DIRECTOR'S REPORT

History will almost certainly judge the current era of biology as one of the most productive periods of scientific endeavor, comparable to the dramatic discoveries in quantum physics in the early half of this century. The discoveries in physics led to a fundamental understanding about the nature of the atom and the beginnings of time. The understanding was so deep that it drove some to philosophy to ·explain" the unexplainable, whereas others pursued more practical endeavors that prepared the way for a major technological revolution. On the other hand, the dramatic increase in our ability to study life means that experimental biologists will be kept busy for at least the next 100 years and thus may not have time for more philosophical pursuits. Moreover, because advances in biology are so intimately linked to human health, the biologists will always have important practical problems to unravel. How this might be done best sl1ould be a topic of constant conversation.

Advances in the basic biomedical sciences are coming at a very rapid pace, and from all directions. The current efforts to sequence the genomes of many organisms, the daily identification of interesting new proteins and discovery of their functions, and the remarkable ability to investigate gene function using powerful genetic manipulations offer unparalleled opportunities for medicine. The amount of biological information that is emerging from this revolution is staggering, and there is an urgent need for more efficient ways to keep track.

Luckily, within the last year or so, there has surfaced a potential solution to the information storage and retrieval problem. A number of journals are now completely available in electronic form on the Internet (for example, the *Journal of Biological Chemistry* is a particularly useful online resource). In the best cases, the full text of the journal can be rapidly searched for information. Key words and references in the research articles are electronically linked to information databases, such as databases containing genome and protein sequences, genetic and disease databases, and even other scientific literature. This makes it relatively easy to seek out relevant information that is connected to the original research. I suspect that in the very near future, a substantial amount of biology can be "done" by computer informatics experts who seek connections between published experimental results. It may well be that a new field of biology, "virtual physiology,· will emerge as an essential contributor to progress in the biological sciences. Ideally, these virtual physiologists will link up with the experimental scientists so that biology does not become completely theoretical. For example, even today there are those who make claims about the function of proteins based on DNA sequence similarities when they have no intention of following up on these claims.

At the same time, scientific meetings such as those held here at the Laboratory will be ever more important as the amount of information increases. Such conferences provide to a scientist an overview of a field in a matter of a few days which probably would take weeks or even months to comprehend by reading the literature.

As exciting as the advances in modern biology are, there is a pressing need for institutions such as our own to better facilitate connections in biology, particularly the transfer of the exciting advances in basic science to clinical research. Interaction be-

tween basic and clinical research groups is now cast by the National Institutes of Health (NIH) as "translational" research, but more often this term is used by scientists to secure grant funds than it is for advancing real transfer of information between the sciences.

There are often long lag times between basic research discoveries and clinical applications. It is common for the brightest minds that contribute to the spectacular advances in basic research to be unaware of the day-to-day problems faced by the clinician. It is equally common for the clinician to be unapprised about new discoveries in basic research. As the advances in basic science become more extensive and complicated, it will be increasingly necessary to bring those interested in transferring basic discoveries to the clinic together with the clinical researchers. This will be particularly necessary for the critical design of patient-based research because of the complexities in planning good clinical studies and the enormous costs that are often associated with this type of inquiry. How clinical research might be best done and how basic scientists might contribute are problems that need attention.

With these thoughts in mind, a meeting was organized at the Banbury Conference Center in October, 1995, that focused on neurofibromatosis type 1 (von Recklinghausen disease, NF1), a devastating disease that affects about 1 in 4000 people throughout the world. This dominantly inherited trait causes learning disabilities in young children, and children and adults are affected with a variety of deformities, such as café-au-lait spots, neurofibromas, optical and bone problems, and malignancies. The NF1 mutations were mapped to chromosome 17 in 1987, and the altered gene that causes these severe abnormalities was cloned in 1990 through a cooperative research effort, spearheaded by Francis Collins, now head of the National Center for Human Genome Research at the NIH.

The protein product from this gene is large and its full functions are not known, but the protein displays similarities to a known regulator of the human RAS protein. As shown by Michael Wigler and his colleagues at Cold Spring Harbor, as well as others, when mutated, the human *RAS* oncogene contributes to cancer progression in a large fraction of human tumors. This provides an interesting, but still speculative, link between tumor formation and the NF1 protein. Because of the links with human cancer, a great deal has been done on the biochemistry of the RAS protein. This information has come from basic research on the RAS protein in species as diverse as yeasts, the fruit fly *Drosophila*, and mammals such as mice, and there are very interesting potential anticancer drugs that have been developed by the pharmaceutical industry based on this basic research.

There is thus an enormous amount of information known about the biochemistry and genetics related to NF1 disease. The gene that causes the primary problems is in hand and a great deal of information is known about the possible biochemical pathways the NF1 protein controls. Yet there are significant problems that clinicians have in diagnosing and treating the disease. Despite the apparent genetic simplicity, there is extreme clinical variability in the outcome of the disease; diagnosis, particularly of the cognitive deficits, is a major problem for the clinician and a detailed description of the nature of some of the clinical defects is lacking. Because these clinical problems still exist, but also because there is a strong interest by scientists in the biology of the NF1 protein, it seemed that a meeting that brought together clinicians, scientists interested in clinical and basic research, and investigators from the pharmaceutical industry to discuss the disease would be valuable. Although there have been other meetings on NF1, the charge at the Banbury meeting was to discuss how clinical science and medicine would be best advanced by the better design of clinical research and better coordinated basic

research. Another goal was to explore progress in both clinical research and therapeutic strategies targeted at all aspects of the disease. Because so much is known about the underlying mechanisms that lead to NF1, our agenda was to assess critically how this understanding was being exploited for further treatment and what might be done to speed clinical progress. Our intention was to use NF1 as a model disease to determine some of the problems that arise in moving basic research into the clinic and how best to facilitate good clinical research. In this respect, the meeting was an outstanding success.

It was apparent during the meeting that while basic research on this disease was progressing well, clinical research lagged sadly behind and many translational opportunities were missed. There appeared to be too many cases where there was insufficient clinical information available to enable therapeutic strategies to be assessed. For example, it was clear that there was a dearth of systematic, longitudinal studies on the development and growth of neurofibromas. Even the origin of the cells in the neurofibromas remains an enigma. In another case, it was very clear that although the vast majority of human cancers containing mutations in the RAS protein affected one of the three RAS proteins in humans (K-RAS), the best animal model available for assessing drugs that target the RAS pathway is a transgenic mouse expressing an activated form of a different human RAS protein (H-AAS). Thus, the relevance of this animal model to human disease and for testing existing drugs that target the RAS pathway is questionable. The latter deficiency has implications far beyond NF1 research.

As a result of lengthy discussions at the meeting and conversations since then with many investigators, a series of recommendations emerged that I believe may greatly enhance clinical studies on NF1. More importantly, however, this type of approach could become a paradigm for facilitation of needed clinical research generally.

The NF1 community of basic scientists and clinicians present at the meeting, including representatives from large pharmaceutical houses, decided to establish small working groups whose charge is to solicit consensus opinions on the deficiencies in translational and clinical research. The groups chosen for NF1 covered five areas: orthopedics, cognition, neurofibromas, malignancies, and optic glioma. Each of these areas was selected because they represent distinct clinical problems. Each group has a Chair to coordinate the agenda, which is to identify deficiencies in the clinical knowledge base, initiate new ideas for clinical research, coordinate multicenter clinical proposals, and maintain limited databases of information. These groups in turn will report to a parent steering committee (headed by Dr. Bruce Korf at the Children's Hospital in Boston) that will oversee the progress of the individual groups, coordinate research between the groups, and set any recommendations that might be forwarded to the NIH. These recommendations could be then sent to the office of the Director at an appropriate Institute within the NIH where they could decide, in consultation with the working group Chair, a suitable method of approach. In many situations, this could be a very effective mechanism for the NIH to identify high priority areas for program announcements for future peer-reviewed research. This mechanism would then ensure that the research was investigator-initiated, was deemed by 11 12 the scientific community to be of high value, and that any research funded did not bypass the normal stringent NIH standards for reviewing and funding science.

As a result of the Cold Spring Harbor meeting on NF1, the mechanism has been established, and already the groups are working to discuss how clinical research in this area might be enhanced. There is every reason to believe that this experience with NF1 could be copied for many other areas of clinical research that are tied to specific dis-

eases or groups of disease. The NF1 meeting held here, and importantly, the mechanism for generating subsequent recommendations, could become a model for future meetings on other equally pressing medical research. It should be the responsibility of research institutions to facilitate such meetings, to host the initial meetings where the problems that exist are discussed, and then to facilitate the establishment of working groups. Ideally, institutions should coordinate these meetings with the NIH by inviting Institute Directors or appropriate program staff, as well as with research foundations and academic or research societies. Certainly, the ability to access and exchange information on the Internet will also help in such endeavors and may ultimately provide a vehicle for providing information about the disease to the public. In many ways, the search for the affected gene and a possible cure for Huntington's disease that was coordinated by Nancy Wexler from Columbia University is a shining example of how clinically relevant research might be advanced by discussion groups. Unfortunately, not every important problem in medicine has someone like Nancy Wexler to keep the momentum going. Perhaps the example set at the Banbury Center will become a valuable precedent, and it is hoped that this mechanism for facilitating clinical research will spread throughout the biomedical research community.

The NIH would need to be receptive to such proposals, but clearly if highly relevant and important science, particularly in the clinical arena, were to derive from such meetings, then I believe they would be more than welcome. At present, in many Institutes at the NIH, it has become the role of program staff to initiate and solicit new research via the "Request for Application" (RFA) mechanism. It is my experience that many of these RFAs happen to be in obvious well-funded areas and that they shy away from the "not-so-obvious" basic research and clinical research. The NF1 model will allow clinicians, scientists, and the pharmaceutical experts to provide important advice and suggestions to the Institute Directors and program staff at the NIH prior to decisions they make on the general directions for extramural research. I believe the mechanisms discussed above will not only further progress in clinical research, but also provide a valuable mechanism to collect scientist- and clinician-driven rationales for convincing the public and Congress to continue to support biomedical research.

April 26, 1996 **Bruce Stillman**