Neural prosthetic interfaces with the nervous system

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Once damaged, the adult mammalian nervous system is capable of little functional regeneration. Thus, clinical disorders such as deafness, blindness and paralysis have been treated primarily by substitution rather than correction (e.g. teletype for telephone, braille for print, wheelchair instead of walking). However, recent advances in the technology of miniature electronic implants and in the basic understanding of sensory and motor functions have made it possible to build neural prosthetic devices that work by exchanging information directly between computing devices and neurons. Such devices are already permitting thousands of otherwise deaf patients to hear sounds directly; some have appreciable speech comprehension without visual cues. There is active research on restoring many types of sensory, motor and autonomic function. Two interesting synergies have emerged. The first stems from the recognition that the biophysical processes involved in stimulating and recording from neurons are universal; thus, technical advances have broad implications in many clinical areas. The second stems from the unique opportunity that such prostheses present to conduct neurophysiological and psychophysical studies directly in conscious human subjects.

Neural control interfaces

Most neurons transmit information in a digital stream consisting of impulses of ions flowing in an aqueous medium. Most computers transmit information in a digital stream consisting of impulses of electrons in metallic conductors. Neural prosthetics involves electrochemical and mechanical interfaces between the two. The goal is electronic instrumentation that obtains its control signals directly from the electrical activity of neurons and that conveys sensory information and/or motor commands directly to the nervous system.

Electrical stimulation and monitoring of physiological processes have been developed over the past century as primary research tools of neurophysiologists. Over the past 25 years, relatively simple versions of such interfaces have been engineered as clinical prostheses to control respiration1, alleviate pain2, and stimulate bladder evacuation3 (see Fig. 1). Although there is much work still to be done in those areas, this review considers sensory and motor applications in which function requires multiple, parallel information channels having a temporospatial resolution that is consistent with the normal function of the nervous system. Such sophisticated interfaces have provided the impetus and, in some cases, the tools to advance knowledge in fundamental areas of neuroscience.

Cochlear prostheses

Sensorineural deafness often results from relatively selective loss of the cochlear hair cells, which

Neural control Interfaces now being developed

- Replace eye - stimulate cortex
- Replace ear - stimulate auditory nerve
- Stimulate skin nerves for pain relief
- Stimulate back muscle to stop abnormal spine curvature
- Record sensory feedback from hand
- Activate paralysed hand muscles

The field of neural control

1. Chronic recording
   - Neurophysiological research tools
   - Myoelectrically controlled prostheses
   - Monitors of command signals

2. Functional electrical stimulation
   - Pacemakers
   - Tissue growth stimulators
   - Neural prosthetics
   - Single-channel activators
   - Multichannel sensory replacements
   - Sensorimotor coordinators

Fig. 1. A wide variety of devices are in various stages of development, from feasibility studies to clinical trials to marketed products.
transduce the mechanical vibrations of the basilar membrane into synaptically driven neural activity in the spiral ganglion cells comprising the auditory nerve. A cochlear prosthesis restores perception of sounds by stimulating the remaining spiral ganglion cells with electrical patterns derived from a microphone. Even a single electrode located in or near the cochlea produces complex sound sensations whose loudness and cadence provide useful acoustic information for the otherwise profoundly deaf patient. Documented benefits include identification of common ambient sounds (e.g. car horns, telephone), improved speech modulation and clarity, and improved speech reading (by providing clues about low frequency voicing information that is most difficult to read from lip motion); however, similar benefits have been claimed for vibrotactile aids that transduce sound into mechanical stimuli on the skin.

**Biophysics of electrical activation.** The real goal is speech perception without visual cues, such as that required for use of the telephone. For that, it is necessary to replace not only the transduction property of the cochlea but also its spatial filtering property. Typically, an array consisting of multiple, independently addressable electrode contacts is inserted about 20–25 mm into the scala tympani. The various contacts can then be used to activate, selectively, small subpopulations of spiral ganglion cells closest to each contact (see Fig. 2). In order to quantify and improve this selectivity, different geometric arrangements of mono- and bipolar stimulation contacts have been tested in animals while recording from single neurons in the auditory nerve or brainstem auditory nuclei. Other investigators have used mathematical models to predict the spread of stimulus current through the complex compartments of the cochlea and the effects of different current waveforms on the excitability of spiral ganglion cells. As might be expected, bipolar pairs with the contacts arranged radially with respect to the cochlear spiral (and thus parallel to the apical dendrites of the spiral ganglion cells as in Fig. 2) appear to give the best selectivity, but in practice, such an electrode has been very tedious to construct.

**Encoding of sensory information.** Even the most selective electrode operated near threshold for auditory sensations produces a complex sound with an overall pitch that is related to place of stimulation along the basilar membrane, but is not at all tone-like in quality. Given a small number of these noisy channels, how should the acoustic signal from a microphone be processed into electrical stimuli? Three basic multichannel strategies have evolved. The simplest is a set of bandpass filters whose center-frequencies correspond approximately to the pitches produced at each stimulation site. The analog output of each filter is used as the actual stimulus waveform (after considerable compression of dynamic range), in the hope that some of the temporal information contained in the acoustic waveform will be represented in the timing of the evoked neural activity. Two devices tested clinically have used this type of four-channel processor (‘UCSF–Storz’ and ‘Utah–Symbion’). Some of the patients tested with these devices have been able to understand a significant percentage of words in everyday sentences (without visual cues) but others have shown little benefit beyond what would be expected from a single channel. This appears to be related to the highly variable condition of the surviving spiral ganglion cells, because poor subjects generally have higher electrical thresholds and narrower dynamic ranges, suggesting poor survival of the apical dendrites that are normally closest to the electrode contacts.

Recently, some of the UCSF–Storz patients have shown improved speech perception when stimulated with brief pulses on each electrode, for which temporal overlap of stimulus current on adjacent channels can be avoided. The electrodes are scanned in a basal-to-apical direction at the fundamental frequency of vocal cord vibration, with the amplitude of each stimulus pulse determined by the rectified and smoothed output of each corresponding bandpass filter. An eight-channel version of this strategy is now being developed by Minimed Corporation in Sylmar, California.

Even more processing is involved in the ‘Nucleus’ system, the only device currently market-approved by the Food and Drug Administration of the USA. A computer in the external package identifies the center frequencies and relative amplitudes of the various speech formants and selects one or two stimulus sites along the 22-contact electrode on the basis of a patient-specific map of the pitch sensations they have evoked. The Nucleus system seems to produce more consistent (although still highly variable) results in speech perception tests under acoustically controlled conditions, but the formant-extraction algorithms may become confused by ambient noise and some clinicians feel that they interfere with use of the prosthesis to identify non-speech ambient sounds.

A 90-patient, randomized prospective study of the Nucleus, Utah–Symbion and Vienna-3M (recently withdrawn) devices is now being carried out by the US Veterans Administration, but results will not be available for at least two years.

**Activity-dependent development of cognition.** Perhaps the most controversial application of cochlear prosthetics is in prelingually deaf children (recently reviewed). Implants in adults who became deaf as young children have produced poor results, suggesting that these patients have missed some critical period in the development of their auditory nervous systems (much as there is known to be a critical period in visual cortical development). This suggests that deaf children cannot afford to wait for the next generation of improved devices. However, the nature and timing of this hypothetical period is completely unknown. Furthermore, it may involve two or more separate processes. Beyond their inability to hear sound, prelingually deaf children have difficulty in establishing substitute communication skills such as sign-language and speech-reading. This may be related to their lack of awareness that such capabilities even exist; thus, even crude devices such as single-channel cochlear and vibrotactile prostheses appear to be useful beyond the amount of acoustic information that they can be shown to convey in a speech perception test.

Also, a deaf child with an immature nervous system may learn to deal better than an adult with the novel temporospatial patterns of neural activity produced by multichannel prostheses, specifically because the child is free to develop new approaches to infor-
mation processing rather than looking for recognizable similarities to previously learned patterns of neural input. This ability may be related to the phenomenon of the 'star patient' that has confounded comparison among the various cochlear prostheses. Most projects, including those pursuing single-channel devices, have had the occasional adult patient whose speech understanding with the device alone (no visual cues) is far better than would be expected, given the amount of acoustical information transfer that could be measured in simple psychophysical tests. Designing psychophysical strategies to stimulate and evaluate cognition in nervous systems with no prior experience of a particular sensory modality represents a difficult but fertile research area.

Visual prostheses

Ironically, one of the first neural prosthetic applications to attract significant applied research and government funding was potentially the most sophisticated – achieving useful vision in the blind. Most of this work focused on using multiple, independent electrodes on the surface of the occipital lobe to activate the retinotopic map known to reside in striate cortex (area 17, V1). Twenty years ago, Brindley implanted an array of 85 platinum electrodes, each driven by its own inductively coupled stimulator, in a blind volunteer. Stimulation of most contacts near threshold produced a 'phosphene', described by the patient as a small, white light at arm's length, located in an orderly retinotopic position in the visual field.

Neuropathology of electrical stimulation. The obvious extension of this finding to the composition of complete pictures based on large numbers of such phosphene-pixels was confounded by a host of electrochemical, biophysical, and neurophysiological problems. Central among these was the very high current required to activate cortical neurons from the pial surface (1–2 mA for 250 μs pulses). These high currents resulted in electrochemical reactions at the metal/electrolyte interface that damaged both neurons and electrodes, and they resulted in such widespread activation of neurons that simultaneous stimulation of adjacent electrodes produced unpredictable phosphene interactions. Microstimulation using fine, intracortical electrodes requires about one-hundredth of the current, but the current density at their tiny tips actually tends to be even higher (see Fig. 3).

While clinical work on a visual prosthesis all but disappeared, the application became a benchmark for a wide range of fundamental materials science, biophysical and neuropathological studies, many funded through the Neural Prosthesis Program of the US National Institute of Neurological Disorders and Stroke. Perhaps the most useful advance has been an elucidation of the electrochemical and metabolic mechanisms of neuronal damage that may be caused by chronic electrical stimulation and the development of clear proscriptions on the selection of electrode materials and stimulus waveforms for avoiding such damage:

- Stimuli should always be delivered as biphasic pulses so that there is no net direct current. This is most easily achieved with a series capacitor.
- Charge density per phase should be minimized (stimulus current multiplied by duration of each phase divided by surface area, including roughness factor, of the electrode contact). Because of the relatively short chronaxy of most myelinated neurons, brief pulses (20–50 μs) are...
Fig. 3. Restoration of functional vision by electrical stimulation of the surface of the striate cortex (two disk-shaped electrodes at left) has been unsuccessful because high-stimulus currents are required to activate the deeper-lying neurons, resulting in interactions between the potential gradients set up at adjacent sites (dashed lines). Intracortical 'floating' microelectrodes produce punctate visual sensations at much lower currents (center) and can be fabricated in arrays complete with multiplexing circuitry (right). It may even be possible for these arrays to receive their power and control signals by radio frequency or optical coupling, facilitating the hundreds or even thousands of channels that must be present to generate visual displays with useful resolution.

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<thead>
<tr>
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<th>Surface macrostimulation</th>
<th>Intracortical microstimulation</th>
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<tbody>
<tr>
<td>Contact area</td>
<td>1 mm²</td>
<td>0.001 mm²</td>
</tr>
<tr>
<td>Impedance</td>
<td>10 kΩ</td>
<td>100 kΩ</td>
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<tr>
<td>Current</td>
<td>1 mA</td>
<td>0.01 mA</td>
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<tr>
<td>Pulse duration</td>
<td>0.1 ms</td>
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<tr>
<td>Mean rate</td>
<td>20 pps</td>
<td>20 pps</td>
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<tr>
<td>Charge density</td>
<td>10 μC/cm²</td>
<td>100 μC/cm²</td>
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<tr>
<td>Mean power</td>
<td>20 μW/channel</td>
<td>0.02 μW/channel</td>
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Some 'biocompatible' metals such as gold and stainless steel corrode quite rapidly at relatively low interface potentials in chloride-containing solutions; even platinum has fairly modest charge-density limits for chronic use. Two important new materials have been developed for high charge-density applications. Sintered tantalum can be anodized to form a 'capacitor-electrode' in which a stable, dielectric layer of tantalum pentoxide prevents current passage except by double-layer charging and discharging of the convoluted surface. Iridium can be 'activated' by cyclic voltammetry, forming a stable coating of iridium hydroxide in which iridium ions can cycle through a range of stable valences from +2 to +4, thereby reversibly converting electron fluxes into hydroxyl ion fluxes.

- Even when fully reversible, and hence 'safe', chemical reactions are used, physiological responsiveness may decrease. Electrical stimulation can produce non-physiological rates of synchronous activity in local populations of neurons, which may exceed the microvascular and glial mechanisms for coping with their metabolic demands. This necessitates neuropsycho-pathological studies of the tissues around typical arrays following chronic stimulation in animals.

Recently, I and my colleagues at the NIH and University of Western Ontario have used extremely fine, intracortical iridium microelectrodes to produce phosphenes at low thresholds (20–80 μA) in three patients studied during neurosurgical exploration under local anesthesia for treatment of intractable epilepsy (Loeb, G. E. et al., unpublished observations). However, intracortical insertion of large numbers of even the most benign electrodes suggests additional biocompatibility hazards from the mass effects of mechanical damage, as well as posing severe surgical handling problems. Even a crude but functional visual prosthesis will probably require hundreds of independently addressable stimulation sites. For these reasons, microfabrication techniques are being developed that permit multiple electrodes and their associated control circuitry to be made on a monolithic silicon substrate, which is then etched photolithographically into a comb-like array of long, slender tines (see Fig. 3). Even so, a functional artificial eye is at least a decade away.

**Functional neuromuscular stimulation (FNS)**

**Control theory.** In many forms of paralysis, including those caused by strokes and spinal cord injuries, the peripheral neuromuscular apparatus (including motoneurons and somatosensory reflex loops in the spinal cord) is completely intact. Since the experiments of Luigi Galvani, it has been known that electrical stimulation can reanimate such a paralysed limb. Thus, the clinical problem is primarily one of command and control (recently reviewed). Unfortunately, the block diagram in the lower half of Fig. 4 includes many boxes for which there are no satisfactory algorithms either in theoretical biology or in robotics. Furthermore, conventional control theories usually assume linear transformations working with idealized input signals for voluntary commands and proprioceptive feedback (as shown), which will almost
FNS research can be divided into six major areas.

1. Hybrid systems, in which FNS is combined with modification of the mechanics of the limb, either through external braces (which may be electromechanically active) or surgical procedures such as tendon transfers and joint fusions.

2. Recruitment of motor units, using animal experiments and mathematical models to develop reliable approaches to producing a predictable, finely controlled force output under dynamic conditions.

3. Closing the control loop to achieve stability by feeding back signals from motion and pressure sensors to the stimulator control systems.

4. Effects of residual neural reflex loops, whose hypersensitivity produces a debilitating spasticity in many patients with an injured spinal cord. Chronic activation of muscle afferents by FNS has been reported to reduce spasticity. Some groups have actually used cutaneous stimulation of flexor reflexes to produce coordinated leg-lifting patterns.

5. Planning and coordination in multiarticulated systems. Newtonian mechanics are required to break down complex movements into the effects of active joint torques, mechanical coupling between skeletal segments, and gravity. Techniques for apportioning the active torques among the muscles are greatly complicated by the fact that many of the muscles cross more than one joint.

6. Command interfaces, whereby the willful intentions of the patient are rapidly and accurately sensed and sufficient kinesthetic feedback is provided for the patient to understand the mechanical state of his limb and its interactions with external objects.

**FNS-Demonstration system**

Command → Stimulus pattern → Muscles → Movement

visual feedback

**FNS-Marketable system**

Patient needs → Command → Motion planning and coordination → Stimulus delivery system → Fitting and recalibration → Orthotic aid

Musculo-skeletal plant → Actions

Proprioception → Exteroception

*Use-dependent adaptation.* One of the historically important topics of neuromuscular research has been the trophic factors that shape the mechanical and metabolic properties of different muscles in response to different exercise regimes. Chronic electrical stimulation provides a valuable tool to control the temporal pattern of motoneuronal activation; FNS research has provided a powerful impetus to settle long-standing disputes in this area because of the need for predictable and desirable contractile properties in the target muscles. It now seems clear that the specific frequency of motor unit firing has relatively little influence on contractile properties or fatigue resistance. Fatigue resistance tends to develop in response to almost any pattern of electrical stimulation as long as it is delivered over several hours per day for several weeks. It is usually accompanied by a reduction in maximal tetanic force and a prolongation of twitch rise and fall times, all of which are useful in FNS to produce finely graded, well-fused contractions at stimulus frequencies that do not unnecessarily fatigue the muscles. Conditioning for maximal force output seems to require higher stimulation rates simply because these are necessary to produce the large forces that are a necessary stimulus for hypertrophy of the muscle. However, these use-dependent effects are superimposed on certain tendencies that are fiber-type specific in adults and which themselves may depend on both gene expression during muscle fiber differentiation and chemotrophisms from innervating motor axons.

On the clinical front, some of the investigationalf devices for both walking in paraplegic patients and grasp in quadriplegics have produced impressive results. However, there are no commercial manufacturers yet and the current devices are intended primarily for laboratory evaluation. Researchers are now moving away from skin surface and percutaneous wire electrodes and toward fully implanted, inductively powered and controlled.

*Fig. 4.* Functional neuromuscular stimulation (FNS) produces musculoskeletal movement by electrical activation of motor nerves and muscle fibers. In the demonstrations to date, electrodes have been applied to the skin surface, by percutaneous insertion into muscle, and by surgical fixation to peripheral nerves and perimysial connective tissue. As these interfaces have become more reliable, research has turned toward the complex systems integration required to achieve useful and reliable function in everyday use by paralysed patients.
multichannel systems with electrodes implanted directly on individual muscles and/or nerves. Development of electromechanical sensors and cutaneous stimulators for proprioceptive feedback is a high priority. Voluntary commands are now obtained from intact musculature by recording EMG or, more often, joint motion. Recording command signals directly from motor cortex remains a distant hope but will require improvements in chronic, recording electrode arrays and better understanding of biological motor programs.

**Promise and problems**

Neural prosthetics is a complex, expensive and still technically limited approach to a wide variety of sensory and motor handicaps. As a strategy, prothetic replacement must always rank behind prevention and biological cure. However, for many of these disabilities, neither prevention nor cure seems likely in the near future. Furthermore, these patients constitute a disproportionate percentage of those whose rehabilitation offers the largest economic benefits, being often young, usually intellectually intact, and requiring expensive, personal support to deal with their handicaps. Thus, research and development in this area is likely to expand. Neuroscientists have much to contribute and much to gain, particularly if they grasp the larger perspectives of the effort.

**Threshold of clinical utility.** Progress on the cochlear prosthesis was facilitated by the fact that even a very primitive, single-channel device produced clinically useful auditory sensations. Thus, it was possible to build from this success to the much larger undertaking of producing multichannel prostheses capable of providing speech perception. Future progress in other clinical areas will depend at least partially on the strategy of identifying particular disabilities that are severe enough to warrant invasive intervention yet simple enough so that relatively primitive devices can produce functionally useful rehabilitation.

**Synthesis into systems.** The divide-and-conquer approach to finding basic science solutions to individual neural prosthetic problems has left the discipline of neural prosthetics fraught with difficulties, though potentially powerful. Clinical applications such as artificial vision and FNS require extraordinarily diverse, lengthy and intimate collaborations among basic scientists, engineers and clinicians, but experienced researchers and critical resources are now thinly distributed around the world. The lack of appropriate project management and funding mechanisms is rapidly becoming a limiting factor in the delivery of clinical prosthetics.

**Reciprocal synergy: basic and applied research.** Basic research fields such as systems neurophysiology are noted for their slow pace of methodological progress and of translation into clinical practice. Neural prosthetic research offers an opportunity to use rapidly developing, 'high-tech' electrophysiological probes in the nervous system of subjects who can report immediately and in detail on the perceptual and functional effects. Given the rising levels of clinical and industrial activity, the results of these and other basic studies are likely to be incorporated rapidly into new prosthetic designs. The cochlear prosthesis has already been through several such cycles. Following the initial clinical successes with single-channel electrodes, multichannel designs were evaluated for their spatial selectivity in animals and then introduced in humans. The discovery that patients were generally insensitive to changes in electrical stimulation frequency above 300 Hz (despite physiological and psychophysical evidence for phase-locking of auditory nerve activity to acoustic and electrical stimuli up to 3000 Hz) led to further animal experiments and to new theories of pitch perception. This, in turn, led to new algorithms for processing speech signals into patterns of electrical stimulation that have dramatically improved prosthesis performance in some patients. Similarly, one can imagine a number of interesting experiments on the psychophysics of visual percepts that result from artificially generated, temporospatial patterns of neural activity in striate cortex.

Neural prosthetics today is at a level of development comparable to cardiology 25 years ago, when pacemakers were novel and primitive, ECG interpretation was largely subjective and empirical, and artificial hearts were a dream. The nervous system is certainly more complicated than the heart, but our technology is now vastly more sophisticated and more rapidly delivered. The next 25 years will be seminal for applied neuroscience.

**Selected references**

Why We Sleep: The Functions of Sleep in Humans and Other Mammals

by James Horne, Oxford University Press, 1988, p. 49.95 ($ x + 319$ pages)
ISBN 0 19 261682 X

James Horne's book is particularly memorable for the inaccuracy of its title – Why We Sleep. His book, like so many decades of research into sleep, leaves us groping in the dark. Much more appropriate would have been – Why Do We Sleep? It is not altogether clear why the answer to such a straightforward question has proved so elusive. But even for those not in touch with current sleep research or thinking, this book maps out the facts and assesses the theories in a usefully lucid way.

Comparative studies have produced their usual assortment of correlations: large animals sleep for longer than small ones; rapid eye movement (REM) sleep is longer in the more encephalized mammals and in the newborn; among humans, individuals who habitually sleep for longer increase only particular types of sleep, which Horne terms 'optional sleep'. Such are the baseline observations, now for the experiments. But there's the problem. Some experiments are possible, like sleep deprivation studies of humans which seem to indicate that we can get by on less sleep than we often think and that we only need to make up certain types of sleep, those that constitute 'core sleep'. But experiments on animals are invariably marrered by confounding variables and the failure to produce suitable controls. For example, deprive rats of REM sleep and they lose other types of sleep too, and they are stressed into the bargain. There have been many ingenious experimental designs, but Horne is too good a scientist to overlook the flaws. Fortunately for his reader, he is also a good enough biologist to overlook the flaws. Fortunately for his reader, he is also a good enough scientist to assess the evidence both for and against a variety of theories that seem to fail, and evaluate critically some ideas of his own. For example, he suggests that REM sleep is nothing more than a carry-over from foetal sleep, which may help explain some of its more puzzling characteristics like cessation of shivering and change in thermoregulation status. The foetus does not shiver, and its mother keeps it at the correct temperature. Heaven (unlike Horne) knows why we have to carry such a load of undesired ontogenetic and phylogenetic baggage into adult life if the theory is correct.

He manages in a single volume to review sleep deprivation studies, physiological effects of sleep deprivation, the body and cerebral restitution theories for sleep, the concepts of core and optional sleep, the ontogenetic and phylogenetic patterns, the correlates of REM sleep, and more. At times Horne is too far from his own areas of expertise to be trusted. For example, at one point he suggests that sleep saves local food resources and 'allows more individuals to flourish in the area'. No self-respecting evolutionary biologist would accept such a group-selectionist claim without careful justification. But the quibbles are minor, since so many levels of the biological hierarchy are encompassed by Horne, we should expect the occasional slip.

Unfortunately, the book is forced to finish as it began, on a dismal note: we do not know why animals sleep. If there is a single answer to the function of sleep it will come, claimed Allan Rechtschaffen in 1979, not 'from checking lists of possible interpretations, but from a new idea or result which possibly coalesces our facts and fantasies. It will, probably come at four in the morning in a dingy laboratory in Minneapolis to a graduate student in biology who never read this paper. God bless him'. But if you want to go somewhere, it helps to know where you are starting from. So, if you want to be that graduate student, if you want to prove Rechtschaffen wrong, or if you simply want a non-technical update on sleep research, you could do a lot worse than reading Horne's book. It is not long but it is comprehensive, thoughtful and well written.