Factors influencing future progress in neurosurgery

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Invited Article

NEUROSURGERY is a new specialty: barely 50 years old. It evolved with phenomenal success and perhaps this is our problem; we have been forced to mature too rapidly. Any review of earlier days indicates that this was a period of rapid growth for the content of our discipline. At one time, our major contribution to medicine was the treatment of tumors of the brain and spinal cord. Now this represents a significant but no longer major component of our therapeutic armamentarium. Therapeutic capabilities have dramatically broadened. However, it is the judgment of most of our colleagues in other disciplines that the major excitement is now gone from neurosurgery, and that we are becoming just another surgical discipline. We are no longer the "Queen of the Surgical Arts." There are many reasons for this. The first generation of neurosurgeons felt a keen obligation to make contributions to the field: Cushing, Foerster, Dandy, and Penfield are only a few examples. The current generation of neurosurgeons feels this obligation only weakly. Some would say that many of the younger men we are training are more surgical technicians than intellectual pioneers.

Of course, early progress was easy. There was a concentration of clinical material in the hands of a few, which will never be duplicated. At one time, Cushing had access to almost all the pituitary tumors in the world; Grant operated on something like 1000 patients with trigeminal neuralgia. Enlargement of the therapeutic potential of the field occurred when new types of pathology were described and appropriate therapy was devised. Now progress is slower. The major varieties of clinical entities have all been described, and therapy is somewhat standardized. Great progress has been made in the treatment of aneurysms, stereotaxic surgery, and in other areas. But it is questionable whether we do a much better job with tumors, discs, and trauma now compared with 30 years ago.

This leads to the question: is neurosurgery going to develop into a mundane, routine field relegated to delivering standardized surgical treatment for the public, perhaps analogous to the current status of abdominal surgery? Certainly we need surgeons to do appendectomies, and to remove gall bladders; and we will need neurosurgeons to remove tumors and subdural hematomas. If we are to be satisfied with this, a major opportunity will have been lost.

At this point in history, the potential for unusual progress exists. Neuroscience is now just coming into full flower. Presently, there is more intellectual ferment and potential in neuroscience than in any other field of biological research. Some 2 years ago, the President of the United States appointed a Presidential Biomedical Research Panel. One of their key recommendations deserves serious consideration in anticipation of the future. It is as follows:

"Perhaps the ultimate challenge to biomedical research representing the very pinnacle of our understanding of the human organism, lies in neurobiology; how the brain and nervous system develop, how they function in health and disease, how
thought occurs, how memory is stored, how we reason, how we are motivated, and how we interact with our physical and social environment. . . . The study of brain and mind deserves greatly increased attention not only in the programs of the Federal government, but also from the many different disciplines of biomedical and behavioral science, as well as such fields as mathematics, linguistics, and the communicative sciences. This Panel commends neurobiology as a compelling long-range interest worthy of national attention."

This promise and excitement comes from a group of mature scientists, clinicians, and experts from all fields, and is also well recognized by our young people. They look on neuroscience as the major area of progress for the next generation. Twenty years ago, the number of neuroscientists in the United States was small. The first meeting of the Society for Neuroscience in 1970 attracted almost 600 people. By 1974, the membership had risen to 7500, and the National Academy of Sciences estimates that, by 1985, it will number 15,000. This is the field that is attracting bright young brains.

How can neurosurgery be a part of this new adventure? It will not occur without effort, nor without some changes within our discipline. At the present time, experimental research is clearly moving away from clinical problems. The responsibility for new knowledge is being carried almost exclusively by Ph.D. scientists, and by fewer and fewer clinicians.

Neurosurgical Research Programs

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) of the National Institutes of Health (NIH) dispenses some $150 million annually for support of clinical and basic research and training in the neurosciences. All these programs are overseen by the National Advisory Council, the membership of which includes two neurosurgeons. Review of the supported programs indicates that there is a growing divergence between clinical interests and effort, and the directions in experimental research. The figures document that each year fewer people with the M.D. degree apply for or are awarded support for research. An increasing amount of the support goes to Ph.D. scientists. The competence and capabilities of the Ph.D. scientists are exciting, but, without clinical input and without any contact with clinicians or the problems of human disease, the direction of their interests is significantly different from what it was 15 years ago. One way of judging this is to look at the experimental preparations that are popular. In the past, much research on the nervous system has been carried out on experimental mammals, including such species as rats and cats. Starting with Grunbaum and Sherrington, the appeal of research on subhuman primates grew. It was something of a scientific status symbol to work on monkeys or chimpanzees. The relevance of the results to an understanding of the human brain was obvious to all. This has significantly changed. Nonhuman primates are now used relatively infrequently. In part this is because of the expense. Not too many years ago, a rhesus monkey could be caught in India, transported to the United States, and put in a laboratory for less than $20; now the cost is over $200. However, economics is not the major factor. Interests have changed, as evidenced by the research protocols coming through the NIH Council. At one time a few years ago, the status research was done on a sea slug called aplysia. More recently, it seems that the up-and-coming status preparation is an organism called the Molluca Sexta. This is a species of moth, and it has a larva with unusually large neurons in it, making it attractive for study of single-cell function. But what has happened to studies of the pyramidial tract in the monkey such as used to be undertaken in John Fulton’s laboratory? Are we going to be able to understand the function of the frontal lobes of man by studies on the Molluca Sexta? It is true that the history of science indicates that one can never predict where the essential insight will be generated that permits progress at the human level. Certainly fundamental, undirected research is vital, but we also need balance; we need research which is ultimately relevant to man. And this is essential if the future viability of neurosurgery is to be assured.

Neurosurgeons themselves must be involved in the research process. Some must possess sophisticated skills in experimental research in the various disciplines of the neurosciences. Only in this fashion can credible communication and real collaboration with our basic science colleagues occur. Others of us must possess the necessary skills to engage in innovative and carefully controlled clinical research. Finally, and perhaps most importantly, there must be a perception throughout the neurosurgical profession that these goals have high priority and should be broadly supported.

What must be done? The right people and the right environment are primary needs. An old German recipe on how to make hasenpfeffer beings: “First you must catch the right rabbit.” Then provide an intellectual environment conducive to the exchange of ideas with others in related and even unrelated fields; shield them from nonproductive activities; relieve them from the time-consuming and nerve-wracking experiences of obtaining research support. If they are clinicians, they must not only have an environment for innovative development but must have protection of their time commitments so that they can engage in clinical or laboratory research. They cannot be clinical slaves of the institution. The environment must give them broad access to knowledge.

Clinical Research

It is really not possible for one man to produce, store, recall, and relate all of the knowledge needed for a major advance in medicine. Consider the development of open-heart surgery. In 1954, John
Gibbon performed the first repair of a human heart while the circulation was supported by an artificial heart-lung apparatus. But many others, dating back to the 17th century first had to make essential discoveries; and Gibbon had to know and make use of these. Obviously Harvey (1628) had to discover the circulation of blood; Landsteiner (1900) had to discover human blood groups; Hustin (1914) had to find that citrate was a satisfactory, nontoxic anticoagulant, and so on. Could better interdisciplinary services have brought together the knowledge required for open-heart surgery so that it could be carried out in 1846, shortly after the discovery of surgical anesthesia? That was unlikely because critical, essential knowledge was unavailable until 1934. The critical factor was the need for a heart-lung machine. Some have noted that 1934 was the year that DeBakey published the report on his roller perfusion pump. Yet, a search of the literature would have revealed that the details of such a pump were reported by Van Allen in 1932, earlier by Bayliss and Muller in 1928, and even that a man named Kelly had obtained U.S. Patent #314851 on it in 1885! The pump was obviously not a limiting factor.

The more likely limiting factor was the absence of a nontoxic anticoagulant. It is hardly accidental that Gibbon began his long research program on a heart-lung machine in 1934, the very year that heparin became commercially available. However, the laboratory discovery of crude heparin was made in 1916, and an earlier Gibbon might have forced its purification 10 to 15 years earlier than 1934. Maybe work on the heart-lung machine began in 1934 partly because the essential knowledge became available in that year, but it is more likely it was because Gibbon became available that year. More than the presence of Gibbon may have been necessary. It is important to remember that Gibbon spent 13 years trying to perfect the heart-lung machine, not for open-heart surgery, but to allow time for a surgeon to remove an embolus blocking the pulmonary artery. It was only in 1947 that, on the urging of Alfred Blalock, he switched his goal to providing an instrument that would permit repair of cardiac defects.

It is imperative that we have people in neurosurgery doing research. They must be people who are aware of existing developments in the rapidly expanding field of neuroscience, and who can quickly grasp the clinical potential of new concepts so that they can be developed to enlarge our therapeutic horizons. Through continued building and maintaining the interface between research and clinical practice, exciting new horizons will open to neurosurgery. Two examples easily come to mind. The technique of stereotaxis will be extended in many directions, and will include not only definitive therapy by the production of localized lesions, but the development of techniques for activating circuits by local stimulation through implanted stimulating devices. We will become much more competent in providing real therapeutic help in dealing with trauma of the brain and spinal cord, for which we really do very little at the present time. The list could easily be expanded.

Randomized Clinical Trials

This progress will bring its own problems. As new surgical approaches are developed, techniques must be developed for documenting their efficacy and safety. This has not been done adequately in the past and this lack can be demonstrated in other surgical fields.

In 1877, Nikolai Eck carried out the first experimental portocaval shunts in eight dogs, of which one survived for a number of weeks, thus establishing that the procedure was not incompatible with life. Early in this century, the procedure was occasionally carried out in attempts to control hemorrhage or ascites in patients suffering from cirrhosis of the liver. As there were no long-term survivors, the operation fell into disuse until it was reintroduced by Whipple in 1945. Subsequent series of shunts of various types reported by Blakemore, Linton, Rousselet, and others established that hemorrhage from esophageal varices could be prevented in most patients. The operative mortality was high initially, but so was the mortality of recurrent hemorrhage with medical management. The apparent success of the procedure was such that it was many years before the value of the operation came into serious question. It was not until 1954 that it was recognized that portal systemic shunt in man is often followed by a severe intermittent encephalopathy, now recognized to be related to disordered amine metabolism in brain. This serious, and often lethal, complication led many clinicians to doubt the value of shunt surgery; but the unquestioned protection shunts provide against hemorrhage presented an argument that seemed difficult to challenge. There was, in fact, little serious debate concerning the appropriateness of shunt surgery in patients who had already bled from esophageal varices; the debate centered around the issue of whether shunt surgery should be performed as a prophylactic procedure. Here there was sufficient professional uncertainty to justify careful randomized clinical trials, and these were carried out. The results revealed no difference in survival between patients who had been selected at random for medical therapy and those similarly selected for surgery; very few of the surgical group had subsequent hemorrhage, whereas those under medical therapy often bled. The surgical patient, however, suffered a high incidence of progressive hepatic failure and encephalopathy, with a subsequent mortality approximating that from hemorrhage in the medically treated group.

With the prophylactic shunt discredited, the value of therapeutic shunt in patients who had already bled from varices was re-examined. It now appears that the "therapeutic" shunt provides, at best, slight survival value, although it does protect against hemorrhage.

As one reviews the disorderly history of the innovation of these shunting procedures, it is obvious that decades (at least 30 years) were wasted by the failure of
to introduce, standardize, and carry out randomized clinical trials from the beginning. Such trials were finally carried out because of two events: one was the recognition of an iatrogenic complication (encephalopathy) potentially as serious as the original condition; and the second was the effort to extend the treatment beyond original indications to situations where genuine uncertainty existed. Before these events, it could be argued (and was) that randomized clinical trials were neither necessary nor ethical.

This may sound vaguely familiar to a neurosurgical audience. We went through a somewhat similar process in dealing with aneurysm surgery where there was great difficulty in setting up randomized clinical trials because the operation was well established by that time, and all neurosurgeons were convinced that the operation was worthwhile. In fact, much of the most useful data obtained in the Collaborative Study came from our British colleagues who participated in that study. As a result, there are still some lingering doubts in some minds that surgery for at least some aneurysms may not be any improvement over the natural history of the disease. A similar situation may be developing with respect to the extracranial-intracranial bypass graft operation for occlusive disease of intracranial vessels. The NINCDS has sponsored a controlled study to determine the efficacy of this procedure; but already the operation is becoming so popular that it may be too late to undertake an appropriate study of this kind. We may be in the same position as the coronary bypass operation for coronary artery disease which is so popular in North America. But there is still no firm evidence that this cardiac operation prolongs life.

Interestingly enough, the development of the total hip replacement operation occurred in a logical way; but largely by accident. The first successful prosthesis was described by Charnley at the University of Manchester in 1961. Initial problems with the plastic were corrected by the use of a high-density polyethylene methyl methacrylate. In the United States, a casual inquiry regarding the possible interest or concern of the Federal Drug Administration (FDA) with the implantation of methyl methacrylate elicited the prompt institution of FDA regulations as for any other investigational new drug. Approval of the FDA is required before any new drugs can be marketed, and they treated methyl methacrylate as a drug. Thus, FDA regulations required that orthopedic surgeons submit full particulars of proposed experimental protocols before they were allowed to proceed with the new operation. The information so collected provided nationwide data from the outset and made available a knowledge of surgical outcome which was comprehensive and almost unique. By late 1971, clinical experiments were considered to have established the safety and efficacy of methyl methacrylate, and the FDA released it for general use.

The neurosurgical profession can and should evolve techniques for developing and proving the usefulness of new operations without the inefficiencies and burdens of governmental involvement, regardless of how well intentioned these may be.

Techniques for Experimentation

A new procedure must be developed before it can be tested clinically. Even this is difficult in modern times. The central factor to this process is innovation. Here history speaks against initially rigid control, inasmuch as such control may lead to premature evaluation. It is now a requirement in all the major hospitals in the United States that there be a “human experimentation committee.” This committee, composed of clinicians and scientists, must approve the procedures involved in any experimental study involving patients or human volunteers in treatment that is not “established” therapy. Their major concern is that the subjects involved be well protected by informed consent, and, for the most part, the system has operated well thus far. However, it is quite possible that today’s human experimentation committees would not have conditioned the more than 50% mortality of the first operations for mitral stenosis; or the 33% mortality of the first portacaval shunts at the Massachusetts General Hospital; or the large failure rate in Charnley’s first series of total hip replacements.

We must find a way of establishing that the initial innovation is a “feasibility study,” during which the surgeon-investigator refines the new procedure and defines diagnostic criteria for its application. It should be possible to develop adequate safeguards for the public. Thereafter, such procedures can be tested by large-scale clinical trials. However, these developments will not occur if the profession does not address itself to these important issues. It is our obligation to the public to improve our capability to help the sick and suffering, and to do so in a safe, responsible, and accountable way. If we do not take these steps, it is clear that society will impose regulations that it thinks are appropriate. This would certainly be less desirable and may block progress very effectively.

The field of neurological surgery has an exciting future, but some efforts must be pursued to plan its destiny. Continuing research is essential, and neurosurgeons must be involved in the research process. Strategies must be developed so that new forms of therapy can be safely developed and objectively tested. None of these changes that are essential to future progress will occur without modifications in the current structure and goals of organized neurosurgery.

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