs in vascular medicine. Vascular surgery should not be left behind. Vascular surgeons must be active participants in the changes occurring both in laboratory research and in the treatment of clinical vascular disease to avoid being relegated to the role of being simply highly skilled technical surgeons. The Society for Vascular Surgery (SVS) should take a leadership role in eliminating the perception that laboratory research and the practicing vascular surgeon represents an oxymoron. Although all practicing surgeons will
certainly not be laboratory researchers, the SVS should support basic laboratory experience for not only young vascular surgeons but also young vascular biologists working in collaboration with vascular surgeons. The SVS should provide a forum for presenting fundamental work in vascular biology both by surgeons and nonsurgeons. Vascular surgeons should promote and be receptive to the advances in understanding basic cellular and disease mechanisms. Vigorous support and growth of laboratory science in vascular surgery will bode well for the future well-being of our academic discipline.

DISCUSSION

Dr. G. Patrick Clagett (Moderator). A problem with large randomized trials is that by the time they are published, the conclusions may not be terribly relevant to contemporary practice. Dr. Hobson, is this a problem with the Veterans Administration (VA) cooperative study in patients with asymptomatic carotid disease?

Dr. Robert W. Hobson. Our group of principal investigators and I believe that the Veterans Administration clinical trial on asymptomatic carotid stenosis will be relevant to current practice when data are published in mid-1991. Most of us are still basing our selection of patients on clinical assessments including routine noninvasive studies. Although additional data obtained from prerandomization CT and magnetic resonance imaging (MRI) scans for example would have been valuable, absence of these data should not detract from the report's value to clinicians. Unfortunately, once a clinical trial is initiated, additions to the protocol are not easily accomplished, and newer technology can not be added without altering the original study design. Furthermore, since the VA trial randomizes adult male patients, it will not be universally applicable to our clinical practice. However, its results should represent a contribution to our care of these patients as well as an added stimulus to complete randomization of male and female patients to the other major clinical trial on asymptomatic stenosis—the National Institutes of Health (NIH) Asymptomatic Carotid Atherosclerosis Study (ACAS) trial.

Dr. Wesley S. Moore (Los Angeles, Calif.). Dr. Strandness rightfully pointed out some of the problems with randomized trials, but I think that it is also important to recognize the necessity of a controlled study. Certainly, none of us involved in laboratory research would carry out an experiment without suitable controls. Admittedly, randomized trials are imperfect, but at the moment I am not aware of any other method in clinical research that is any better. Would you like to respond and perhaps give us a better idea of where the randomized trial should stand in our armamentarium?

Dr. D. Eugene Strandness, Jr. You have raised an important question. The reason I chose the lipid lowering trials as an example of the problem is that they were considered to be the most likely to succeed. As you know, hundreds of studies have pointed out the relationship between cholesterol levels and coronary artery disease. Even with this mass of data implicating cholesterol as a risk factor, it was considered essential to test this hypothesis by definitive clinical trials. The trials I discussed were among the best clinical trials ever designed in this country. They were in many respects a failure. A total of 280 million was spent. What can one conclude from the results? The National Heart, Lung, and Blood Institute (NHLBI) and interested scientists were forced to point out that all of the previous (nonrandomized) studies were in fact correct and the randomized trial conclusions should be ignored! In fact, the NHLBI mounted the National Cholesterol Education Program.

Having served on a data monitoring committee, I learned first-hand how difficult it is to conduct a clinical trial. As you know I have been very critical of the Veterans Administration symptomatic trial in carotid disease that is underway. I strongly believe this trial will fail for lack of proper, experienced leadership, and we as vascular surgeons will pay a price for this.

I believe that smaller clinical trials that are tightly controlled is where the money ought to go. It is possible with modern study techniques to study problems in more depth with smaller number of patients at much less cost. Unfortunately, the small trials do not have the same national appeal as a factor in dictating medical practice. There is no doubt that the outcomes of the “megatrials” can and will change medical practice.

Dr. Christopher K. Zorins. I agree. The major problems with randomized clinical trials are preconceived goals and inappropriate generalization when such goals are realized. This has certainly been the case in the lipid trials where the goal has been to prove that cholesterol lowering is of benefit in coronary artery disease. This goal was not achieved in the very expensive Multiple Risk Factor Intervention Trial (MRFIT), and thus the pressure to achieve a “positive” result in the Lipid Research Clinics Trial was great. In that study a p value of less than 0.05 was finally eeked out of a highly select population of hypercholesterolemic white, middle-aged men, which by the way is representative of only 1 to 2 million Americans. Once the p value was in hand, there was no limit to the enthusiasm to generalize it to the population at large, including women, children, blacks, and the elderly. Thus I think that the biggest danger and the biggest argument against randomized clinical trials is that once a significant p value is attained, minor differences are frequently magnified and inappropriately generalized to a much larger population. Unjustified and inappropriate generalizations, based on
the “proof from randomized clinical trials” are rarely criticized.

**Dr. Moore.** Dr. Strandness, you say it is better to participate in a small, tightly controlled randomized trial; but, if you require 500 or more patients, as is the case with the carotid trials, how are you going to do that at a single institution within a limited period of time?

**Dr. Strandness.** With regard to the case of carotid endarterectomy, there are only two issues as far as I am concerned. One is the safety and the other is the indication for operation. These were the issues that Dr. Henry Barnett and other neurologists were most concerned about. Most of the published reports show that carotid endarterectomy can be performed safely, but this is not believed by our critics. They tend to believe the poor results that appear in the literature. What if the surgical morbidity and mortality rates in the large clinical trials are worse than can be achieved? What would you conclude?

**Dr. Richard H. Dean** (Winston-Salem, N.C.). I believe that the more tightly, scientifically controlled the clinical trial, the less applicable it is to the general population. Another problem in surgical trials involves the quality of the surgery. If the quality of the surgery is above or below average to a significant degree, then the results cannot be extrapolated to “average” surgical practice. This is a real problem in medical versus surgical treatment trials and small, single-institution studies. These points aside, one of the greatest values of the randomized prospective clinical trial is that it gives you the best picture of the natural history of disease with no intervention.

**Dr. Zarins.** However, a medical treatment not much different from the natural history of the disease may be perfectly acceptable and widely recommended if supported by prospective clinical trials, whereas meaningful differences are required of surgical studies. If one were to look at the natural history of high-risk hypercholesterolemic patients in the Lipid Research Clinics (LRC) trial, one would conclude that the risk of dying is small, and that lowering cholesterol levels will not reduce the risk of death. The benefit of drug therapy was a mere 1.6% reduction in the incidence of heart attacks over 7 to 10 years with no difference in mortality rate. Such a difference would have been discounted in any surgical study, despite the p value. Thus one could have concluded from the LRC study that drug therapy for hypercholesterolemia was not cost effective and of little benefit. Quite the opposite was concluded, as we know, and we have embarked on a costly, massive cholesterol lowering effort.

**Dr. Strandness.** Let me give you another example with regard to the cost of large clinical trials. The European carotid endarterectomy trial is being conducted at a minimal cost. By American standards this trial is not tightly controlled, and this is worrisome. Although the study is ongoing, the results (if the rumors are correct) will not be favorable for carotid endarterectomy. It appears that the morbidity and mortality rates may be much higher than we would consider acceptable.

**Dr. James C. Stanley.** At the University of Michigan we have been involved with a number of small prospective randomized clinical studies designed and conducted by ourselves, as well as three large multicenter studies, including one of the carotid endarterectomy trials being discussed. An uncontestable problem with most clinical research is that the small study performed at an individual institution may not be directly applicable to the general patient population, and in the case of the larger studies patient entry is often liberalized to the degree that subsets clearly exist that will influence outcome. We would not be having repeated discussions regarding the value of prospective randomized clinical trials if one could develop protocols allowing for precise stratification of patients entered, definition of relevant variables, and guaranteed compliance by all contributing investigators. A second problem, and one that has not been addressed other than in passing by Dr. Strandness, is the prohibitive cost of clinical trials. Unfortunately, many of the outcomes occur with such small frequencies that large numbers of patients must be entered. Indirect costs for nonpharmaceutical and nondevice oriented clinical research is more than 60% at many universities and greatly increases the expense of these studies. Large scale trials have become a rare part of clinical science in the United States, in part because of these excessive indirect costs.

**Dr. Hobson.** I agree with Dr. Dean that the natural history information from clinical trials on asymptomatic stenosis will be as valuable as the medical versus surgical management question. Collection of these data has not been encouraged uniformly by medical colleagues, and yet the information is crucial to our management of carotid occlusive disease. Although all questions regarding medical and surgical management schemes will not be answered by clinical trials, the follow-up on the medically treated cohort of patients from the asymptomatic stenosis trials will also assist us in decisions regarding care of these patients.

I appreciated Dr. Strandness’ remarks; however, his examples really constituted *abuses* of the clinical trial model. Although some clinicians may misuse clinical trial methodology or propose inappropriately designed protocols, discarding the valuable data derived from clinical trials would be a mistake. Although data from single institutional reports are useful, the clinical trial is valuable because of its design and reduced bias in the assignment of patients to clinical treatment categories. As surgeons we should be as knowledgeable as you are regarding the conduct of an appropriate clinical trial because of its influence on our clinical practices. I noted with some interest your lack of comments regarding a prior clinical trial on cerebrovascular insufficiency—the Extracranial/Intracranial (EC/IC) trial. Although some have considered it to be flawed in several respects, its negative impact for our colleagues in neurosurgery was substantial. I suspect that we are in general agreement—clinical trials are, in fact, useful methods for us to understand and to use provided the proper questions are addressed and realistic expectations are considered at the
initiation of the study. I recommend our active participation in well-conceived clinical trials addressing important surgical questions.

**Dr. Strandness.** In response to Dr. Hobson, there is a possible adverse effect from the EC/IC trial. It appears that there is a small subset of patients that might benefit from this procedure but they were lost in the large numbers. There are patients who are unable to autoregulate their cerebral blood flow when the perfusion pressure falls. Given the negative results of this trial, it is nearly impossible to develop a study that would include this group of patients. I think that this is unfortunate.

**Dr. Dean.** I view Dr. Stanley’s thesis proposal as a laudatory attempt to elevate the stature of the subspecialty of vascular surgery by putting finishing touches on the product of our training programs. But should we not really be concentrating on those individuals whom we might attract into this field, including extending our efforts to the medical student level? It would seem that more effort should be directed at identifying innovative and intelligent individuals at the earlier stages of their training and attracting them into our discipline, rather than modifying existing training program requirements.

**Dr. Stanley.** Clinical medicine as well as biomedical science needs critical thinkers who are creative. Most of us would agree with Dr. Dean that student exposure to our discipline is important. Recently the North American Chapter of the International Society for Cardiovascular Surgery successfully implemented undergraduate and medical student research fellowships for up to 20 individuals annually. Drs. Robert B. Smith, III, James S.T. Yao, Christopher K. Zarins and I served on the committee responsible for proposing this program, and we, like you, felt quite strongly that this was an appropriate commitment for Society resources.

However, undertaking an effort in one area should not preclude us from recognizing opportunities in another. In this regard most of our candidates for vascular surgery fellowships come from the pool of general surgery trainees. The breadth and excitement of existing vascular fellow research, from my perspective, has not been very visible to the average general surgery trainee. Just a listing of papers and presentations by the fellows would add credibility to our discipline. For the most part vascular surgeons and vascular surgery fellows are viewed as individuals who work 18 hours a day in the operating room and clinic. If others could recognize the intellectual accomplishments in both laboratory and clinical research of our discipline, the arduous nature of our practices might be much more attractive to younger individuals. Whether we like it or not, many view us as tradesmen. My proposal regarding inclusion of a thesis as part of fellowship training is a means of capturing what we are already doing, and establishing a nontradesman reputation for the discipline of vascular surgery.

**Dr. Clagett.** So many of our fellows come to us with 2 years of research already. Now you are going to tack on additional time to complete a thesis. Is that not prolonging things a bit?

**Dr. Stanley.** Some individuals might view the requirement of a thesis as a mandate to add additional training time. That was not the intent of my proposal. Given the fact that such a large number of programs already have laboratory experience and the remainder provide excellent clinical research opportunities, it is unreasonable to presume that a fellow would be incapable of assimilating data during the course of an existing fellowship and use it as the basis for preparing a thesis.

**Dr. Clagett.** They also have their General Surgery Board Examinations that year.

**Dr. Stanley.** Given the quality of individuals entering vascular surgery training programs, it is unlikely that many of them will have to have considerable amounts of time to prepare for their General Surgery Board Examinations. On the other hand, it would be an onerous burden to have to have a thesis in hand on June 30 when most individuals complete their fellowship. However, given the 1 or 2 years of most fellowships and the 2 years that pass before sitting for the written examination for Added Qualifications in Vascular Surgery, most individuals should be able to organize data acquired during their fellowship and complete their thesis in the time frame proposed. If our fellows are eventually going to be true leaders in vascular surgery and communicate equally on a cognitive basis with their peers in nonsurgical disciplines, the preparation of a thesis should be an easily accomplishable deed. Most individuals I contacted in gathering data for my presentation expressed the opinion that preparation of a thesis as part of fellowship training would add considerable stature to the veracity of a young surgeon entering academic or private practice.

**Dr. G. Melville Williams** (Baltimore, Md.). I have concern about the economics of Dr. Stanley’s proposal. At the Johns Hopkins Medical School, the average student finishes $40,000 in debt. This influences career choices with many bright students entering lucrative specialties that have shorter residencies. Many general surgery residencies already require 2 years in the laboratory, and vascular surgery fellowships will require an additional 1 or 2 years. Some surgical subspecialties have created educational and research foundations to which their membership contributes with matching funds from industry. These funds are then used to help support advanced training positions. I believe we must consider such an approach if we are going to insist on additional requirements for fellows entering training programs in vascular surgery.

**Dr. Stanley.** Dr. Williams’ point is well taken. Indeed the Society for Vascular Surgery is in the process of establishing endowed fellowships as part of its Life-Line Foundation, which would in part meet some of the needs for funding research training. From a pragmatic perspective it is important to realize that probably less than a dozen of the 80 fellows completing existing training programs do not publish either laboratory or clinical papers as part of their training efforts. My proposal regarding theses does
not mandate additional training time, only that the fellow prepare material in the form of a thesis rather than a simple clinical or laboratory research paper. In some programs, such as my own institution, these completed works may have the appearance of an advanced degree thesis, where as in others they might not be significantly different from extended manuscripts submitted to medical periodicals for publication. The issue is that we have not made visible to the health care community at large, the accomplishments that we have already achieved in the field of laboratory research. There is not another medical specialty that I am aware of that has anywhere near the laboratory research exposure that vascular surgery currently offers its fellows. To be considered tradesman with this sort of commitment is demeaning. My proposal requires some risk in that it asks that we formalize our existing efforts and make “thinking” as visible as “doing” in our educational programs. This is not an undefensible position for us to take as the alleged leaders in vascular surgery.

Dr. Francis Robicsek (Charlotte, N.C.). Many of our trainees are in their mid 30s with families, and it may be very difficult for them to enter the laboratory to take part in extended research programs.

Dr. Clagett. I would like to ask Dr. Barnes, a member of the Residency Review Committee (RRC), is there any way to compress our training?

Dr. Robert W. Barnes (Little Rock, Ark.). The RRC and the American Board of Surgery are looking at the issue of education reform. I think there may be a light at the end of the tunnel—I hope it is not the train coming at us! I do think that we will looking at strategies to perhaps accelerate educational pathways for those who wish to differentiate while at the same time enhancing the role and scope of general surgery. Progress goes somewhat slowly in this area, but several people on the Board and in the RRC are interested at least in opening our minds a bit at conceptual change in the way we turn out our products, and some of the issues you raised this morning may well benefit from such efforts.

Dr. Mitchell H. Goldman (Knoxville, Tenn.). Do you believe that those individuals taking 2-year fellowships currently are doing this for academic purposes or are they entering these longer programs for the purpose of obtaining clinical training at a given institution so that they may enter lucrative private practices. How many of our fellows are going into academics and staying there?

Dr. Stanley. Because the definition of academics is somewhat arguable my response may seem ill defined. Although one may perceive that most fellows view training programs as a ticket to clinical practice, indeed a little over half those fellows who experienced laboratory research during their training entered academics. My personal perspective is that the purpose of laboratory research may not be so much to train one to enter academics, as to encourage individuals to become critical thinkers and better represent our discipline in whatever environment they eventually find themselves. One could make a very strong case that the very best private practitioners have been those individuals who have been exposed to laboratory or clinical research during their fellowship, and have gone through the rigors of preparing manuscripts on focused subjects about vascular disease and vascular surgery.

Dr. Harry L. Bush, Jr. (New York, N.Y.). Clearly we are viewed as tradesmen by many internists, and yet how we practice our clinical craft is extremely important. But as we emphasize training in vascular biology and clinical evaluation techniques, we are coming up against two emerging disciplines. One is vascular medicine and the other is interventional radiology. How are we going to stay in the forefront of this three-ringed circus, and how are we going to maintain control of our patient's vascular management? Is it by expanding the base of our profession to include more vascular medicine and radiologic techniques, or should we remain pure surgeons?

Dr. Zarins. I think the way to stay in the forefront is to be the doctor for patients with vascular disease. I think that research is very important to provide the scientific basis and foundation for our specialty, but to maintain the discipline of vascular surgery and not have it all disappear to vascular medicine or cardiology, we have to retain our position as the doctor. We must oversee the noninvasive vascular laboratory, we must carefully evaluate the patient and control his risk factors, we must talk to the patient, the family and the referring physician, and we must be viewed as the clinician who has the most knowledge and experience in decision making, and not as simply a highly skilled technician called in to perform a procedure.

Dr. Stanley. Dr. Zarins is correct, but I would admonish us to not perceive that we have reached the goal of being complete vascular physicians. Although we may believe that we are total physicians and know more about arteriosclerosis and thrombosis than others, such may not be the case. For many of us, our understanding of lipid disorders and coagulopathies is not perfect. We certainly can have a broader understanding of vascular disease. The competence of our trainees, may be well served by encouraging our fellows-in-training to be more academic in preparing a thesis as part of the early education in becoming a more complete vascular surgeon.