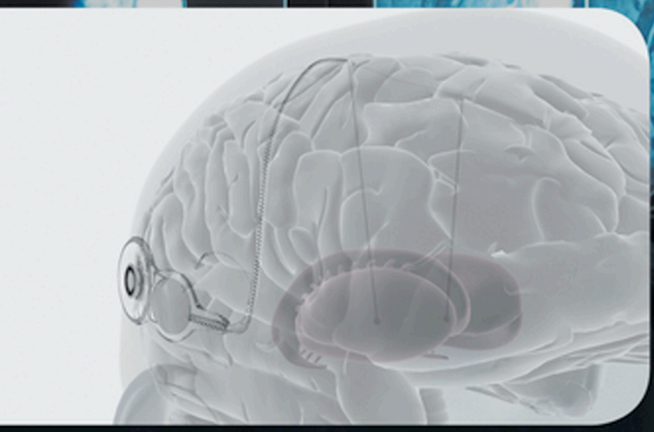
NEUROBIONICS

THE BIOMEDICAL ENGINEERING OF NEURAL PROSTHESES



EDITED BY

ROBERT K. SHEPHERD

WILEY Blackwell

NEUROBIONICS

NEUROBIONICS

The Biomedical Engineering of Neural Prostheses

Edited by

ROBERT K. SHEPHERD
Bionics Institute & The University of Melbourne, Australia

WILEY Blackwell

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

Library of Congress Cataloging-in-Publication Data:

Names: Shepherd, Robert K., editor.
Title: Neurobionics : the biomedical engineering of neural prostheses / edited by Robert K. Shepherd.
Other titles: Neurobionics (Shepherd)
Description: Hoboken, New Jersey : John Wiley & Sons, Inc., [2016] | Includes bibliographical references and index.
Identifiers: LCCN 2016002807 (print) | LCCN 2016004110 (ebook) | ISBN 9781118814871 (cloth) | ISBN 9781118816141 (pdf) | ISBN 9781118816035 (epub)
Subjects: | MESH: Nervous System Physiological Phenomena | Bionics | Neural Prostheses | Brain-Computer Interfaces
Classification: LCC R857.M3 (print) | LCC R857.M3 (ebook) | NLM WL 102 | DDC 610.28–dc23
LC record available at http://lccn.loc.gov/2016002807

Cover image: Getty/Hemera Technologies

Inset image: Inset Photo used with permission of the Bionics Institute, East Melbourne, Australia

Typeset in 10/12pt TimesLTStd by SPi Global, Chennai, India

10 9 8 7 6 5 4 3 2 1

This book is dedicated to my wife, Ursula, for her wonderful support, encouragement and counsel over the last 40 years; to our children Damon and Anna; their partners Jo and Junior; and our grandchildren Harley, Michaela, Jordan and Heidi who enrich our lives daily.

CONTENTS

CONTRIBUTORS

David Borton Department of Engineering and Physics, Brown University, Providence, RI, USA

David M. Brandman Department of Neuroscience, Brown University, Providence, RI, USA

Giles S. Brindley (Retired) Implanted Devices Group, Department of Medical Physics & Bioengineering, University College London, London, UK

Paul M. Carter Cochlear Ltd, Macquarie Park, NSW, Australia

Stuart F. Cogan Department of Bioengineering, University of Texas at Dallas, Richardson, TX, USA

Nick Donaldson Implanted Devices Group, Department of Medical Physics and Bioengineering, University College London, London, UK

James B. Fallon Bionics Institute & Medical Bionics Department, University of Melbourne, East Melbourne, Victoria, Australia

David J. Garrett Department of Physics, The University of Melbourne, Parkville and The Bionics Institute, East Melbourne, Victoria, Australia

Rylie A. Green Graduate School of Biomedical Engineering, UNSW, Sydney, NSW, Australia

Leigh R. Hochberg Department of Neuroscience, Brown University, Providence, RI, USA

Frank J. Lane Illinois Institute of Technology Rehabilitation Psychology, Chicago, IL, USA

Kristian P. Nitsch Department of Clinical and Rehabilitation Psychology Lewis College of Human Sciences Illinois Institute of Technology Rehabilitation Psychology Chicago IL, USA

Arto Nurmikko Department of Engineering and Physics, Brown University, Providence, RI, USA

Douglas McCreery Neural Engineering Program, Huntington Medical Research Institutes, Pasadena, CA, USA

Hugh McDermott Bionics Institute & Medical Bionics Department, University of Melbourne, East Melbourne, Victoria, Australia

John L. Parker Saluda Medical Pty Ltd, Artarmon, NSW, Australia

Marcia Scherer University of Rochester Medical Center, Rochester, NY, USA

Jens Schouenborg Neuronano Research Center, Experimental Medical Science and Nanometerconsortium, Lund University, Lund, Sweden

Peter M. Seligman Bionics Institute & Medical Bionics Department, University of Melbourne, East Melbourne, Victoria, Australia

Robert K. Shepherd Bionics Institute & Medical Bionics Department, University of Melbourne, East Melbourne, Victoria, Australia

Mohit N. Shivdasani Bionics Institute & Medical Bionics Department, University of Melbourne, East Melbourne, Victoria, Australia

Ming Yin Blackrock Microsystems, Salt Lake City, UT, USA

PREFACE

Neural prostheses are active implantable devices designed to: (i) provide therapeutic intervention, sensory feedback or motor function via electrical stimulation of nerves or muscles following trauma or disease; and/or (ii) record the electrical activity from nerve or muscle to detect disease states, enable the voluntary control of external devices such as prosthetic limbs, or to provide closed-loop feedback to modulate neural prostheses.

Since the introduction of the first commercial heart pacemakers in the late 1950s, there have been many devices approved for clinical use, resulting in a dramatic impact on the quality of life of millions of people around the world. Implantable heart pacemakers and defibrillators are a multi-billion dollar per annum industry. While the neural prosthesis industry is much younger, with an early wave of commercial devices appearing in the late 1970s, this is now a flourishing industry with impressive annual growth rates (Cavuoto *et al*. 2016). Four devices dominate this field: spinal cord stimulation for treatment of chronic pain; cochlear implants for stimulation of the auditory nerve in deafness; vagal nerve stimulation to treat epilepsy; and deep brain stimulation (DBS) to control motor disorders associated with Parkinson's disease and essential tremor.

Significantly, the development of neural prostheses is currently undergoing unprecedented expansion. There are a large number of devices in development or an early stage of commercialisation. These include visual prostheses for stimulation of the retina or visual cortex in blind patients; functional electrical stimulation to provide coordinated activation of nerve and muscle to assist with movement of the hand, arm and gait in stroke and spinal cord injury; DBS to treat pain, epilepsy or severe depression and related psychiatric disorders; vestibular prostheses to assist patients with balance disorders; and neural interfaces that record from the central or

peripheral nervous system to monitor for the onset of seizures or to control external devices for amputees and severe spinal cord injured patients.

Recently neural prostheses have experienced an exciting new phase of innovation generated by the Obama Brain Initiative that encompasses the National Institutes of Health and the Defense Advanced Research Projects Agency, as well as GlaxoSmithKline's entry into the field to develop "electroceutical" techniques (Birmingham *et al*. 2014). These initiatives call for greater multidisciplinary collaboration, including the development of detailed anatomical and physiological maps of neural circuits associated with disease and treatment combined with neural modelling to optimise the development of therapeutic stimulation strategies. While outside the scope of this book, we will watch with great interest as outcomes from these initiatives are delivered to the clinic over the next decade.

Given the multidisciplinary nature of neural prostheses, the field has adopted multiple terminologies that are reflected across the 11 chapters. "Bionics", "medical bionics" or "neuroprosthesis" are used synonymously here with "neural prostheses". We have used additional application-specific terms: "neuromodulation" refers to the stimulus-induced modulation of neural activity for therapeutic purposes – DBS for the control of motor symptoms associated with Parkinson's disease, or spinal cord stimulation to alleviate back pain are examples; "functional electrical stimulation" refers to stimulation of peripheral nerve and muscle to assist in the movement of limbs following paralysis; "sensory neural prostheses" refers to devices that operate under sensory control such as cochlear (auditory) and retinal (vision) implants; "neurobionics" refers to neural stimulation treatments for disorders of the central nervous system (e.g. DBS for the treatment of movement disorders, epilepsy and pain); and "closed-loop" describes a feedback mechanism, typically based on electrophysiological recordings, used to modify the electrical stimulation parameters delivered via a neural prosthesis for improved efficacy.

New developments in neural prostheses are built on advances in electronics, materials science, electrochemistry, battery technology, neuroscience, clinical and surgical practice, and rehabilitation techniques. This book provides a comprehensive historical overview of the field (Chapter 1); it covers the key sciences underpinning the technology including the electrode-tissue interface (Chapter 2); electrochemical principles of safe electrical stimulation (Chapter 3); principles of recording from and stimulating neural tissue (Chapter 4); wireless technology (Chapter 5); and preclinical device testing (Chapter 6). Subsequent chapters describe specific clinical applications, citing devices that are both commercially available and in development, including cochlear implants and vision prostheses (Chapter 7); neurobionics in the treatment of Parkinson's disease, severe depression, obsessive compulsive disorder, pain and epilepsy (Chapter 8); and brain machine interfaces for the control of external devices such as prosthetic limbs (Chapter 9). The final two chapters provide important insight into the process of regulatory approval and commercialisation – issues critical to the successful translation of research to the clinic (Chapter 10); and the key ethical considerations associated with the development of these devices (Chapter 11). Finally, the Appendix provides a list of companies and research organisations currently developing and/or manufacturing neural prostheses.

There are many individuals who have been instrumental in ensuring the successful completion of this book. I gratefully acknowledge the authors of all the chapters – it has been a privilege to work with such a professional and knowledgeable group of individuals without whose efforts and attention to detail this publication would not have existed. In acknowledging our authors I would like to highlight Professor Giles Brindley's contribution to the chapter on the historical foundations of bionics (Chapter 1). Professor Brindley is a pioneer of the field – developing the first visual prosthesis in the 1960's (Brindley and Lewin 1968) – it is to his great credit that almost 50 years after this seminal work – and now in his 90th year – he continues to make important contributions to the advancement of neural prostheses. I am very grateful to Berenice Hale, Lyndal Borrell and Lauren Hill from the Bionics Institute for providing important administrative assistance; Justin Jeffryes, Stephanie Dollan and Allison McGinniss from Wiley for their endless advice and support for the project; and finally I acknowledge the staff and students of the Bionics Institute for providing such a stimulating environment in which to work.

Robert K. Shepherd

Melbourne, Australia.

REFERENCES

Birmingham, K., Gradinaru, V., Anikeeva, P., Grill, W.M., Pikov, V. et al. (2014) Bioelectronic medicines: a research roadmap. *Nat. Rev. Drug. Discov.*, **13**: 399–400.

Brindley, G.S. and Lewin, W.S. (1968) The sensations produced by electrical stimulation of the visual cortex. *J.Physiol*., **196**: 479–493.

Cavuoto, J. (2016) The market for neurotechnology: 2016–2020, *Neurotech Reports*, 1–350.

PART I

FUNDAMENTALS OF NEURAL PROSTHESES

1

THE HISTORICAL FOUNDATIONS OF BIONICS

Nick Donaldson and Giles S. Brindley

Implanted Devices Group, Department of Medical Physics & Bioengineering, University College London, London, UK

1.1 BIONICS PAST AND FUTURE

In 1973, Donaldson and Davis published a paper called "Microelectronic devices for surgical implantation" in which they listed neuroprostheses in use and under development: pacemakers for the heart (fixed-rate, atrial-triggered and demand), incontinence devices, visual prostheses, dorsal column stimulators and electromyogram (EMG)) telemeters[1]. The field of bionics was then very young, the idea of surgically implanting an electronic device was new and very few people had worked on the technical difficulties entailed. Only pacemakers were then commercial products and there were no regulations in force. Now, 40 years later, there are many more types of device, both in clinical use and under development. A number of these devices will be described in Chapters 7–9 and include implants for addressing sensory loss (e.g. hearing, sight, balance), disorders of the brain and the mind (e.g. epilepsy, migraine, chronic pain, depression), as well as brain-machine interfaces. Manufacturing these devices and going through the process of regulation is now a multi-billion dollar industry.

The year 2013 may be remembered as the year in which GlaxoSmithKline (GSK) announced that they were to invest in the development of neurobionic devices, which

[1]The phrenic nerve stimulator ("Diaphram Pacer") of Glenn *et al.* (1973) was described in the same year.

Neurobionics: The Biomedical Engineering of Neural Prostheses, First Edition.
Edited by Robert K. Shepherd.

they call *Electroceuticals* or *Bioelectronic Medicines*[2] (Famm *et al*. 2013; Birmingham *et al*. 2014). The notion is that these will interact with the visceral nerves that innervate the internal organs to treat specific diseases. These diseases are not normally thought of as neurological (e.g. inflammation), but nevertheless there is some neural control. The announcement by GSK shows that the company thinks that implanted devices may become an alternative to some drug treatments. The motivations for their development no doubt include the rising costs of new drugs, better targeting of the causes of disease, and the realisation that implants might treat some of the increasingly prevalent diseases that threaten to overwhelm healthcare budgets (obesity, diabetes). They cite an example as the recent trial of a treatment for rheumatoid arthritis by stimulation of the vagus nerve (Koopman 2012). Some of the new implants will require surgical techniques new to human surgery, for example the splitting of spinal nerve roots in continuity into many fine strands. Only time will tell whether this vision is realistic, but it shows the huge rise in confidence that implanted bionic devices may be practicable and important in future healthcare.

The first electrical device implanted into a patient was the cardiac pacemaker of Elmqvist (1958), so the field is now nearly 60 years old (Figure 1.1). While Chapters 7–9 will review some of the types of implant with respect to their clinical

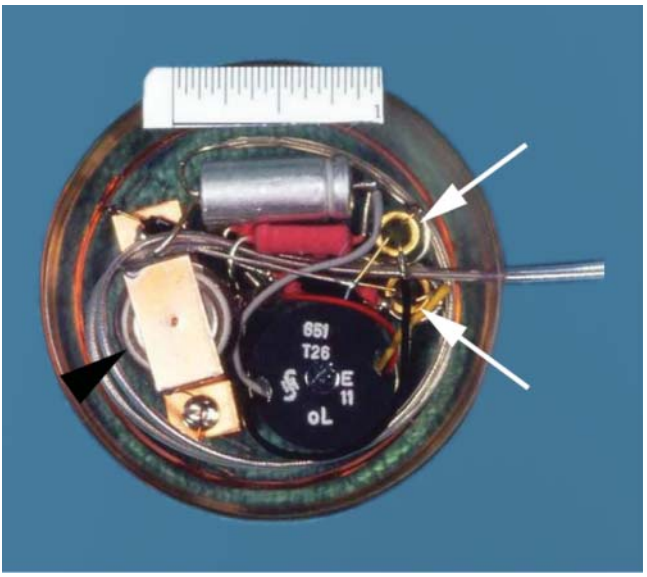


Figure 1.1 Elmqvist-Senning pacemaker of 1958. It is powered by two nickel-cadmium cells (arrowhead) which can be recharged by induction. The two transistors are on the right (arrows). The encapsulant is epoxy resin. An external valve oscillator was used for recharging at a frequency of 150 kHz. Scale bar = 1 inch.

[2]It will be interesting to see whether one of these names sticks, because both seem a misleading description of surgically-implanted devices.

function, Chapters 2–6 will review the field on which implant engineering is based, much of which has been built in this 60-year period. If we consider that the construction work in that period is the history of neurobionics, the purpose of this chapter is to look back to the pre-history, the foundation of the field, from the time before work began and probably before it was even conceived.

We have worked in London during the historical period (see Box 1.6: MRC Neurological Prostheses Unit) and the story is slanted toward our view of the significant technology.

1.2 HISTORY IN 1973

Donaldson and Davies (1973) suggested that neurological prostheses were the confluence of four streams of development: biomaterials (known from literature dating as far back as 1000 BC), electrical stimulation of nerves (Galvani 1791), electrophysiological recording (Matteucci 1842) and transistors (1948).

1.2.1 Biomaterials

A textbook by Susrata from 1000 BC describes the use of catgut for sutures. In Europe, from the 16th to the mid-19th century, linen and silk were the normal materials for sutures and ligatures; for sutures, horse hair, catgut and cotton were tried occasionally, and for ligatures, strips of leather. But these seem to have been passing fashions, and most surgeons continued to use silk or linen. Whatever the material, it was not a biomaterial in the modern sense; it was not expected to remain in the body for years, but either to be removed by the surgeon within a week or two, or to be extruded through the skin as part of the healing process within a few months.

The first internal fixation of a fracture with a metal plate and screws was performed by Lane in 1895, but Lane's plate and screws were of ordinary steel, and would certainly corrode. Stainless steel (*18-8* 18% chromium, 8% nickel) was patented in 1912, but the original stainless steel corroded badly in sea-water. It was not until about 1926 that a modified stainless steel, *18-8-SMo*, which had an additional 2–4% of molybdenum was developed, which resisted corrosion in sea-water and so could reasonably be expected to remain uncorroded in the body. This stainless steel was widely used in the internal fixation of fractures in the 1930s, and sometimes remained uncorroded for years (Haase 1937).

The variability remained mysterious, but it was made unimportant by the invention (1932) and introduction into bone surgery (1937) of Vitallium, an alloy of cobalt, chromium and molybdenum, which has never been reported as corroding in the body (Venable and Stuck (1938). The first widely successful artificial hip (though not absolutely the first artificial hip) was the cup arthroplasty (Smith-Peterson 1939). It used a *Vitallium* cup which was not bonded either to the head of the femur or to the acetabulum. Modern artificial hips have a ball bonded to the femur and a cup bonded to the pelvis. Problems of fixing the ball and cup to the bones and of wear at the articulating surfaces have been largely overcome. For artificial finger joints, it has been possible

to avoid articulating surfaces by using adequately flexible silicones (Williams and Roaf 1973). Silicones were first used in medicine as coatings for syringe needles for reduced blood clotting (1946). In the same year, silicone rubbers were first used for surgical repairs and, in 1956, for the first hydrocephalus shunts (Colas and Curtis 2004). Thus by 1973 the field of biomaterials was established as a collaboration between surgeons, biologists and materials scientists, who had made progress by innovation with new materials, better designs and improved surgical techniques.

Less was known about implantable electrical materials: the first electrical implant in an animal was described by Louks (1933) and that was simply a coil, insulated with Collodion varnish, connected directly to electrodes; the experiments continued for 12 days. Clearly the idea that artificial materials can be implanted into the body was well established by 1973, but the specific difficulties of electrical devices were new.

1.2.2 Nerve stimulation and recording

It was established by Galvani in 1791 that nerves could be stimulated. The idea that nerves carried sensory messages to the brain and commands back to the muscles was stated in the 1st century AD by Galen, who argued for it against contrary opinions of some classical Greek authorities; he thought that the nerve signal was transmitted by fluid flow. However, when Leeuwenhoek looked at nerves in cross-section using his new microscope (1674), he was not convinced that there was any tubular structure to carry the fluid.

Newton wrote in 1678 about "a certain most subtle spirit which pervades and lies hid in all gross bodies, by the force and action of which … all sensation is excited and the members of animal bodies move at the command of the will, namely by the vibrations of this spirit, mutually propagated along the solid filaments of the nerves, from the outward organs of sense to the brain, and from the brain into the muscles." For the optic nerve, Newton repeated this opinion in his "Opticks" (Newton 1730): "Do not the rays of light in falling upon the bottom of the eye excite vibrations in the tunica retina? Which vibrations, being propagated along the solid fibres of the optic nerve, cause the sense of seeing?"

Since 1745, when the Leyden jar was invented, it was well known that electricity passing through human skin causes strong and often painful sensations. At least since 1738 (Swammerdam) it was known that if, in a preparation consisting of a frog's gastrocnemius muscle and sciatic nerve and little else, the nerve was pinched, contraction of the muscle followed immediately. Galvani (1791), using just such a preparation, showed that passing electricity from a frictional machine through the nerve had the same effect. He also did experiments using dissimilar metals, which he misinterpreted. Volta confirmed and extended Galvani's experiments, interpreted them correctly, and used them as the basis of his invention of the battery (1800), which quickly led to the discovery of the relation between electricity and magnetism, the work of Oersted, Ampere, Ohm and Faraday, and the great advances in electro-technology from which we all benefit today.

The action potential of the nerve was first detected by Matteucci (1842). The speed of conduction of the nerve message was measured by Helmholtz (1850) by

comparing, in frog nerve-muscle preparations, the difference in timing of the muscle contraction according to whether the near or the far end of the nerve was stimulated electrically. He found it to be about 20 m/sec. In 1856, Herrmann measured the speed of movement of the action potential directly, and found that it was the same as that of the message as measured by Helmholtz, thus making it almost certain that the action potential was a true sign of the message.

The time course of the action potential at any one point on the nerve was known only very roughly until the development of valve amplifiers during the First World War. Gasser and Newcomer (1921) were the first to apply such amplifiers to nerve action potentials, and to display them on a cathode-ray oscilloscope. During 1921–1930, Gasser and Erlanger, in a long series of papers in the *American Journal of Physiology*, described these techniques and others to elucidate the form of the action potential and the influence of fibre diameter and myelination on it and on the speed of conduction. It was already known, from theory and from observations made with older equipment, that if both recording electrodes were placed on an intact nerve, a biphasic action potential was found, the potential difference reversing as the active region moved from one electrode to the other. However, if the end of the nerve was crushed and one electrode placed on it, a nearly-monophasic response was found. Gasser and Erlanger, with amplification, cathode-ray oscilloscope, a limb nerve (ulnar) and one recording electrode on an intact nerve at least 20 cm from the stimulating electrodes and the other on the crushed end of the nerve, found a monophasic response when they used weak stimuli, but with strong stimuli it became polyphasic, the additional peaks coming later than the one that was already present with weak stimuli. By good arguments from the results of further exploration, taking into account what was already known about the anatomy of limb nerves, they concluded that their nerve contained fibres of many different diameters. The largest conducted fastest and were most electrically sensitive. Smaller fibres were slower and less sensitive. The speeds of conduction did not follow a Gaussian distribution; they were strongly grouped into five classes, called Aα, Aβ, Aγ, B and C, by Erlanger and Gasser (1930). It soon became clear that the C fibres were unmyelinated and the A and B fibres were myelinated.

From about 1910–1930, there was much interest in how the amplitude of a rectangular pulse just sufficient to stimulate a nerve, nerve fibre, muscle or muscle fibre, varied with the duration of that pulse. Such measurements could be (and were) made with great accuracy, and easily showed that long pulses favoured unmyelinated nerve fibres and skeletal and cardiac muscle fibres, and that short pulses favoured myelinated nerve fibres, which were the most sensitive even to long pulses (say 10–20 milliseconds), but immensely so to short pulses (<0.5 msec). These experiments added little to our understanding of how the nervous system works, but are useful to the designers of bionic devices.

In 1939, A.L. Hodgkin made two steps towards understanding the nature of the nerve impulse. First he proved what had been suspected before but never proved: that the fraction of the action current of one node of Ranvier that is conducted along the axoplasm to the next node of Ranvier in a vertebrate myelinated nerve fibre is sufficient to stimulate this (next) node. Then, in the same year, Hodgkin succeeded

in recording the action potential of the giant nerve fibre of the squid from an electrode inserted into the fibre. Further research was interrupted by the war, but in 1952 Hodgkin and A.F. Huxley used intracellular recording from squid giant fibres to establish a thorough understanding of the electrical and ionic basis of the nerve impulse.

In contrast to the purely electrical transmission within a nerve cell and its processes, transmission from one neurone to another, sometimes excitatory but sometimes inhibitory, is almost always carried out by means of chemical transmitters. There are at least 20 of these. A few were discovered in the 1930s, many more in the 1950s and 1960s, and there may still be a few unidentified. One transmitter may have different actions on different postsynaptic neurones. Often (perhaps always) these different actions depend on different receptor molecules.

Much of our knowledge of the function of structures in the brain comes from observations of the effects of lesions, occurring in disease or (less often) produced experimentally. Observations of the effects of disease have led to new neurophysiological knowledge almost only when followed by good postmortem examination of the brain.

It was widely (though not universally) believed throughout the first two-thirds of the 19th century that all parts of the cerebral cortex were alike in function, with the reservation (going back to Hippocrates) that the left hemisphere was more concerned with the right half of the body and the right hemisphere with the left half. Such "equipotentiality" within each hemisphere was not disproved until 1863, when Broca observed that lesions of one small area of the left hemisphere caused inability to speak, and in 1871, when Fritsch and Hitzig showed that electrical stimulation of different parts of the cerebral cortex caused movements of different parts of the contralateral half of the body.

The effects of electrical stimulation *within* the brain became known only when Horsley and Clarke (1908) designed their apparatus for stereotaxic surgery, which allowed the end of a probe to be accurately placed almost anywhere within the brain. The tip of the probe carried an electrode, so the brain structure in which it lay could be stimulated electrically, or electrical activity recorded from it, or a lesion of controlled size made in it by diathermy. The Horsley-Clarke apparatus, originally for the human brain, was soon adapted for use in experimental animals.

1.2.3 Transistors

The transistor was essential for pacemakers and in fact the first human pacemaker was made just after silicon transistors became available with their lower leakage current. However, inductively-powered stimulators with tuned coils and solid-state rectifiers, not requiring implanted transistors, could have been made earlier; such devices have been very valuable in the development of neuroprostheses because of their simplicity and reliability. For example, the first visual prosthesis did not use implanted transistors, and the inductively-powered sacral anterior root stimulator uses them only in external equipment, including the oscillators that provide the radio-frequency magnetic fields. However, the arrival of transistors in the 1950s clearly showed the possibility for future small low-powered electronic devices, small