Neurology in the 21st Century
Ronald M. Andiman, MD
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The science fiction writer Arthur C. Clarke once remarked that any sufficiently advanced technology would appear to a more primitive people as magic. Those primitives, our grandparents and great-grandparents, would have seen some of our current neurology practice as magical if not outright magic. Given the advances of the last century what might we project would be the advances of the next hundred years? To put things into perspective note that nearly 100 years ago, in 1905, Santiago Ramon y Cajal received the Nobel Prize for the "neuron doctrine." That is to say, the fundamental notion that individual nerve cells, neurons, are the basic units of function within the nervous system is less than a century old.

The task of trying to predict future "progress" in medicine as in all technical arenas is peppered with pitfalls. Any of us who read the lay press in the agitated days before the turn of the millenium were treated to exerpts of articles written by our forebears at the turn of the 20th century predicting what advances would be made in the century just past. They were of course amazing for their short-sightedness in many cases; but their optimistic expansiveness in other instances leaves a chasm of unfulfilled expectation. Even the implied promises made closer to our time at the Worlds Fairs of 1939 or 1960, seem not even close to our current reality a mere few decades later. They suffer from the limitations of science fiction movies: the technology and decor is always conceived of in contemporary terms.

Some of the progress will likely be continuations of the works-in-progress of our current era, such as the exploitation of the fruits of the Human Genome Project or faster and more sophisticated brain scanners and the like. But some of the innovations will be discontinuous with what we know today. A mere fifteen years ago no one would have predicted the degree to which the internet might transform the practice of medicine, from the availability on-line of the complete texts of the major medical journals or the instant access patients have to technical information. Until the advent of the MRI Scanner who among us would have suspected that nuclear magnetic resonance, a technique previously applied to chemical analysis could, when linked with a fast computer and sophisticated software, make an image of the inaccessable, living brain in the kind of detail only previously available post-mortem.

The Human Genome Project, to be completed in a year or so, will give us the sequence of the four DNA building blocks (the nucleotides cytosine, guanine, adenosine and thymine) that are strung along in the 23 pairs of human chromosomes to create the genes that direct the structure, organization and function of the human body. The sequence is three billion nucleotides long. They are organized into about half a million genes and one quarter of these are thought to be expressed in the adult neuron. Once the genes are isolated and identified it will be possible to determine the structural proteins or the regulatory enzymes that they define and to correlate these with normal human variation or disease states. The specific molecular characterization of any disease is the basis for rationally devising its treatment or cure.

Does this mean that we can look forward to the elimination of such diseases as stroke as a significant public health problem, to the elimination of the scourge of brain tumors or to a newly given power to reverse the inexorable paralysis of Lou Gehrig Disease (amyotrophic lateral sclerosis)? To some extent progress will be made in all of these areas, but the task is great and in contradistinction to our ability to put a man on the moon, (the basic theory of which was known to Isaac Newton in the 17th century) we really don't understand the fundamentals of how genes interact with each other to allow the smooth sequencing of biochemical and physical events that enables, for instance, one nerve cell to grow out it's axon and synapse with another. We don't yet know how regulatory genes regulate functions within a nerve cell; and certainly not how genes help to coordinate functions between neurons and their supporting cells the glia or among neurons across the brain to create "whole brain phenomena" such as memory or consciousness or creativity. These issues will comprise the work of the 21st century.

Perhaps with the availability of the new genetic tools many of the major neurological diseases will succumb. After all wasn't general paresis (a form of brain disease associated with tertiary syphilis), one of major causes of dementia during the early part of this century, now almost unknown? One may think of the tools currently being developed being transformed into weapons in the war against neurological disease. Such characterizations of medical research as "war" and disease as"enemy" are ill-conceived. They may be useful politically or for fund-raising but don't accurately represent the process. In neurology, during the foreseeable decades of the 21st century, the targets are too ill-defined to warrant the aim of heavy artillery. We need to explore broadly and with circumspection.

Stroke is generally a consequence of atherosclerotic disease. But what is atherosclerotic disease? How much of this disorder is genetically determined? How many genes are involved? What do these genes actually control in the inner workings of the cell on a molecular level? What is the relationship between those specific genes, if they exist, and the genes for known risk factors such as diabetes, hypertension and hyperlipidemia? What is to come of the research that suggests that there may be an infectious factor involved just as was discovered in recent decades for stomach ulcers? What is the role of environmental factors, psychophysiological stresses and the like? These are the important questions and the research involved in their answer is likely to be arduous and circuitous with many equivocal or confusing outcomes before the major insights that will lead to breakthroughs.

Closer at hand are likely to be technical patches on the gaping wound--ways of dealing with the already established disease states to prevent complete decompensation of the system. More sophisticated drugs for the dissolution of the occluding clots within the vascular system are likely to come in the foreseeable future. Microsurgical and micromechanical invasive techniques will allow angioplasty of partially blocked vessels both intra- and extracranially. One might speculate that in more far-off times micromachines might be introduced to perform repair of at-risk blood vessels robotically under control of a "surgeon" sitting at a computer console.

Perhaps of greater general application will be the characterization of the cascade of events that occurs in the early phase of stroke evolution when brain tissue deprived of oxygen and nutrients begins to die and, in the course of doing so, engenders the release of chemical substances that impair the function of otherwise normal brain tissue in regions proximate and distant to the primary area of ischemia (loss of blood supply). Once this is better understood, pharmacologic interventions will lead to minimization of the volume of brain tissue destroyed or compromised permanently.

Pharmacological research will make even more amazing strides in the next few decades than in the last century. The chemical composition and the three dimensional structure of nerve cell receptors will be better understood. Thus, the chemical messengers that mediate the transfer of information from one neuron to another, the neurotransmitters, will be redesigned or modified to act as therapeutic agents that are more restricted in side effects or more specific in target response.

But is not always the chemical agent itself that is as crucial as its delivery system. A pill designed for the brain is absorbed in the blood stream and distributed throughout the body causing unwanted side effects. Only a small fraction of a given dose of medication ever reaches the target. Furthermore, the brain is isolated from the rest of the body not just by virtue of its location within the bony cranium but also physiologically by the structures that bound the blood supply, known as the blood-brain barrier. The design of delivery systems that limit systemic absorption and maximize absorption across the blood-brain barrier as well as direct the drug to the target brain structure or system remains a current challenge.

We have seen in our time the beginnings of such pharmaceutical innovations with the development of the primary medication for the treatment for Parkinson's disease which contains both the precursor of the neurotransmitter dopamine (the precursor can cross the blood-brain barrier and dopamine cannot) and another drug which inhibits the enzymne in the body which would break down the precursor before getting to its target in the brain. But some of the side effects are caused by the inability of the drug to be more specifically targeted in the brain. Solving such problems will require innovation and technical skill.

But perhaps another approach is valid. We have already seen in recent years attempts to transplant dopamine secreting tissue derived from sources outside the body to the specific site that will allow improved function. A moratorium has been declared on the use of fetal tissue for this purpose. Recently neural stem cells have been found in the adult human and methods are being developed to isolate and grow such cells in tissue culture. As we learn more about nerve cell development it should be possible to direct the developmental pathway toward a specific endpoint and thereby grow the dopamine secreting cells relevant to Parkinson's disease or perhaps the cells of the caudate nucleus that seem to fail first in Huntington's disease. Encouraging the neural networking of such cells after transplantation is apt to be an interesting challenge and will have its application to the treatment of traumatic and other brain injury, spinal cord trauma and even peripheral nerve injury. Thus the concept of brain transplantation in the 21st century is apt to call up very different imagery than the wired up brain in the bell jar of the 1930's science fiction classic Donovan's Brain.

I would be remiss if I did not mention the strides to be anticipated in the control of misdirected immune function in such conditions as multiple sclerosis. The first generation of immunomodulatory agents is already available to us and has revolutionized the treatment of a disease with few treatment options. As the highly complex nature of the immune process comes under critical surveillance and the multiple intersecting components of an immunological event get teased apart designer therapies will evolve. Similarly, we can look forward to the development of techniques by which the immune system can be challenged to increase its surveillance of "deviant" tissue that might characterize the primary brain tumors. Thus such infiltrative multicentric radiation-insensitive tumor may be routed by specific antibodies which seek out and kill off tumor cells but not normal tissue.

As one discourses in this manner it is easy to develop a n optimistic frame of mind. After all, are not several approaches to the control if not the cure of Alzheimer's disease ~~are~~ already under development? Are we not assured of the availability of new techniques for the more effective management of chronic pain ?

The ills of humankind can be eradicated...

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But clever solutions to our neurotribulations will create other issues to deal with and if we fail to deal with the consequences of our most brilliant innovations we will be troubled, as in the Biblical injunction, for generations to come. As in the Sondheim musical Into the Woods, the slaying of the giant leads to a very short-lived happy ending.

In this world of cost control and managed care will there be the resources or the willingness to pay for our beautiful innovations? And where a third of working people in this country do not have medical insurance who will benefit from the technological breakthroughs to come? In a national climate in which it is the rare new medication which costs less than two dollars a pill, how can one even conceive of the dissemination of the medical technology of this new millenium to the billions of needy individuals in Asia, Africa and Latin America?

Then there are, of course, the ethical issues, already alluded to in the lay press for years, of how genetic data on any individual is to be used. Once an individual is identified as being at-risk for stroke will he be able to get life insurance? If a genetic test for Alzheimer's disease is available before useful treatment for that disease how should that information be used? who should know the results and who should not? how should the information be protected or accessed?

Our awareness of the special senses and sensitivities of animals is increasing. In sharing with non-human beings the ineffable gift of life and our mutual fate on this (Carl Sagan's) same "blue dot", spaceship Earth, how can we sanction their use in biological experimentation? Which species might be used and which not? What are the criteria for making such distinctions?

The practice of medicine is apt to undergo vast changes in a changing social environment. The need to control human error of well-meaning practitioners will likely result in the institution of systems management techniques that will make for greater uniformity in the handling of complex as well as routine procedures. Physicians will be under greater pressure to justify their use of diagnostic tests and treatment. Currently an international movement known as "evidence-based medicine" has arisen which seeks to review the scientific basis for why we do what we do in terms of verifiable efficacy. This seems to be the initial step in the development of expert systems which will be able to guide physicians in the management of a whole host of simple or complex neurological disturbances. In a recent article in the New Yorker, Jerome Groopman described the medical systems that would be needed for a reasonably safe journey to Mars. Because of the distances involved, communications between the spaceship or the Martian landing site and Earth, would not be instantaneous--it might take twenty minutes or so for a radio message travelling at the speed of light to travel in one direction.

Therefore in case of an emergency or for ongoing management of a crucial situation expert systems would need to be available to guide the on-site physician in its management even to the extent of assisting him in the performance of a sophisticated surgical procedure with which he is unfamiliar.

The question then becomes whether physicians will be necessary in such a world. Much of the work might be done by well-trained medical technicians under the guidance of a computer-based expert system. One might easily conceive of a robotic system performing the neurologist's exam with the equivalent of reflex hammer, safety pin and tuning fork attached to special sensors which could extract and analyze the data.

At the other end of the spectrum are treatments currently felt to be "alternative" whose value is attested to by their popularity despite not being covered by many insurance plans. Acupuncture and the application of surface magnets are among such therapies whose physiological rationale are yet to be understood.

There are, of course, therapies which have stood the test of time and which are not yet "bottled" for commercial use. Conceivably, the "mechanisms" by which prayer and intimacy, loving and hugging, caring and compassion exert their effects may be elucidated in the new millenium. The heretofore inscrutable mechanisms by which a human touch and humane word of sympathy help to heal may be described in biophysical terms. What is unclear is whether such description will entirely explicate the mysterious soothing of the human touch even if the event were probed to the ultimate subatomic level of quantum mechanics and superstrings.

The coming age of neuroscience is apt to be an adventure. Like most great human enterprises the soaring accomplishments will be bound to our human foibles. One hopes that a better appreciation of human nature will come from the neuroscience research of the next century. May it also bring a modicum of the wisdom needed to avoid the more egregious consequences of our being all too human.