Mosby's

Biomedical Science Series

UNDERSTANDING *Neuroscience*

William R. Klemm

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Biomedical Science Series

Understanding Neuroscience

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Series Preface

Science textbooks are commonly entitled "Principles of ..." Yet almost all of these books go far beyond principles to specify so much detail that they often obscure the principles. Too often the emphasis is on currently accepted facts, with principles used only to illustrate the facts, rather than using the minimum amount of fact to illustrate principles.

This situation argues for a new kind of textbook, one that focuses on the first principles of the discipline. In addition to encyclopedic tomes for each discipline, we need small texts that give the big picture and explicitly describe the basic foundational principles of the discipline—and no more!

As a start to what I hope will be a new movement in science education we are initiating a series of biomedical science teaching books that really are about principles. These books aim to be quick, yet elegant, overviews of the essence of the respective disciplines. The newcomer to the subject should find the preparation needed to understand the more comprehensive and detailed traditional textbooks and research journals. Maybe even highly specialized experts can find some useful perspectives from this approach. Senior people tend to get wrapped up in the details of their specialty and sometimes take the principles for granted.

We must have some kind of working definition of "principle." While many ways can express the idea, this Series of texts uses the following working definition:

> A principle must go beyond a collection of observations. Principles integrate multiple observations and help to explain these observations, providing understanding and insight. A principle embodies the underlying rules or mechanisms of structure, organization, or operation that give rise to the observations. We distinguish principles from concepts only in the sense that concepts often embody more than one principle.

In identifying these principles, we must recognize that they are basic tenets; i.e., commonly held *beliefs* about what is true and fundamental. Not everyone will agree that each of these "principles" deserves such lofty status. However, there is a fine line between principle and theory. Theories serve to inspire better theories that can establish principles more firmly.

Many of the statements of principle are incomplete. They may also lack sufficient qualification. Statements of principles serve to inspire more complete or precise exposition. The effort to identify principles comes at a cost: arbitrariness, uncertainty, controversy—but the cost is worth the price. *The search for principles is the Holy Grail of science.*

The practical value of such texts may lie in their pedagogical approach, which is the opposite from the tack taken in many textbooks on biological and medical subjects. Students are fed up with encyclopedic subjects. Students and professors alike are tired of an educational process devoted to pouring information into one ear while it spills out the other. The exponential expansion of new knowledge is causing cognitive overload in students and professors, short-circuiting their ability to sustain perspective about the whole of biomedical science and to think coherently about the details of how the body works in both health and disease. We are learning more and more about less and less, and that causes a progressive loss of capacity for synthesis and ability to think about the larger meanings of biomedical science. The texts in this series require the student to be actively involved in completing missing detail and providing the qualifications of special relevance.

Why These Books are Needed

- Traditional texts are too big, too detailed, too indigestible
- Biomedical information is accumulating faster than students can handle
- Students are learning more and more about less and less
- Students, and even teachers, have trouble discerning the "must know" from the "nice to know"
- The new emphasis in teaching of biomedical sciences will be on how to manage, integrate, and apply information. That requires identification and understanding of the basic principles of the discipline.

The advantages of books in this Series, as I see it, are as follows:

Advantages to Students:

- Students more likely to "see the forest instead of the trees"
  - What is important is made explicit
  - Cognitive overload can't obscure perspective and insight
- "Less is More"
  - Less material is easier to comprehend and remember
  - It is easier to remember unifying principles and concepts
  - Understanding principles empowers students to get more from new information
- Promotes active learning, critical thinking, insight, understanding
- Very useful in self-paced or collaborative learning paradigms
  - Helps assure that students have the required background
  - Students are better prepared to understand what they read in journals and reference books—with minimal help from professors
- Books are smaller, cost less, are more portable, and are easier to peruse

- High portability and condensed nature encourage frequent review
- Longer half-life
  - Traditional texts are out of date as soon as printed
  - Principles are "eternal"

Benefits to Professors

- Allows specialized instruction with less fear that basics are being missed
- After mastering principles, students are equally prepared for subsequent instruction
- Enlivens the lecture period. Meaningful discussion and debate facilitated

Benefits to Graduates

- Quick way to review latest concepts, especially in fields in which they have not kept up
- "User-friendly" access to specialties or to especially complex disciplines

As professors increasingly recognize, the proliferation of research literature has made it difficult to decide what is fundamental about their discipline that must be taught to students. The books in this Series aim to help professors identify that core understanding. Even where a professor may disagree with certain statements of principle, the books provide a focus and a stimulus to the professor to refine those statements of principle with which they disagree.

Where professors believe that more factual detail is needed, they can provide it or direct students to it with some reassurance that students still understand the central core of the discipline. Thus, these books can substitute for the standard, fact-filled textbook and give professors the flexibility to use other instructional media, such as computer-assisted instruction, journal articles, and even standard textbooks as reference sources to complement the Mosby's Biomedical Science Series.

Books in this Series would seem especially important for curricula that stress problem- or case-based learning (PBL). In recognition of the cognitive overload problem some medical schools (McMasters, Harvard, Southern Illinois, Bowman Gray, University of New Mexico) have pioneered in converting the traditional lecture-based curriculum to a tutorial, group-based learning format where critical thinking and information management skills are emphasized rather than rote memory. Some veterinary colleges are also making similar curricular changes. This trend will surely grow, because it is aimed at teaching students to *manage* and *integrate* an ever-expanding biomedical data base.

However, many institutions have thoughtfully considered but rejected PBL-type curricula out of fear that students will have huge gaps in their understanding of the core biomedical science disciplines. Books in this Series not only help PBL students to know what the fundamental principles are, but present them in a quick and easily digestible form. Understanding these principles increases the likelihood that PBL students will truly understand what they read in journals and reference books as they try to apply it to the clinical cases or academic problems.

Organization of These Books

The first—and most difficult—part of writing this kind of text is the identification and terse statement of the first principles of a discipline. Then principles are consolidated, if necessary, and grouped into categories to make it easier to organize and remember them.

Each category has an Introduction that states the principles in that category. There is also a "concept map," which is a diagram that shows the interrelationship of the principles in that category. The authors treat each principle as a module that states the principle and identifies its category. Then the principle is explained, including the use of one or more examples, accompanied by one or two diagrams or pictures. Another section defines key terms, and yet another lists other principles that are most directly related. Finally, a reference section lists two or three key references, along with a list of "Citation Classics,"* where possible. At the end of the modules in a given category, a review section presents some open-ended questions for review and debate.

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*A "Classic" is a highly cited publication (on the order of 500 or more citations) as identified by the *Science Citation Index*, published by ISI Press, Philadelphia. For some of these, there is an associated publication that appeared in the ISI publication, *Current Contents* that contains a history that led up to the research that enabled the publication to have such a major impact. In some cases, the author has taken the liberty to list a publication that in his opinion should have been accorded formal "Classic" status.

Introduction

> *"Science is not a collection of facts or of unquestionable generalizations, but a logically connected network of hypotheses that represent our current opinion about what the real world is like."*
>
> —P.B. Medawar

What the brain produces is a kind of mental model of the world, a system for handling the information that flows from sense organs to the generation of appropriate responses. The integration of the sensory data is central to monitoring the world "out there" and to creating a model of it "in here." The "in here" becomes the real world as far as animals and people experience it. To explain what we know about how all this occurs in the brain is no trivial task. Too many books, in my opinion, fall short of clear explanations because they are so heavily laden with technical detail that the essence of understanding is often obscured. Students are easily confused over what they *must* know as opposed to what is *nice to know*. What a student-oriented text should be is one that focuses on principles and concepts.

Many of the textbooks that claim to be about "principles" are really about principles only in the sense that a forest is about ecology or equations are about mathematics. The standard science textbooks have gotten progressively larger, serving a better role as a reference book than as a textbook. This trend is especially pervasive in such active research areas as neuroscience, where students and teachers alike are swamped with new information.

How bad have things gotten? We can best illustrate the problem by the annual meeting for the Society of Neuroscience. For years now, the attendance has been running about 18,000 and the number of papers presented hovers around 10,000 each year. The professors can't keep up with all that. How can students do so?

This learning problem is especially acute for professionals who are not neuroscientists but whose work must be informed by neuroscience. These professionals include physicians, osteopaths, veterinarians, dentists, clinical and experimental psychologists, computer scientists, bioengineers, animal behaviorists, biologists, nurses, and allied health workers.

An early, well-known neuroscience principles book is *Elements of Neurophysiology* (by Ochs, 1965, Wiley & Sons). This book took 621 pages to specify the "Elements" (principles). Now, the most popular book, Principles of Neural Science (3rd ed.), is by Kandel et al., 1991, Elsevier. This book is **1,135 pages long.** Clearly, such a book tells most readers more than they want or need to know.

The situation argues for a new kind of textbook, one that is focused on the first principles of the discipline. In addition to encyclopedic tomes for each discipline, we need small **supplementary** texts that give the big picture and explicitly describe the basic foundational principles of the discipline—and no more!

Most of what everybody needs to know about the nervous system can be summarized in a list of about 80 principles. This book of principles is aimed at people who are not neuroscientists but who need to understand the basics. The book hopefully gives an overview of what is most important for our understanding of how the nervous system works. Readers in other scientific disciplines or newcomers to neuroscience need a concise presentation of all the relevant principles of the nervous system.

For the student or the newcomer to a given area in neuroscience, the learning tactic should be to study this book *first*. Then the reader is better prepared to understand and view with better perspective what is read in other textbooks, reviews, and primary literature. Even professional neuroscientist need the opportunity to step back from their myopic subspecialty perspective and view the nervous system less reductionistically and more comprehensively—at least that is what I discovered as I developed this book of neuroscience principles.

This book is written to help the learner, not to impress fellow neuroscientists. As such, many professional neuroscientists may fault the book for not providing enough factual material and experimental evidence—in short, it is not the encyclopedia that we have come to expect in textbooks. My justification is that books should have a focus, and you can't simultaneously focus on the "forest" and on the "trees." Excellent neuroscience books already exist that focus on trees.

A more serious criticism is that some of the neuroscience principles I have identified are not universally accepted as such. In other words, some critics will complain that the book is too speculative and theoretical. But science is driven by theory and controversy over theory. What can be wrong about encouraging students to participate in such controversy? Indeed, I think that a major value of the book is that it encourages teacher and student alike to think critically and creatively. One practical way that teachers can exploit this feature of the book is to let the stated principles serve as a focus for classroom analysis and debate or serve as a point of reference for evaluating current journal articles.

Organization of the Book

Principles are grouped into categories to make it easier to organize and remember them. The categories are:

Overview

Cell Biology

Senses

Information Processing

States of Consciousness

Emotions

Learning and Memory

Motor Output and Control

Development/Trophism

Each category section begins with a short introduction that presents an overview of the principles in that category. There is a "concept map" that helps to display graphically the relationships among the various principles. A succession of modules follows, each of which covers one of the principles in that category. Each module has a principle name, followed by a terse and explicit statement of the principle. Then the principle is explained and one or more examples are given, usually accompanied by one or two diagrams or pictures. Another section contains a definition of key terms, and there is also a listing of other principles that are most directly related. Finally, a reference section lists two or three key references, along with a list of "Citation Classics."*

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Contents

Introduction

Chapter 1 Overview, 1
2 Cellular Biology, 40
3 Senses, 93
4 Information Processing, 117
5 States of Consciousness, 168
6 Emotions, 198
7 Learning and Memory, 207
8 Motor Output and Control, 232
9 Development, 251

List of Neuroscience Principles

Overview

Behavior
Brain Size
Circuit Design
Homeostatic Regulation
Hierarchical Control
Modularity
Neurohormonal Control
Neuron Numbers and Types
Neuron: Operational Unit
Stochastic and Deterministic Properties
Symmetry and Hemispheric Lateralization
Topographical Mapping

Cell Biology

Action Potentials
Allosterism
Calcium and Transmitter Release
Electrotonus
Ending Neurotransmission
Ion Channels
Membrane Receptors
Neurochemical Transmission
Nodal Point
Receptor Binding
Second Messengers
Transport
Two Basic Actions

Senses

Feature Extraction and Binding
Frequency Tuning
Sensory Coding
Sensory Modalities and Channels
Sensory Selectivity
Receptive Field
Transduction

Information Processing

Cognition
Cortical Columns
Emergent Properties
Feedback and Re-entry
From Input to Output
Information Carriers
Information Modification
Inhibitory Routing
Inhibition
Lateralization
Parallel, Multi-level Processing
Reciprocal Action
Reflex Action
Rhythmicity and Synchronicity

States of Consciousness

Conscious Awareness
Dreaming
Pain Perception
Readiness Response
Selective Attention
Sleep

Emotions

Motivation
Neural Origin of Emotions
Reinforcement

Learning and Memory

Ensembles of Dynamic Neural Networks
Learning and Habituation
Long-term Synaptic Potentiation
Memory Consolidation
Memory Kinds Reflect Memory Mechanisms
Memory Processes

Motor Activity and Control

Coordination
Final Common Path
Fixed Action Patterns
Motor Preparation
Neurohormonal Control
Visceral Control

Development

Early Death
Epigenetics
Migration
Neuron Division
Neural Induction and Trophism
Neuronal Targets
Plasticity
Programmed Development

CHAPTER 1

Overview

Absolute truth is like a mirage; it tends to disappear when you approach it ...
Passionately though I may seek certain answers, some will remain, like the mirage, forever beyond my reach

— Richard Leakey and Roger Lewin

Perhaps nowhere in science is this quote more appropriate than in neuroscience. We live in the "Decade of the Brain," so-called because we believe that a critical mass of information and understanding now exists that tempts us to believe we can understand the great mysteries of brain and mind. Yet our search for full and absolute truth may well prove to be forever beyond our reach.

A beginning point in this search is to ask, "What is a nervous system for?" Plants don't have one, and plant species generally seem to survive just fine. Clearly, a nervous system is not necessary for evolutionary success—at least for organisms that do not move about in their environment. But creatures that move about in their environment have the opportunity to change their environment, unlike plants, which have no choice. That ability allows such organisms to have more options for survival. In short, there are ecological niches for organisms that are flexible enough to change their environment. And that is why those niches have been filled with organisms with nervous systems (Figure 1-1).

To be able to move about and change the environment, organisms have certain special needs not required by plants. Obviously, they must have a mechanism to move their protoplasm around in the environment, and it certainly helps to have a control system for coordinating movements. Additionally, such organisms need an array of sensors that inform them of environmental conditions, as well as a processing network that decides whether the environment is optimal or whether "better" conditions should be "sought."

Even the most primitive one-celled animals, such as Paramecia, have some of these capabilities. The evolution of higher life forms could be regarded as Nature's way of evolving more efficient and powerful ner-

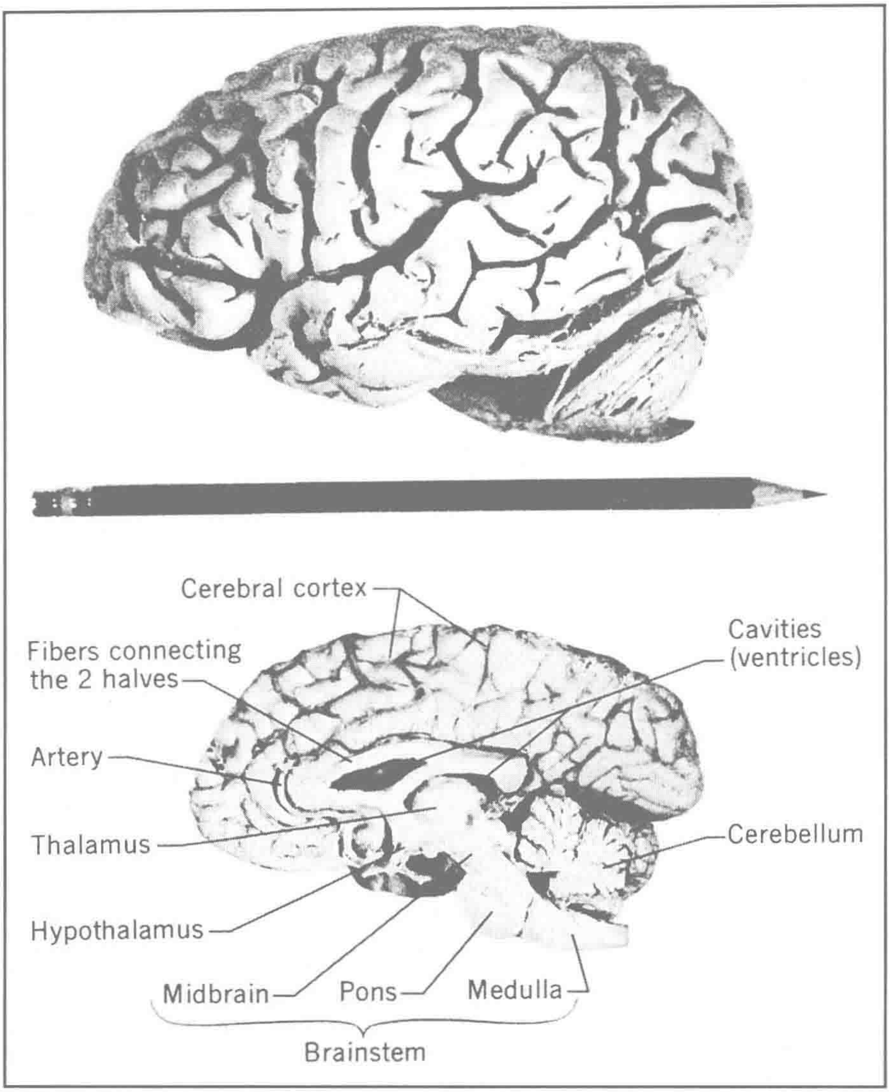

Fig. 1-1 The human brain.

vous systems. Indeed a progressive refinement of nervous systems is a major theme of animal evolution, culminating in the extraordinary mental powers of humans.

In this overview category of twelve nervous system principles, we begin by identifying the basic operational unit of the system: the **Neuron.** Next, we introduce the principle of **Neuron Numbers and Types,** the idea of differing kinds of neurons and the importance of their occurrence in large numbers in the higher animals and humans. Then, we deal with the perplexing issue of **Brain Size,** which seems to be related, but only incompletely so, to the computational power of nervous systems.

Operations of neurons paradoxically exhibit both **Stochastic and Deterministic** (random and non-random) properties that give animals a basis for self-generating and initiating function, as well as a sensitive ability to change function in response to changing conditions.

The neurons are organized into various complex **Circuit Designs,** which route information flow. Organization of these circuits tends to have **Symmetry and Hemispheric Lateralization,** yet another paradox in which seemingly incompatible functions co-exist. We describe how many of these circuits are organized to act with **Modularity** and thus constitute a system of interacting modules.

Then, we discuss **Topographical Mapping,** the idea that much of the world, including an organism's own body, is mapped in the brain. By such mapping, the brain has a way to represent the world within its circuits and a way to issue output commands that are appropriate to that world. Next we identify a principle of **Hierarchical Control** in the nervous system, one that provides efficiency of operation typical of hierarchies in general. But the hierarchical organization of complex nervous systems is adjustable to biological demands, and thus the nervous system can be flexible. **Homeostasis** is a process of servo-regulating control that keeps the various nervous operations in balance. A key to the ability to exert homeostatic control is **Neuro-hormonal Control.**

The collective influence of these various principles leads to our last principle in the overview category, **Behavior.** We can regard behavior from a simple mechanistic perspective of patterned activity of glands and muscles.

Any overview of nervous system principles rightfully begins with the basic operational unit (neuron) and the ultimate product (behavior) (Figure 1-2). Once these principles are understood, the reader should have the perspective to appreciate and understand the other categories of nervous system principles that provide a more detailed perspective on how nervous systems actually enable their host organisms to move about and change their environments (see box on pp. 4 and 5).

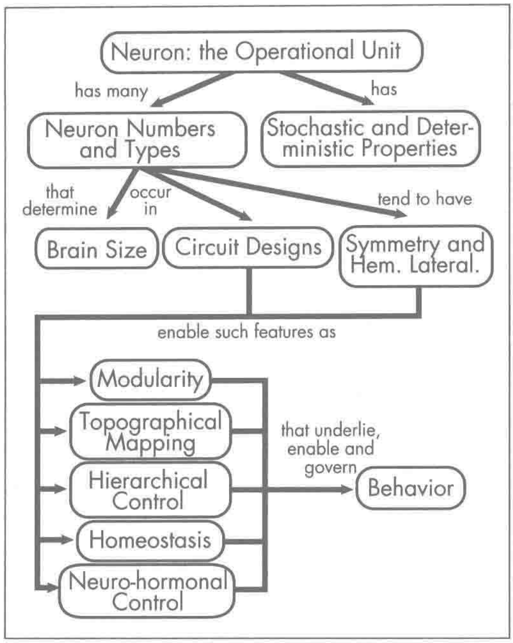

Fig. 1-2 Concept map for the principles that provide an overview of the nervous system.

List of Principles

Neuron: The Operational Unit The basic cellular unit that mediates the information processing actions of the nervous system is the single cell type called a neuron. The essence of neurons can be captured in three words: they are **specialized, numerous,** and **hyperdense** in their interconnections.

Neuron Numbers and Types Brains have enormous numbers of "computing" elements (neurons) that accomplish sophisticated computation because of their large numbers, extensive interconnections, and their high degree of specialization into different types of neurons.

Brain Size Brain size and neuron number are related to mental and behavioral capabilities, but not always in any clear, simple, or linear way.

Stochastic and Deterministic Properties The brain is a highly complex system that has both stochastic and nonlinear, deterministic properties. These are big words, loaded with meaning. But they provide a crucial perspective from which to comprehend how the brain operates.

Circuit Design Neural circuits are organized in certain basic ways: converging, diverging, parallel, and feedback. This provides an anatomical basis of distributed, parallel processing.

Symmetry and Hemispheric Lateralization The brain is basically bilaterally symmetrical, which is a fundamental biological principle of vertebrate structure. Many functions in the brain are not bilaterally symmetrical, but rather are controlled by neuronal groups in one or the other hemisphere. These lateralizations seem to involve higher nervous system functions only and seem to involve only cortical regions of the brain.

Modularity The nervous system is organized as interacting subsystem assemblies of neuronal ensembles.

Topographical Mapping Major sensory and motor systems are topographically mapped. That is, the body, both inside and out, is mapped by the nervous system. Major sensory systems map the external world within their own circuitry. Likewise, the nervous system contains a mapped control over the muscles of the body. Mapped regions may have different inputs or outputs or may share the same ones. Maps are interconnected so that projections from one map to another trigger a back projection to the first map. Mapping can persist at all levels in a given pathway.

Neurohormonal Control A major function of the nervous system is to release certain chemicals into the bloodstream that act as hormones to regulate various hormone-producing glands.

Hierarchical Control The nervous system functions as a hierarchy of semiautonomous subsystems whose rank order is variable. There is no permanent "supervisor" neuron or population of neurons. Any subsystem may take part in many types of interrelationships. Whichever subsystem happens to dominate a situation, each subsystem is independent only to a certain extent, being subordinate to the unit above it and modulated by the inputs from its own subordinate subsystems and by other subsystems whose position in the hierarchy is ill-determined. This design feature of the mammalian nervous system provides maximum flexibility and is probably the basis for the brain's marvelous effectiveness.

Homeostasis The brain regulates the bodily internal milieu through coordinated control over hormones and the nerves that supply viscera.

Behavior Behavior is what emerges from the nervous system's output to glands and muscles, particularly muscles.

NEURON: The Operational Unit

The basic cellular unit that mediates the information processing actions of the nervous system is the single cell type called a neuron. The essence of neurons can be captured in three words: they are specialized, numerous, and hyperdense in their inter-connections. Neurons are also polarized, both in the sense of their input/output relations and in terms of being electronegative, inside relative to the outside of the cell.

Explanation

The neuron is a single cell that is the basic functional building block of the nervous system. Most neurons have many cytoplasmic processes that give them the appearance of a bush or a tree. These branches are called "dendrites" and "axons." Dendrites bring electrochemical stimuli into the neuron, and axons carry electrochemical output away from the neuron toward other target cells. The target cells of a neuron are muscles, glands, or—within the nervous system itself—other neurons (Figure 1-3).

Axons terminate in branches that interact with branches of other neurons. These *synaptic* contacts permit impulse transmission between neurons, typically from one neuron's axonal branches to the short dendrites of an adjacent neuron body. The active region of a synaptic membrane is presumed to be the isolated dark patches near the membrane that are seen in electron micrographs.

Neuron organelles function similarly to those of any cell: chromosomes carry "ancestral wisdom," mitochondria regulate energy supply, microsomal particles control biochemical synthesis, and cell membranes surround the cytoplasm and regulate transport of solutes. Mature neurons are unusual in that they normally do not divide. We don't know why mature neurons do not divide, but it may relate to one or more of the other unusual features of neurons: (1) they express a higher fraction of the genome than other cells, (2) the RNA is clustered as "Nissl substance" on endoplasmic reticulum, (3) they are closely invested by supporting cells (glia), (4) they continuously exhibit pulsatile membrane voltage changes and associated ionic fluxes, and (5) they have an extensive cytoskeleton of tubules and filaments for transporting chemicals throughout an extensive proliferation of protoplasmic processes. Finally, a special pigment, lipofuscin, accumulates in the cytoplasm as the neuron ages, or if its mitochondria or lysosomes are damaged.

The neuron is "polarized," in more than one sense of the word. In one sense, the neuron is polarized so that it can more or less simultaneously respond to input and deliver an output. In an electrical sense, the membrane of a neuron is polarized, having a voltage difference (about 70 mV) between the inside of the neuron and the extracellular fluids that surround it. The inside is electronegative. Responsiveness to input is achieved by