Current Challenges in Clinical Research

Edward D. Frohlich, MD

Clinical investigation is that area of academic and clinical medicine in which the physician explores in depth a specific question that relates directly to patients seen in clinical practice. This investigative approach allows the physician to satisfy intellectual and academic curiosity about disease and its management either through bedside or laboratory research. To my way of thinking, this is one of those unique opportunities that provides exciting and fulfilling experiences for a physician with interest and imagination. It satisfies a thirst for new knowledge, and a means to affect the course of disease. It is a truly unique privilege for an inquiring physician to develop new fundamental knowledge about disease and to apply that information at the bedside.

The clinical investigator, therefore, must be trained to apply the scientific method to basic problems presented by the patient. This process follows the very same principles pursued by any scientist: formulation of a hypothesis from the question generated which is subsequently re-tested by controlled experimentation. Of course, the data derived must be reproduced until the final principle or answer is achieved or refuted. These principles have been applied over the centuries with the same rigor. However, more recently, the nature of the clinical problems and the means for pursuing answers have been rendered more complex by many new constraints levied by society. In previous years, many of the questions suggested clinically could be resolved by careful and objective description of one's clinical observations. The complexities surrounding clinical investigation today include the necessity to obtain funds to conduct modern research and to satisfy the rigorous ethical and regulatory controls imposed by our social structure. Notwithstanding these constraints, the opportunities and excitement for the clinical investigator remain limitless.

THE INVESTIGATOR

In the infancy of clinical medicine, knowledge of disease was thoughtfully developed by astute physicians who carefully provided beautifully detailed descriptions of diseases, thereby crystallizing in one's mind the scattered observations of the ill patient. Upon the shoulders of Hippocrates, Avicenna, Osler, and those that came before and after, diseases were clearly categorized and systematically described and compiled, and the need to understand underlying disease mechanisms became necessary. With the acquisition of knowledge derived from measurable changes in physiological parameters, in gross and microscopic anatomy and in the internal biochemical milieu of the body's composition, newer concepts of disease dramatically evolved. Thus, during the latter half of the 20th century more information became available to clinical medicine than was known in all the preceding generations of humankind.

At the turn of the 20th century, Abraham Flexner's indictment of the teaching of medicine led to the closure of most of the medical schools in the United States. Similar criticisms were leveled at the schools in Europe. In subsequent years, Flexner, funded through the Carnegie and Rockefeller Foundations, insisted that professors at medical schools in the clinical years do spend their full time in private medical practice for personal aggrandizement. Moreover, they should focus their remaining time in the medical school hospitals, teaching students and postgraduate trainees about disease management and caring for indigent patients as well as in conducting clinical research. This led to vast improvements in medical education, the establishment of formal research programs in teaching hospitals and in institutions, and the founding of professional societies organized to conduct peer-reviewed research. These drastic changes in academic medicine were responsible for the present day leadership of this country in world medicine.

EXPLOSION IN NEW KNOWLEDGE

Most of us reading this discussion can only reflect with amazement on the astounding changes in our time. For example, when I began my medical education, complications from hypertension were major causes for most of the hospital admissions, including patients with stroke, cardiac failure, myocardial infarction, renal failure, and hypertensive emergencies. Today, Ochsner Clinic Foundation no longer maintains a hypertension hospital service; hypertensive emergencies now are rarities, and deaths from stroke and coronary heart disease in this country have decreased by over 70 and 50 percent, respectively. These changes have resulted from the tremendous advances in our understanding of the underlying mechanisms of the hypertensive diseases and related advances in the treatment and management of these clinical problems.

Recognition of this concept has a very important bearing on our understanding of disease causation. In the early years of the 20th century, causation of disease required satisfaction of the Koch's postulates since the most important illnesses encountered were infectious in causation. That is to say, identification of a specific and offending organism postulated to cause disease was necessary, and its eradication must be coincident with reversal of the disease. Today, most of the diseases that we face are not produced by a single factor; their causations are multifactorial in nature. Multifactorial causation is a concept attributable to the Pagean Mosaic, which has been so useful in our understanding of the underlying pathogenetic factors of essential hypertension.

Consider for a moment the explosion of new knowledge about normal bodily functions and the impact of disease on regulatory mechanisms. Further, consider the opportunities provided by the recent identification of the entire human genome, which has been elucidated in one relatively brief period. Also, reflect briefly on the new fields of molecular biology and those "high tech" procedures that have extended the scope of the disciplines of physiological and biochemical inquiry. They have permitted the application of information heretofore inconceivable in order to comprehend new disease mechanisms. Consider still further the innovative diagnostic and therapeutic concepts that have been afforded to today's medicine through "gee whiz" new technology. Each of these mind-boggling advances has been impacted by the more recent constraints imposed by society. These societal and ethical developments have been introduced to satisfy the need for approved and sound research protocols, implementation of institutional human research committees, and the imposition of countless regulations by a vast number of local, national, and international regulatory bodies. It is easy to see how the conduct of clinical investigation has dramatically expanded from the bygone years of descriptive medicine to its present day complexity.

ETHICAL CONSIDERATIONS

It was during the 20th century that a number of unimaginable social and political events took place that required preventive measures to ensure that they would never again happen. Moreover, even if adverse events occurred because of good intentions, current practice now requires careful monitoring and peer review. Thus, at one end of the spectrum was the deliberate, ugly expression of man's inhumanity to man. In Nazi Germany, inmates of hellish concentration camps were subjected to brutal torture and inconceivable acts of human experimentation. At the other end of the spectrum were more innocently intended practices related to advances in medical science in which new means of treatment were evaluated in clinical studies (e.g., Tuskegee Study) that failed to employ more reasoned and disciplined peer-review of clinical investigation and "human use" committees. The perpetrators of the atrocities in the Nazi concentration camps were brought to prompt trial in Nuremberg; and the resulting recommendations of these proceedings resulted in the promulgation of the Nuremberg Code that provides ethical standards for clinical investigation. Because of the other clinical studies involving new treatments or the follow-up of patients with disease conducted without adequate review and approval, additional and more strict regulatory measures were adopted to prevent future unwarranted occurrences.

Measures resulting from these events included: international acceptance of the Nuremberg and Helsinki Codes; broadening of regulations developed by the Food and Drug Administration in the United States to prevent injury and deaths associated with new drug and device evaluation; legislation requiring institutional human experimentation committees (HEC); review of all experimental protocols prior to instituting all clinical research studies; and requirements by all peer-reviewed medical journals for statements in research publications of protocol approval before initiating a study. As a result of the wide acceptance of these varying measures, institutions in which clinical research is conducted are subject to extramural inspection, intensive external review and, if necessary, penalties for all inappropriate research activities. To assure compliance with the guideline measures for the ethical conduct of research, Federal legislation mandates that all institutions in which this research is conducted must assure specific regulatory bodies (e.g., Food and Drug Administration, National Institutes of Health) that all clinical investigators have been fully informed of the required regulations and that they have passed written examination concerning these regulations.

THE FUTURE OF CLINICAL RESEARCH

As long as disease affects human beings, as long as keen interest, intellectual curiosity, and caring remain imbued within the physician's credo, and as long as newly generated knowledge stimulates further questioning, the future of clinical investigation will continue to be bright. Medicine will always be stimulated by new clinical problems, and unknown challenges will inevitably appear. Opportunities for further areas of investigation will only be limited by imagination, curiosity, and the ongoing need to satisfy these problems. The need to close the gaps raised by more recent investigations, the necessity for improved means for diagnosis and treatment, and the questions raised by patients will, undoubtedly, persist in perpetuity.

New areas of inquiry generated by the identification of each of the components of the human genome, by innovative molecular biological concepts, by more sophisticated appreciation of the inflammatory, neoplastic, and other processes, and by new approaches to clinical research will generate further questions and interest. This is the nature and wellspring of modern clinical investigation. Further questions, no doubt, will be generated by these more recent disciplines of medicine, including the need for improved therapies generated by updated knowledge of the mechanisms of disease and improved pharmacological technology and concepts derived from epidemiological findings and outcomes research; and the needs stimulated by innovative disciplines (e.g., health-care economics, medical ethics, and the myriad of social and other problems) which will impact clinical practice. Not all investigators will be able to participate in these new areas, but their interest and participation in the overall scientific society in which they interact will be important in generating continued growth. For example, the geneticist may only be interested in the fruits of laboratory study, but interest in interacting with the questions that are created by genetics will have far-reaching implications for the legislator, sociologist, economist, ethicist, and many other disciplines, as well as the public. What is vitally necessary is the urgency for the clinical scientist to communicate with each of them in a meaningful way.

Always remaining a challenge to clinical investigators is the necessity to secure funding for research and to relate closely with the public, their legislators, publishers of research findings and, of course, their colleagues in industry and academia. Perhaps less emphasized (and possibly among the most important) is the vital need for mentorship. The conduct and process of mentoring is as important as that of the schooling and experience of both the mentor and the student. It requires continuous personal interaction and communication, and must avoid stimulating the transient interest of a student or trainee in order to serve as the investigator's extended hands at the bedside or in the laboratory. Excellence in mentoring is a continuous ongoing relationship involving teaching, reviewing accomplished work, discussing newly published reports, promoting the mentee for memberships in academic societies, and the imbued need for the mentor to relate with the mentee over a lifetime of professional activities and personal interactions. Thus, the ideal mentor is an individual whose professional productivity will be extended to future generations. In the final analysis, this is the very real future and continued promise for clinical investigation!

Edward D. Frohlich, MD
Alton Ochsner Distinguished Scientist

REFERENCES

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