One Step Back and One, Possibly Two, Steps Forward
the Different Approaches to Parkinson's Disease
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Parallel approaches to the development of medical treatment often experience advances in one technology sector and simultaneous setbacks in others. The potential role of medical devices and biomaterials in the treatment of neurological conditions such as Parkinson's Disease is discussed here together with the contrast between the role of devices in tackling the consequences of disease and that of drugs and cell therapies that aim to cure it.

The oscillating nature of research

It is a widely held belief that advances in medical science and technology are slowly but surely revealing the causes and mechanisms of individual diseases and pointing the way to more effective treatment, containment and preventive measures. Identification of genetic factors that predispose people to certain diseases is leading to the possibilities of genetic screening and gene therapy as techniques to minimize occurrence of those diseases. Increased knowledge of the precise causes and electrophysiological mechanisms in cardiac arrhythmias leads to improved methods of cardiac pacing. Identification of molecular mechanisms of organ function is leading to alternative pharmacological treatments, and so on. However, not all "advances" result in perceptible improvements in patient care, and often not for a long time or possibly ever. In the case of some seemingly intractable diseases, it often seems that the media is ready to announce huge advances, only for patients and drug or device companies to be disappointed soon after. Cancer research and cancer care come to mind here. Although there have been significant steps forward, some forms of cancer are on a steep increase in incidence and others remain totally resistant to treatment. The complexity of some diseases results in major oscillations in optimism about their "cure." This article discusses the role of medical technology and materials in one of these situations.

Neurodegeneration and Parkinson's disease

Not surprisingly, neurodegenerative diseases fit into this category of

seemingly intractable diseases rather well. The molecular workings of the brain have always been more difficult to elucidate than those of simpler organs such as the heart or the kidneys. It is also evident that as some other diseases become treatable and average life spans are increased, the degenerative diseases that are normally age related become more prevalent in society at large. Neurologists and neuropsychiatrists are only just beginning to understand Alzheimer's and related diseases, and it is understandable that effective treatments have been hard to find. Medical technology and biomaterials have so far had a small role to play in this area, but the situation may now be changing.

Parkinson's disease is a neurodegenerative disease that is easier to understand than most and consequently there has been some success with treatment. That success, however is limited in that it only tackles the symptoms and slowly becomes ineffective. In these patients, cells in the part of the brain known as the substantia nigra, which have the function of secreting dopamine, are progressively destroyed. Dopamine controls muscular movement and its loss results in tremor. The methods for the treatment of the condition are based on a series of different principles.

Pharmacological approaches

Because the diagnosis of Parkinson's is difficult and can only be made after over 80% of these cells have been destroyed, early pharmacological intervention to slow down the disease is not an option. The principal pharmacological approach is still, in fact, the delivery of agents that circumvent the cellular production of dopamine by providing the body with an alternative route. Unfortunately, pure dopamine cannot cross the blood-brain barrier and thus patients are treated with levodopa, a dopamine precursor that can pass this barrier and is metabolized to dopamine in the striatum within the brain. Levodopa is often administered together with carbidopa to maximize its efficiency and protect against some of the side effects. However, within eight years most Parkinson's patients develop response fluctuations to the drug. Some other drugs have been developed, principally some dopamine agonists that stimulate postsynaptic dopamine receptors and some anticholinergics that block the neurotransmitter acetylcholine to help reduce tremor. But it is widely thought that nonpharmacological methods are more likely to succeed.

Cell therapy

The two most important possibilities here are the surgical replacement of the dopamine-producing cells and surgical intervention to control the effects of Parkinson's. Dealing with the former, a great deal of publicity has been given to this possibility recently, with some indications of good results and some setbacks. The principle is to transplant healthy dopamine producing cells into the relevant part the brain. Obviously it is not a trivial process, surgically and immunologically, but some success has been achieved using fetal cells.

First attempted in Sweden more than a decade ago this method raises a number of ethical issue because it utilizes cells from late-term abortions and a number of fetuses are required to harvest a sufficient number of dopamine-producing cells for one patient. The whole area has had a setback in the last couple of months with the announcement in the United States that the earlier results could not be repeated in a controlled clinical trial. In practice, after a year, some of the recipients who were less than 60 years old seemed better than the non-recipients, but the difference was not significant and, in fact, some of the older patients became appreciably worse. This is a good example of where medical devices can have a significant advantage over more biologically based methods because of the ethical dimensions.

As an alternative to fetal or embryonic cells, it is possible that human stem cells derived, for example, from the bone marrow may be persuaded to differentiate into mature dopamine-producing cells. Obtained from the Parkinson's patients themselves, this potentially gets around the ethical and immunological objections, although the possibility of using immortalized stem cells following genetic manipulation of fetal-derived matter cannot be ruled out as being of greater effectiveness. It has already been shown in mice that embryonic stern cells replace lost brain cells with similar dopamine-producing capability. The role of medical devices here is not clear. Many cases where stem cells could be used, they will be cultured within a biomaterial matrix to generate the required tissue. In this case, it is a chemical functionality that is required rather than structural tissue and the matter may not be that important.

Surgical and device intervention

The potential for medical devices is seen in the alternative rationale to tackling the problem, which involve aiming technology at the consequences rather than the cure of disease. It should be pointed out that there have been several attempts during the past few decades to tackle the condition by the surgical obliteration of the part of the brain responsible for the tremor and other symptoms. Thalamotomy, which is a form of brain surgery that destroys an area of the thalamus that produces the tremor, has had limited success. Pallidotomy is a similar type of procedure that makes a lesion in the ventral aspect of the globus pallidus and is more useful for controlling the rigidity that many patients experience rather than the tremor.

The treatment that has been receiving much attention here, however, is that known as Deep Brain Stimulation, which has its origins in techniques of electrical stimulation such as in cardiac pacing. The technique was developed in France and has been further enhanced by the application of the pacing technology of Medtronic. An implantable system, which consists of a neurostimulator that is placed subcutaneously near the collarbone, a multi-electrode lead that is placed stereotactically in the thalamus, and an insulated wire

connecting these together, is used to deliver mild electrical pulses to the cells of the thalamus. These electrical pulses can block the signals that cause the tremor. The system is magnetically controlled and the patient can determine the level of control that is required depending on the circumstances. Sufficient patients have now been treated to demonstrate that it is an effective method of tackling these tremors.

The placing of electrodes in the brain is not new, but there are significant technical challenges concerning the reliable and safe implantation of multiple active leads in the brain for chronic stimulation. Intuitively, it seems that the brain is a highly sensitive place and few materials could perform there safely. Experience tells us that this may not necessarily be the case, but the long-term neurological biocompatibility of electrically active components is still relatively unknown territory. It is not clear whether the repeated stimulus of the brain tissue by a conducting metallic electrode and the inevitable release of metal ions will cause any response that would ultimately be associated with neurotoxicity and reduced responsiveness of the tissue. Ultimately, it may be these characteristics of the biomaterial that will control success.

This brief outline of current approaches to this difficult disease emphasizes the significant contribution that implantable devices can make in critical areas of medical treatment. It also indicates that biocompatibility of the biomaterial may yet again be the arbiter of success or failure. In addition, it reminds us that progress can ultimately be extremely slow, with almost as many steps backwards as there are forwards.