COMMENTS

We welcome comments by our readers reflecting agreement or disagreement with the material published in this section and at the discretion of the Editor-in-Chief, will publish such comments.

Introduction

We are fortunate to have the opportunity to publish this reflection on the process of clinical research. Dr. Hazzard has had a distinguished career as the director of one of the original clinics of the NIH Lipid Research Clinics Program as vice chairman and chairman, respectively, of the Departments of Medicine at Johns Hopkins and Wake Forest Medical Schools and as a leading gerontologist, now at the University of Washington. As Dr. Hazzard makes clear, the problems facing the clinical researcher are many but the rewards are also many. The challenge is to keep open the door to such a career and to encourage the success of those who pass through.

Robert H. Knopp, MD
Past-President, SEBM

Clinical Investigation: But Why?

WILLIAM R. HAZZARD[1]

VA Puget Sound, Seattle, Washington

When asked what I value most as a senior academic gerontologist, I respond without hesitation, "Clinical Investigation", which for me means research involving people (sometimes called "patient-oriented research"). Especially when the query is posed by a colleague from a nonclinical discipline, my answer predictably prompts another question: "But why?" The short answer is, "Because I'm a doctor!" As an academic physician, research is clearly as central to my professional activity as it is to any other member of the faculty, even as I do my best to balance clinical, teaching, and administrative activities in the way that makes the most sense for me as well as for my institution. For me that translates into an enduring personal focus on research that involves patients—clinical investigation.

It certainly is not because clinical investigation is easier or more guaranteed to succeed than basic research. For example, as a gerontologist and geriatrician with a background in lipoprotein metabolism, I have become fascinated by the metabolic basis of Alzheimer's disease. To pursue that newfound fascination, I have just drafted a protocol to study the mechanism whereby HMG CoA reductase inhibitors ("statins") may retard the pathogenesis of Alzheimer's Disease. To pursue these studies, I must of course submit grant proposals for extramural funding from governmental agencies (the NIH and the VA) or industrial sources. Prior to such submission my protocol must be reviewed by a series of internal committees. Since human volunteer subjects will be involved, the institutional review board (IRB) of the University of Washington School of Medicine must grant approval, an increasingly difficult hurdle to surmount in this era of intense scrutiny of the rights, privileges, and safety of subjects who volunteer for such studies. Since I plan to use the General Clinical Research Center (GCRC) of the University of Washington funded by the NIH explicitly for support of human studies, I must also gain approval of the GCRC review committee. Because we shall assess brain blood flow and metabolism during statin treatment using positron emission tomography (PET scanning), the Radiation Safety Committee must also approve. Because animal studies will be involved (for the generation of antibodies for immunoassays and in parallel nonhuman mechanistic investigations not possible in human subjects), yet another committee must approve my proposal. Finally, after having received approval at each of these levels and with due attention to issues of appropriate distribution of study subjects by gender and ethnicity and the ethical conduct of the studies proposed, my grant will be submitted to NIH to compete in the standard peer-reviewed study section process in a common pool with the far larger number of proposals not involving human subjects.

In the deliberations of such peer-review bodies, studies involving human subjects often fare poorly, in part because of necessary limitations in study design and execution imposed by potential risks involved or invasive interventions not appropriate for human studies (for instance, in studies of beta amyloid deposition in those at risk for Alzheimer's Disease, obtaining tissue biopsies or even cerebrospinal fluid requiring lumbar puncture, or studies employing use of radiolabeled beta amyloid may be deemed unsafe and inappropriate, much less experiments that might employ such con-

[1] To whom requests for reprints should be addressed at S-GEC-182, VA Puget Sound Health Care System, 1660 s. Columbian Way, Seattle, WA 98108.

1535-3702/01/22610-0871$15.00

temporary methods as transgenic or gene therapy techniques). After all, why should research involving humans receive any special consideration when far more specific and state-of-the-art techniques involving nonhuman material might provide more direct answers to the critical questions under study?

When approval and funding hurdles for my studies have been surmounted, then the really hard work begins. Volunteer subjects must be recruited and screened, informed consent obtained, and their studies scheduled in consideration of their personal and family circumstances. Once the study has been initiated, every subject will require frequent contact to answer questions, ensure compliance with study protocols, and reassure them that their personal safety and needs are being met by the investigators and staff. In short, they must feel that we care for them and appreciate their contribution to science and to society. By the same token, any subject may choose to discontinue participation at any time without explanation, justification, or prejudice to their future care. They may (and often do) drop out for no reason at all. They may move, change jobs, become depressed, become ill with conditions unrelated to the study, or become disillusioned with the research process, perhaps because of its slow pace or because their treatment status (e.g., placebo vs. statin) is necessarily blinded until the study has been completed. Hence, research involving people must always be considered high risk, and contingency plans should be developed from the outset to deal with unanticipated problems.

So with all of these special challenges to meet, why indeed do I persist in pursuing human investigation? The simple answer is, because in the words of Alexander Pope, "The proper study of mankind is man." And for me that remains my top priority. After all, I am first and foremost a physician, dedicated to healing the sick and, especially, to preventing illness, disease, and disability. I am a Gerontologist and Geriatrician, fascinated by human aging throughout the lifespan, from conception through death. That perspective demands constant exploration and contemplation to understand the human condition at each stage of life to develop strategies to preserve health and optimize function well into old age, an approach that requires people to be squarely at the center my attention. Unlike an increasing number of investigators who examine large study groups or even populations, I am required to know each of my study subjects as a person, one by one, generally through an extended period of controlled metabolic investigation.

This focus upon individual human subjects to which I steadfastly adhere was born of my training here at the University of Washington in the laboratory of Dr. Edwin L. Bierman and Dr. Daniel Porte, Jr. at the Seattle VA Hospital in the late 1960's and early 1970's. Those of us privileged to learn our trade in the Bierman-Porte laboratory often reminisce at length on those times as the "golden era of clinical investigation." Under the leadership of Bierman and Porte, post-residency fellows, attracted like me to their program, learned the joy and excitement of patient-oriented research. We learned to relish not only the repartee of a lively scientific discussion among the investigators, but also the companionship of all those involved—nurses, dietitians, laboratory personnel, data analysts, and secretaries. We dwelt in a crucible of excitement and discovery at a time when careful studies of our patients with diabetes and dyslipoproteinemia provided constant new insights into these common disorders. We experienced all the challenges and satisfaction of recruiting and retaining study subjects. We learned to design and execute controlled metabolic studies to answer important questions with the same rigor and attention to detail required for nonhuman studies, often demanding more ingenuity because real people were involved. We paid close attention to the safety and welfare of our study subjects, each of whom we came to know as people with all of the foibles of the human condition. And in doing so, we transmitted our commitment and excitement to those subjects who became true collaborators in our research, volunteers who had at least as much invested in the outcome of our studies as we did. We also learned the art of defending our research in forums large and small, both in person and in the literature, and we were exhilarated by the spirit of science that spurred our efforts to every increasing heights. And of course, we constantly wrote grants to compete for the resources to support our research.

Our efforts and frustrations in meeting these challenges were far outweighed by the joy and stimulation of our daily lives as clinical investigators, pursuing answers to questions raised daily in the care of patients with metabolic disorders that we were attempting to better understand, prevent, and treat. And of course we were younger then, with the boundless optimism, enthusiasm, and energy of youth, convinced that our efforts would make a difference in the lives of our patients and the countless others with these disorders. But in spite of the passage of time, the spirit of those heady days has endured through the careers of those of us privileged to be products of the Bierman-Porte era.

Tragically, in 1995 Ed Bierman succumbed at 64 to a rare malignancy and is no longer among us to lend continued inspiration and intellectual stimulation. Porte has recently retired from the VA, though he now prods new colleagues at the University of California, San Diego with his unquenchable scientific curiosity and criticism. The influence and the spirit of human investigation both of these mentors inspired in us—dedicated to the proposition that the proper study of mankind is man—continues to endure in Seattle as well as at the many other academic health science centers throughout the United States and across the world. Their literally dozens of former fellows and other trainees continue to communicate the joys of research experienced under their leadership to succeeding generations of clinical investigators.

So why clinical investigation? Is it difficult? Yes. Is it time-consuming, necessarily complex, and deliberate? Yes! Is it worth it? Yes! Is it still the most relevant biomedical research? Yes! If I were starting today, would I pursue it over studies of genes, tissues, or animal models? Yes! Absolutely!