The Role of Research in the Modern Medical Center: The Ochsner Clinic Foundation Perspective

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American research universities and medical centers have made dramatic contributions to the care of the sick and to our understanding of disease. Their research is the cornerstone upon which modern medicine has been built. Today, changes in the societal context in which research is conducted are placing great strains on academic medical centers while advances in science present them with great opportunities. Here these issues are explored using the experience of the Ochsner Clinic Foundation as a point of reference.

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BACKGROUND

Since the advent of the modern American research university following World War II, academic medical centers in this country have generated a truly remarkable stream of fundamental and applied research discoveries. Through the development of new antibiotics, vaccines, bypass surgery, gene cloning, molecular diagnosis, and a great many other advances, research at academic medical centers has contributed to the health and well-being of innumerable people worldwide. This research also has provided the practicing physician with powerful additions to his disease-fighting armamentarium. At the same time, the research activities of these centers have propelled them to the forefront of modern medical care, attracting intellectually aggressive physicians and providing those physicians with the opportunity to employ cutting-edge thinking and tools in the care of their patients. The names of many of these academic centers have become household words. Today, however, the biomedical landscape is changing in important ways—ways which at once threaten research at academic medical centers and, at the same time, provide unparalleled opportunities. Here some of these changes and related issues will be discussed using the Ochsner experience to exemplify some points. Although the Ochsner research effort is small, it is caught up in many of the same forces that are affecting larger centers, and its responses are in many ways typical.

CHALLENGES AND OPPORTUNITIES

Research has been an integral component of the Ochsner mission since the founding of the Alton Ochsner Medical Foundation. Over the years, a vibrant Ochsner research activity has served to add to medicine's store of basic and clinical knowledge, and has improved the quality of care at Ochsner Clinic Foundation. In part, this is so because Ochsner research programs have provided research opportunities leading to the recruitment of an intellectually aggressive academic staff. Moreover, both clinical and basic research activities have provided novel therapies to Ochsner patients and to others in the Gulf South, thereby expanding the therapeutic armamentarium of Ochsner physicians. Ochsner research has in addition linked not only Ochsner scientists, but also Ochsner clinicians, with academic and research centers around the world, thereby providing new insights and therapies for Ochsner patients from these far-flung academic centers. Thus, the research enterprise is intrinsic to the Ochsner academic and patient care missions. However, as medicine enters the 21st century, the clinical and biomedical landscape is changing rapidly. In addition to well-publicized changes in the manner in which medical insurance is provided and medical care is delivered, changes of comparable magnitude are occurring in the research enterprise. These present both challenges and opportunities for Ochsner research.

Perhaps one of the more far-reaching changes occurring in clinical research relates to the funding of that research. Although the National Institutes of Health (NIH) research budget has increased, it has not kept pace with the demand for research support. At the same time, however, research supported by the pharmaceutical industry has grown rapidly, largely because of not only the increased regulatory requirements associated with the launch of new drugs, but also because of the clear advantage of mounting large-scale clinical trials in the effort to determine the proper use of pharmaceuticals in specific patient populations. For these reasons, the percentage of the national clinical research budget funded by pharmaceutical companies – and therefore, for the most part directed at drug development rather than clinical research per se – has grown. Along with this growth, there has been a shift in the venue in which clinical research is conducted. Whereas 20 years ago the great majority of clinical research was conducted in academic centers and in universities, now an increasing percentage of drug trial research is being conducted by local physicians and by research companies. This potentially can give rise to problems related to the quality of the research product delivered in support of some pharmaceutical industry research projects. It also puts pressure on academic centers such as Ochsner to compete with low cost clinical research providers. Increasingly, academic centers like Ochsner find themselves not dealing with major pharmaceutical companies but rather with contract Clinical Research Organizations (CROs)

hired by pharmaceutical companies to serve as middlemen. These CROs are bottom-line driven and tend to not only baulk at paying what academic organizations perceive to be the full costs of research, but also refuse to pay for any add-on intellectually valuable studies. Thus, the current economic climate is to some degree inhibiting the conduct of quality clinical research.

Moreover, in recent years there has been a dearth of training opportunities for physicians interested in true clinical research activities as opposed to drug development. This coupled with the changing funding landscape has made it difficult for academic physicians such as those at Ochsner to launch scientifically driven in-house studies. One factor on the national scene mitigating this tendency is the realization that the coupling of forefront basic biological research with clinical research can produce a rapid translation of new knowledge from the laboratory to the bedside. Thus, we see clinical studies of new biologics occurring at an increasing rate. The cancer fighting drugs, Gleevec and Herceptin, are examples of this trend. This rapid translation of new biological information from the laboratory to the clinic requires that a cadre of independent, creative clinical investigators be in place and be supported. Therein lies a great opportunity for Ochsner clinical research. Indeed, we currently see considerable academic/biotech collaboration in our Community Clinical Oncology Programs (CCOP) and in our cardiology device trials. It is anticipated that if this activity is nurtured, it will increase over time to the benefit of Ochsner research and patient care.

Yet a final challenge presented by the changing medical landscape is the issue of conflict of interest. Because of the greater emphasis on industry-sponsored research – be it large pharmaceutical industry-sponsored research or biotech research – there is a potential for significant conflict of interest on the part of investigators. One need only consider the Gelsinger case at the University of Pennsylvania to understand the complexities of this issue. Conflict of interest and other ethical and regulatory concerns have required that the Ochsner Clinic Foundation devote ever-increasing resources to assuring compliance with all regulatory and ethical standards. The simple fact is that while deliberate misconduct may be rare, the regulations and the environment are sufficiently complex that considerable diligence must be exercised to avoid inadvertent violation of appropriate standards. Clinician/scientist education in research regulations and practices is becoming an increasingly important component of this effort.

Against these challenges are arrayed, however, a tremendously exciting group of opportunities. At no time in the history of medicine has medical and biological knowledge expanded at so rapid a rate. Indeed, it has been said that the expansion of knowledge is now so great that pharmaceutical companies are more or less paralyzed in their efforts to pick and choose among the potential biological targets that biomedical science is daily identifying for drug development. Consider the new modalities of care which are now emerging. Although the promise of gene therapy is perhaps dimmer now than in recent years because of side effects associated with the vectors currently being employed, gene therapy remains long-term a vibrant and viable therapeutic technology. Indeed, at Ochsner gene therapy is even being studied in animals as an in utero therapeutic intervention to correct heritable diseases before birth. Yet another field, which is progressing rapidly, is the area of stem cell biology. It now appears clear that multiple kinds of stem cells exist, both in the fetus and in adults, and that these stem cells potentially can be therapeutically manipulated to offset degenerative disorders such as atherosclerosis and Alzheimer's disease. Indeed, it is now reasonable to think that a heart attack will in the not too distant future be treated with the replacement of dead cardiac cells through the introduction of targeted stem cells. The emerging fields of genomics and proteomics are rapidly expanding medicine's capability to diagnose disease and disease diathesis long before symptoms ever occur. This potentially means that a new era of preventive medicine is possible. This becomes clearer when one considers that stem cell and other replacement therapies targeted to the young based on genomic findings are likely possible. The advent of the DNA microarray ("DNA chip") has given both diagnostic and basic medical science the opportunity to scan for the presence and activities of a tremendous number of genes in any individual or organism. This, coupled with the results of the human genome project, further expands medicine's ability to diagnose illness and to predict future illness. Indeed, at Ochsner, the Molecular Immunogenetics Laboratory is currently using forefront polymerase chain reaction technology in this effort. It is to be expected that these technologies will become the mainstay of medical diagnosis in the near future. Yet for all this opportunity, one must be alert to the possibility of pitfalls and problems arising from this new knowledge. For example, although human cloning does not appear feasible at this time, few can be certain that cloning and its attendant ethical problems will not someday have to be addressed.

Another opportunity that is presented to the academic medical center by modern biomedical science is so-called translational research—the rapid translation of research findings from the bench to the bedside. As an example of Ochsner translational research one can point to the recent multiyear effort to identify a virus responsible for primary biliary cirrhosis (PBC). Dr. Andrew Mason's group recently succeeded in this effort, and Ochsner has patented the sequence of the putative causative virus. Possible commercialization of this discovery in the form of a test to identify the virus in blood and tissues is being considered. The work was published in the Proceedings of the National Academy of Sciences of the United States. A clinical trial of antiviral therapy in patients suffering from PBC is being planned. This effort is representative of the kind of translational research that is becoming a hallmark of the modern academic medical center. It links basic science, the clinic, and industry. In addition to this classical kind of translational research, Ochsner has established working collaborations between all its basic scientists and clinical departments so as to assure the rapid translation of medical questions from the bedside to the bench, and research insights from the bench to the bedside.

Although, as noted above, pharmaceutical companies are more frequently engaging freestanding practitioners in drug trials, the academic centers, in addition to participating in large industry-sponsored trials, have a unique role to play in clinical research: the design and implementation of single site and multicenter research studies which may or may not involve devices or pharmaceuticals. For example, Ochsner has launched trials studying the optimal strategies for preparing patients for surgery and for determining if

antiviral agents are effective in certain liver disorders. These academic medical center-initiated trials are particularly taxing of institutional resources. They frequently require detailed statistical oversight during trial design, implementation and analysis; safety monitoring during the trial; detailed contract and financial analysis and oversight; and rigorous attention to compliance with multiple regulatory codes. Nevertheless, for all that is involved, these institution-sponsored studies often are more innovative and informative than are commercially sponsored studies. An additional benefit of undertaking these studies is that they immerse the medical center physician staff in questions surrounding the strengths and pitfalls of multicenter trials in general. It is becoming increasingly clear that clinical trials can be over interpreted or misinterpreted when details of study design such as population mix, mode of statistical analysis, details of intention-to-treat analysis, and the interpretation of secondary end points are not properly considered. Exposure to these issues in the design and conduct of an institution-sponsored trial can bring these factors home to the medical center physician corps and thereby improve their overall interpretation of the literature.

One final point related to biomedical research is perhaps worth making in this post-Hurricane Katrina world. Security from natural disaster, acts of terrorism, and war is an issue of major importance for more than the obvious reason of personnel and plant safety. Samples obtained in the process of investigation are in many ways invaluable and/or irreplaceable. This applies to patient materials collected in the course of clinical investigations as well as to cellular and nucleic acid-based reagents of various sorts developed from basic research efforts. The loss of these samples, as well as the loss of data archives and the like, often equates to the loss of untold man-years of work as well as the squandering of considerable research funding. Of perhaps even greater concern is the possibility that during a natural disaster—or a terrorist strike—one or another pathological biological agent is released into the population with harmful effect. Given the severe consequences of natural and man-made disaster, it behooves all research institutions to develop plans to mitigate these outcomes. The counter to the possible adverse consequences of natural and man-made disaster generally must involve two initiatives. First, to the extent possible, back-up archives of biologics, data records, cell lines and the like should be established. Plans for the evacuation and off-site housing of experimental animals should be made. That is, planning should be undertaken aimed at reestablishing the research activity in a post-disaster world. But even more important is the second initiative—protecting the research enterprise from a natural disaster. For example, site security should be in place to prevent unauthorized access to research facilities by terrorist groups of one sort or another. Where flood is an issue, the localized installation of flood doors and levees can be considered. The Houston biomedical community learned this lesson well after being flooded by a tropical storm several years ago, so that during the recent approach of Hurricane Rita, flood doors and bulk-heads protected Texas Medical Center. This preventive philosophy should be carried still further. Communities wishing to attract and grow biotechnology businesses and research entities must focus on security first, incentives second. Or to put this another way, in the post-Katrina world (as was the case in the pre-Katrina world), the single greatest thing which can be done for the New Orleans research enterprise—as well as for a myriad of other activities—is to develop a levee system capable of withstanding a major hurricane. But even when this is done, the other preventive actions discussed above must be attended to.

CONCLUSION

Thus, we see that medicine and medical research are changing. While the basic values of medical research remain constant, it does appear that new solutions will have to be devised to enable the enterprise to productively navigate this changing environment. New challenges will have to be addressed and new opportunities responsibly sought and developed. To fail to do so will, based on all past experience, spell the end of Ochsner's aspirations for future excellence. Ochsner is fortunate to have in its ranks an extremely high quality cadre of basic and clinical scientists who will address these challenges, and we therefore believe that we are well positioned to take advantage of the many opportunities before us.

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