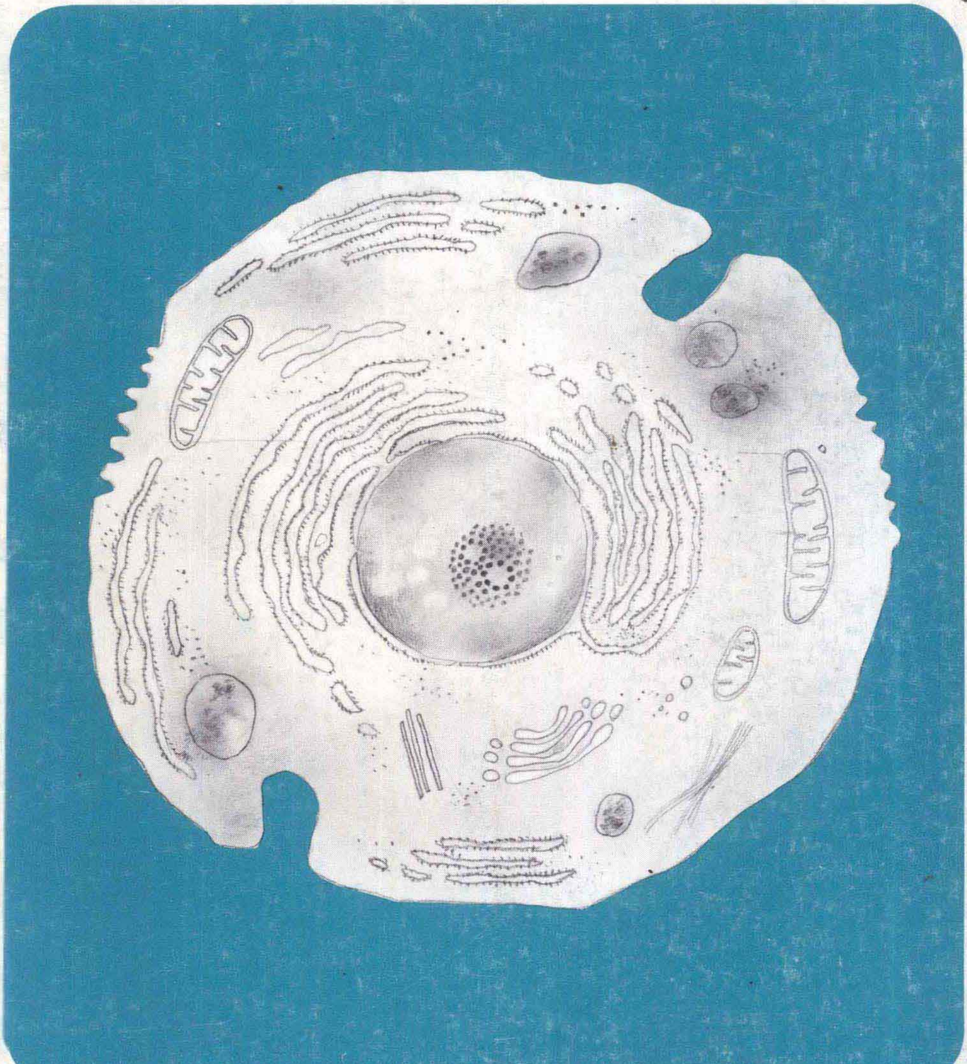
INSIDE THE CELL

The New Frontier of Medical Science



Series: A New Medical Science for the 21st Century

The National Institute of General Medical Sciences (NIGMS)

INSIDE THE CELL

The New Frontier of Medical Science

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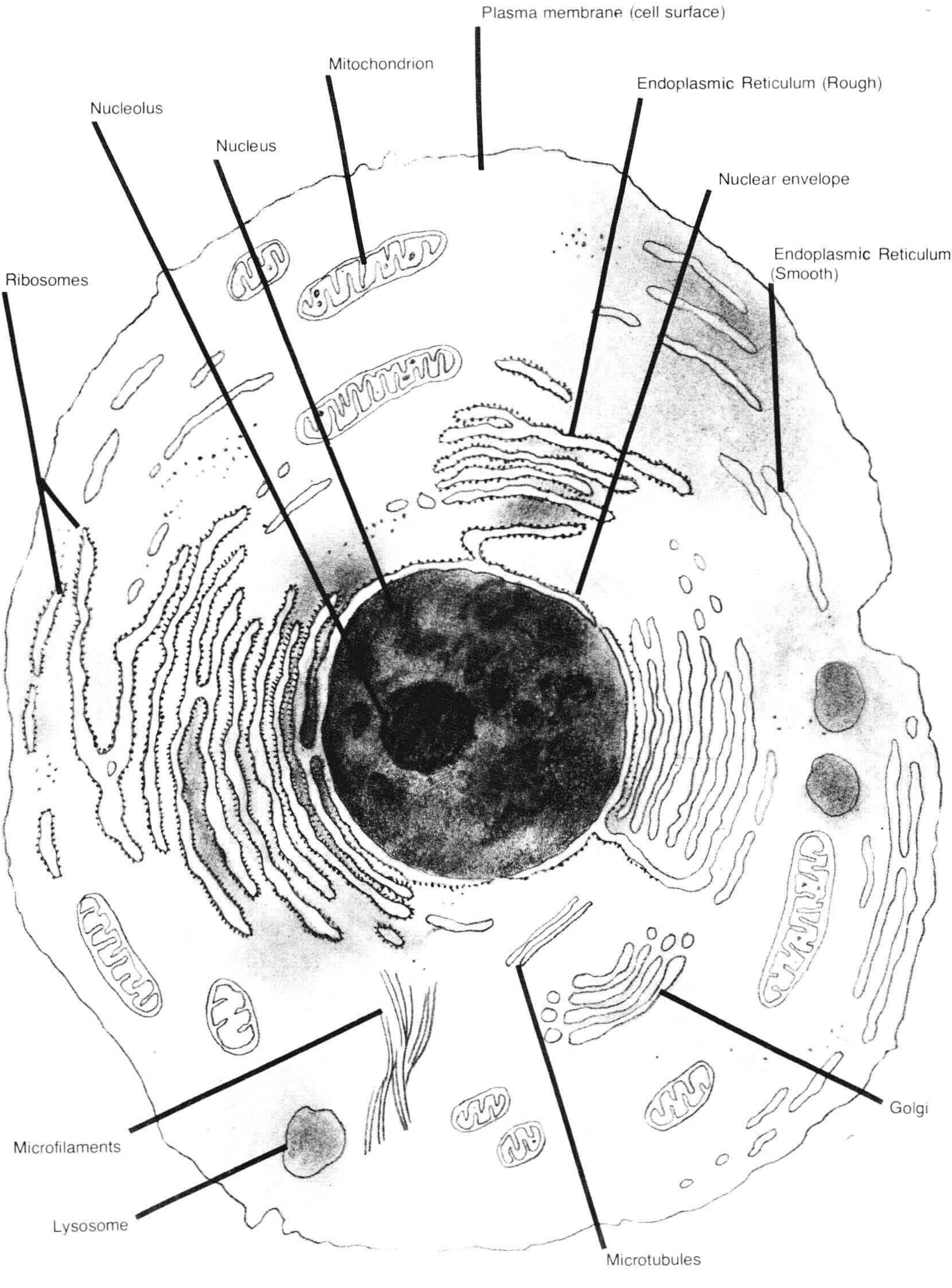
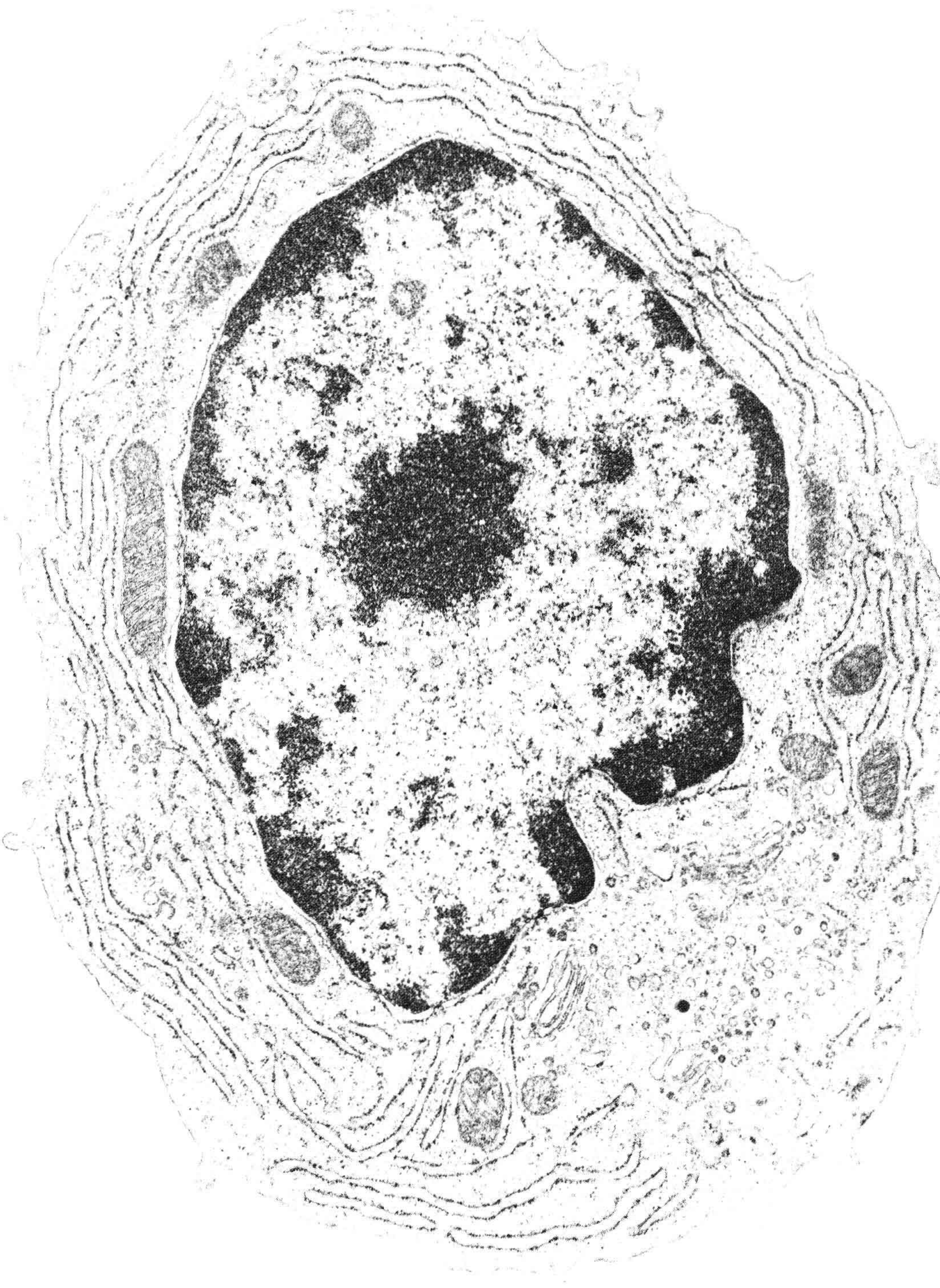


Each human cell has tiny organs (organelles) of its own which are as essential to the life of the cell as the heart, liver and brain are essential to the life of the body. This diagram of a typical mammalian cell shows the nucleus (which contains the genes) and major organelles.

CONTENTS

"We are sick because our cells are sick. We cannot make ourselves well unless we know what is happening inside our cells." **Christian de Duve, Rockefeller University.**



Magnified 21,000 times under an electron microscope, a rat's white blood cell reveals the double membrane around its nucleus, layers of endoplasmic reticulum, several mitochondria, and other organelles.

THE NEXT BIG LEAP

The next big leap in medical science depends largely on how fast and how well scientists succeed in understanding the activity of thousands of tiny organs in a new world which they have only recently begun to explore—the world of the living cell.

This miniature world holds the key to the major health problems of today: cancer, atherosclerosis, genetic diseases, diabetes, mental illness. It is no longer a matter of fighting bacteria or viruses, now that vaccines and antibiotics can prevent or cure so many infectious diseases. The illnesses that still defeat us are far more insidious, for they result from disorders within the human cell, the basic unit of the body. To control these, we need to know much more about what goes on inside the cell.

In the past 30 years, researchers have created a new field, modern cell biology. Through an ingenious combination of electron microscopy, biochemical separations and analyses of cell parts, X-ray crystallography and other means, they have revealed the cell as enormously complex and tightly organized—a strange, watery world in which diaphanous particles of various sizes and shapes float about, in rapid motion, engaged in thousands of chemical reactions. Each cell has its own power plants; its own digestive system; its own factories for making proteins and other essential molecules. Most important, it has an intricate communications network through which it can regulate its own activities (for example, "decide" when to reproduce) as well as receive messages from other cells, sense changes in its environment, and send out messages of its own.

The discovery of this teeming world within the cell and the study of its organization are leading scientists to develop some entirely new concepts of health and disease. Cancer, for instance, can now be viewed— and studied—as a derangement of the cell cycle. No matter what organ of the body is attacked by cancer, the disease always involves tissue whose cells have lost the ability to sense when they should stop multiplying. Normal cells stop reproducing upon contact with other cells, in a process called "contact inhibition." But cancer cells go right on growing and multiplying, even piling up in layers that become tumors, as if their surface membranes could no longer perceive signals from nearby cells. Instead of staying in the part of the body for which they were specialized, they often slide away and migrate to other parts of the body, to form new tumors. The control of cancer may well depend on unraveling these mechanisms.

Other incurable or chronic diseases may some day be related to defects of the cell's mitochondria, the curious, semi-independent little organs (organelles) in the cell which act as the cell's power plants. Mitochondria reproduce themselves with their own genetic material, and many scientists believe that they are descended from bacteria-like parasites which infected a primitive cell billions of years ago and then stayed on, in a useful symbiotic relationship with other parts of the cell. Without the energy produced by the mitochondria, cells could neither move nor synthesize the chemicals they need nor, in the case of muscle cells, fuel their contractions. The study of mitochondria may thus provide us with new ways of preventing or treating a wide variety of diseases —for example, certain diseases involving muscle cells.

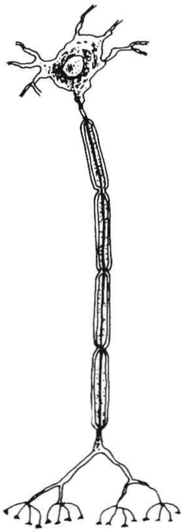
Researchers are also beginning to zero in on the genetic factors which often play such an important role in disease. Many disorders of organelles are hereditary, since the information for making these organelles comes from the genes, the units of hereditary material which are found in the nuclei of cells. Some genetic diseases have been traced to defects in a single gene. In many more diseases, however, including such widespread ones as diabetes, coronary heart disease and schizophrenia, several genes as well as various environmental factors appear to be involved.

Despite all the new clues and the magnificent achievements of the last 30 years, scientists are only beginning to approach the stage where their research will have a major impact on human health. The cell used to be almost virgin territory. The pioneers of cell biology have succeeded in mapping out and analyzing its major features. But they are still very far from understanding the mechanisms which control the organelles' varied activities. They do not know, for example, what regulates the series of orderly changes involved in normal cell growth and development. It is one of the greatest mysteries in biology that although each human being starts life as a single cell, and each cell then divides into two identical cells, which divide again, somehow these cells differentiate in a highly ordered fashion so that some make an eye, some make hair, some make bone or blood, and others make nerves or skin tissue. How do these cells know what to do? Why do certain kinds of cells die, never to be replaced, while others go on reproducing? What happens to our cells—and to ourselves—as we age?

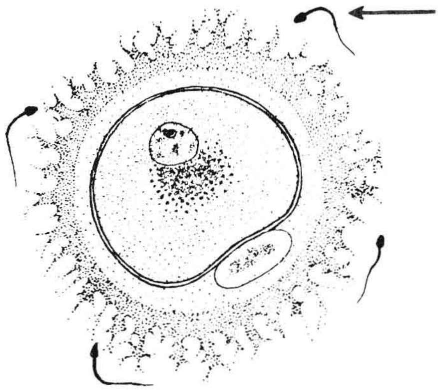
Vast amounts of information about the cell had to be accumulated before scientists could even attempt to study such questions. It is only now that such research on cell regulation is becoming possible.

This pamphlet will describe some of the discoveries that have brought us to this breath-taking stage, and then focus on one of the most exciting areas of current cell research: The study of the cell's ultra-thin but extraordinarily active surface membrane, which plays an important role in many aspects of health and disease. Much of this work is being supported by the Cellular and Molecular Basis of Disease Program of the National Institute of General Medical Sciences (NIGMS), which is part of the National Institutes of Health (NIH), Bethesda, Maryland.

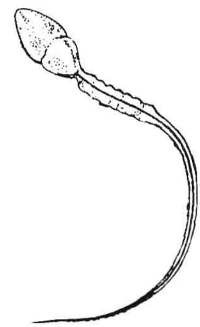
THE VARIETY OF HUMAN CELLS



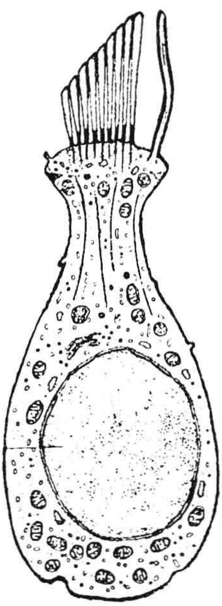
Nerve cell



Egg cell

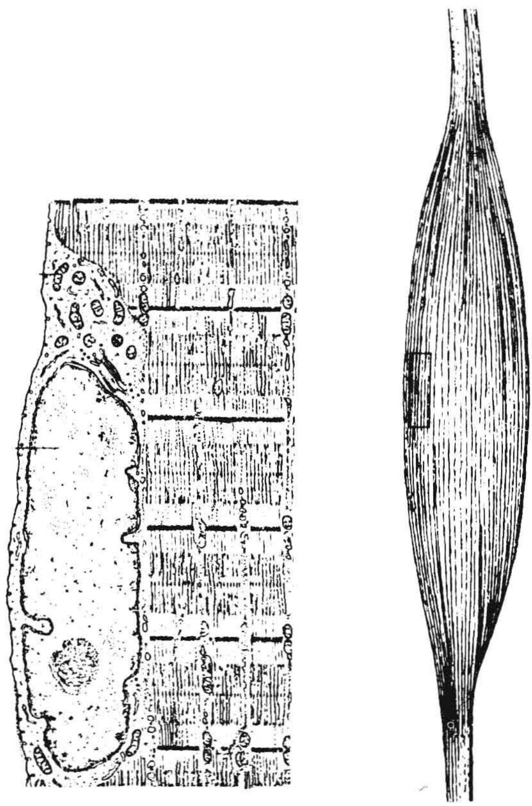


Sperm cell



Hair cell

Rod cell in eye



Muscle cell

The single cell with which we start life divides again and again into many kinds of specialized cells whose structure varies according to their function. Some nerve cell fibers extend over 3 feet in length to reach from spine to toe. The orderly structure of muscle cells is shown here in such detail that if the entire muscle cell were drawn on the same scale as this fragment, it might be 1,000 feet long.

WHAT ARE CELLS?

The idea that every human and animal body is made up of cells emerged with full force from an encounter between two German scientists in 1838. Nearly two centuries earlier, in 1665, the English physicist Robert Hooke had peered at a sliver of cork through a primitive microscope and noticed some "pores" or "cells" in it. But since these looked like cavities (they were actually the cell walls of dead cork tissue), they were believed to serve as containers for the "noble juices" or "fibrous threads" of plant life. Besides, such cells seemed to exist only in plant material.

During a dinner conversation in 1838, however, the botanist Matthias Schleiden, who had been studying plant cells, and the zoologist Theodor Schwann, who had been examining the nervous tissue of animals, suddenly realized that the similarities between the structures they had been investigating were too strong to be accidental. Eventually Schwann showed that *all* animal tissue is composed of cells, including bone, blood, skin, muscle, and glands. Even sperm and eggs are cells. The two men then developed the cell theory, which united plant and animal sciences by recognizing that the cell was the basic building block of all living organisms, from orchids and earthworms to human beings. It was a stunning intellectual achievement.

Within two decades, another German scientist, Rudolf Virchow, founded cellular pathology by showing that the immediate seat of most diseases is the cell.

But what was the cell?

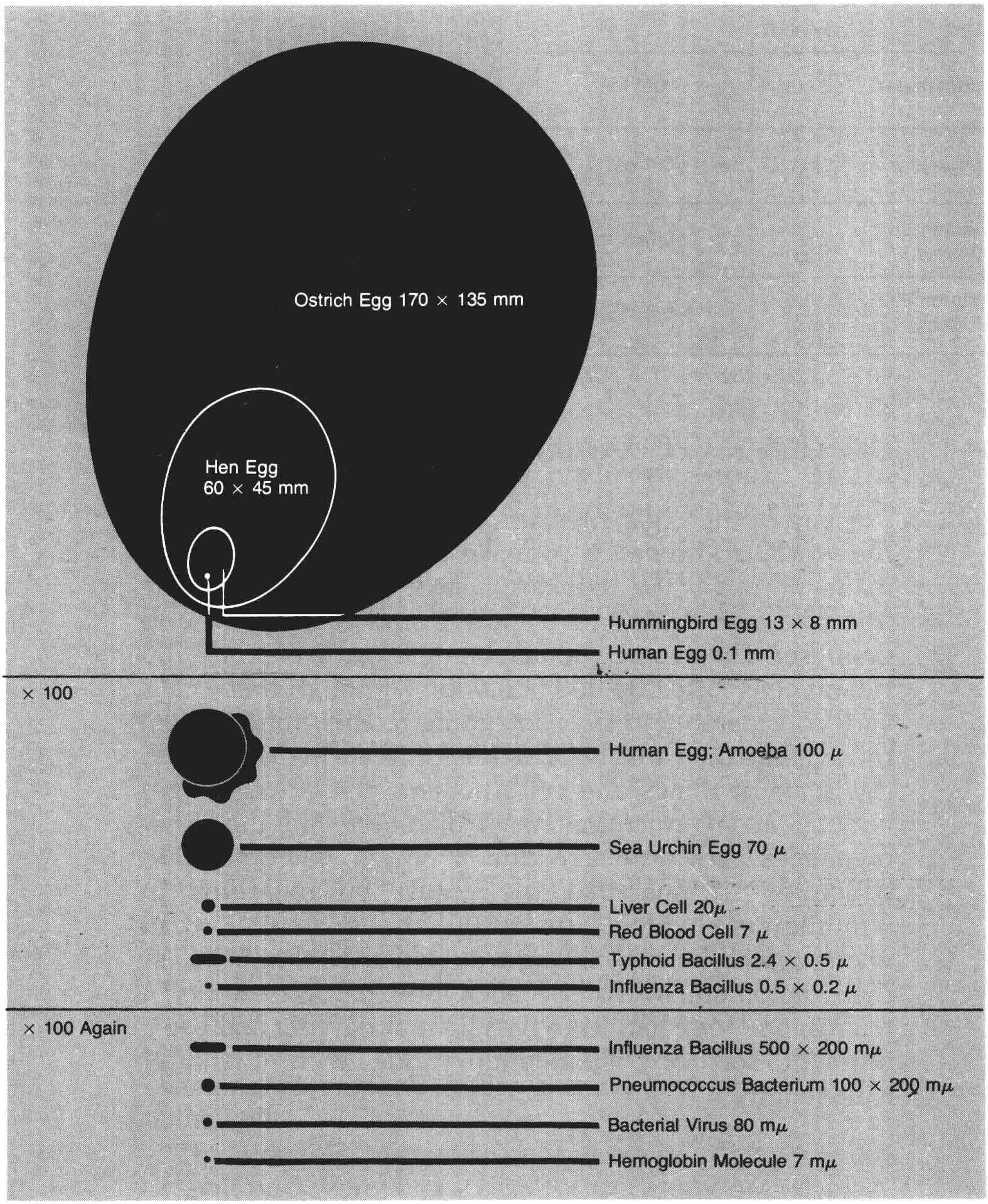
Obviously there were big differences between, say, an egg cell and a sperm cell. Muscle cells which could contract had to be quite different from liver or bone cells. Nerve cells had long, thin fibers which might extend more than 3 feet from the spinal cord to the toes, while blood cells had no fibers at all. Plant cells had a unique ability to use light for energy.

Then what did all these cells have in common? Their basic elements were surprisingly difficult to find. Despite the best efforts of scientists, the cell remained essentially a "black box" for more than a century after the development of the cell theory.

The cell was just a blob of jelly, or some primordial soup enclosed in a bag, thought the early microscopists. For this reason they named the substance "protoplasm," a word derived from the theological term for Adam, the first formed being, "protoplast." As their instruments improved, they noticed that every cell had a denser central area—a nucleus. But for a long time they could not find anything else in the surrounding jelly, which became known as "cytoplasm."

Eventually, with further improvements in lenses and staining techniques, they began to distinguish some other particles in the cell as well. These looked mostly like dots or strands. There was no way to study them in detail with a light microscope. No matter how hard they tried, researchers always came up against an insuperable obstacle: the wavelength of light.

With a light microscope—even one with perfect lenses and perfect illumination—one simply cannot distinguish objects that are smaller than one-half the size of the wavelength of light. Since white light has an average wavelength of 5,500 angstroms, half this size is 2,700 angstroms, or .27 micrometers. (One micrometer is one-thousandth of a millimeter, and there are about 25,000 micrometers to an inch). Any two lines that are closer together than .27 micrometers will be seen as a single line, and any object with a diameter smaller than .27 micrometers will be invisible—or, at best, show up as a blur.



Cell sizes: the largest living cells—the eggs of ostriches and other birds—are shown here at half their actual size, while the red blood cell is magnified 100 times and the pneumococcus bacterium is magnified 10,000 times.

Unit	Symbol		Chief Use in Measurement
Centimeter	cm	= 0.4 inch	Giant egg cells (naked eye)
Millimeter	mm	=0.1 cm	Very large cells (naked eye)
Micrometer (Micron)	μm (μ)	=0.001 mm	Light microscopy Most cells and larger organelles
Nanometer (Millimicron)	nm ($m\mu$)	$=0.001 \mu m$	Electron microscopy Smaller organelles, largest macromolecules
Angstrom unit	Å	=0.1 nm	Electron microscopy, X-ray methods Molecules and atoms

Small, Smaller, Smallest—Units of Measure.

Many of the organelles *are* smaller than that. To enter the world of the cell is to make a voyage such as Alice made through the Looking Glass, where everything becomes smaller and smaller, and curiouser and curiouser. The average human being is made of some 100 trillion cells (100,000,000,000,000). Although these cells vary considerably in size, according to their function, on the average they are about 20 micrometers in diameter. In this scale of things, the cell's nucleus is relatively large: about 5 to 10 micrometers in diameter. But the other organelles vary from a width of only 1 micrometer to structures so fine that they must be measured in nanometers (which are 1,000 times smaller than micrometers), or even in angstrom units (10 times smaller than nanometers). To see such tiny particles under a microscope, one had to bypass light altogether and use a different sort of "illumination," one with a shorter wavelength.

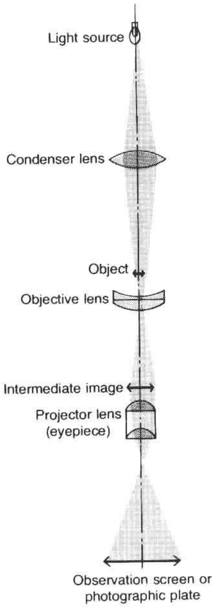
A FRUITFUL FUSION OF TWO TECHNIQUES

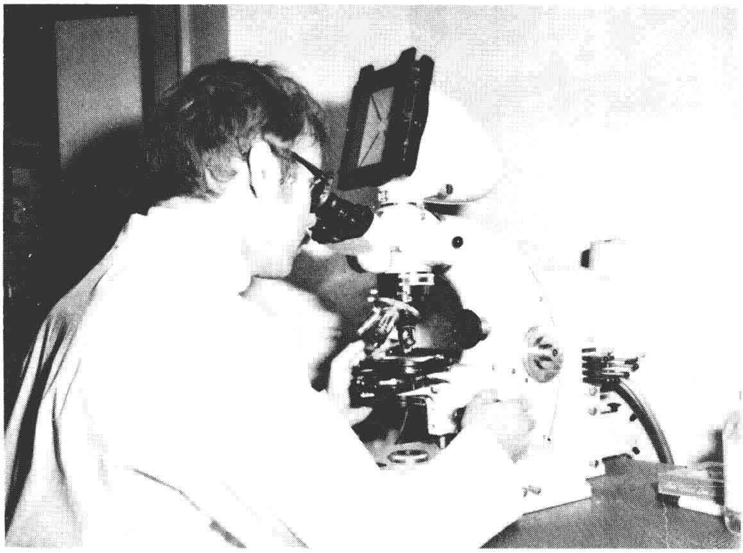
The invention of the electron microscope in the 1930's filled the bill. Electrons can be accelerated in a vacuum until they reach a speed at which their wavelength is only .05 angstroms, one-hundred-thousandth that of white light. In the electron microscope, beams of these high-speed electrons are focused on a cell sample. As the electrons pass through the sample, different parts of the cell absorb or scatter them in different ways, to form an image on an electron-sensitive photographic plate (or a fluorescent screen) with the aid of electromagnetic lenses.

If pushed to the limit, electron microscopes could theoretically resolve objects as small as .025 angstroms, half the .05 angstrom wavelength, which is smaller than the diameter of an atom. Actually, however, the best instrument available today can "see" down to 2 or 3 angstroms—an incredible feat, for although this does not make atoms visible, it does allow researchers, for the first time, to distinguish individual molecules of biological importance. In effect, it can magnify objects up to 1 million times. Nevertheless, all electron microscopes suffer from a serious drawback: Since no specimen could survive under their high vacuum, they cannot show the ever-changing movements and reactions that characterize a living cell.

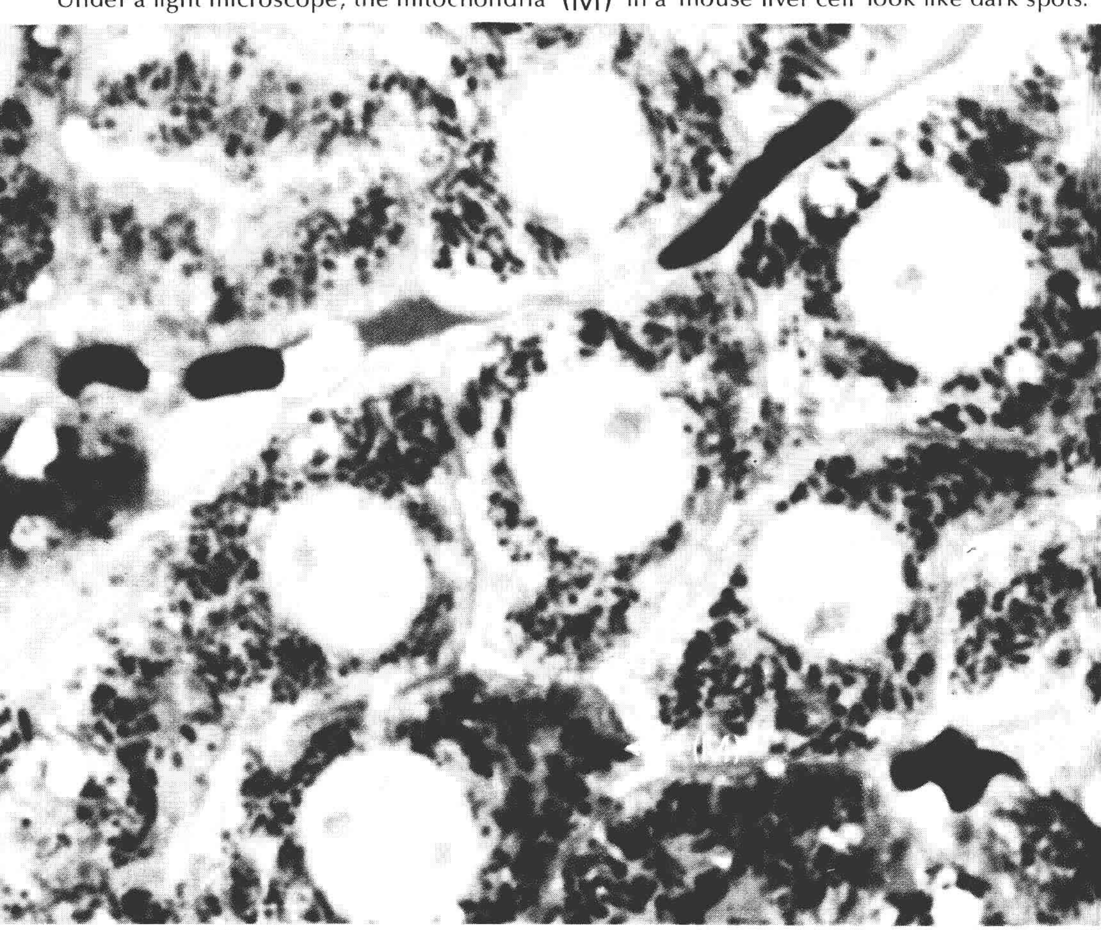
The first electron microscopes were used to study crystals and were impractical for the study of cell structure. It took years to modify and improve them. Simultaneously, researchers had to learn how to cut thinner and thinner slices of cells, sometimes down to a thickness of only a few hundred angstroms, so that electrons

LIGHT MICROSCOPE

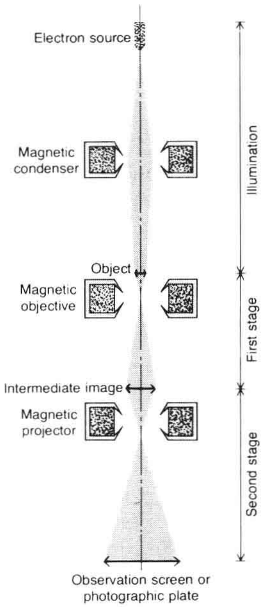




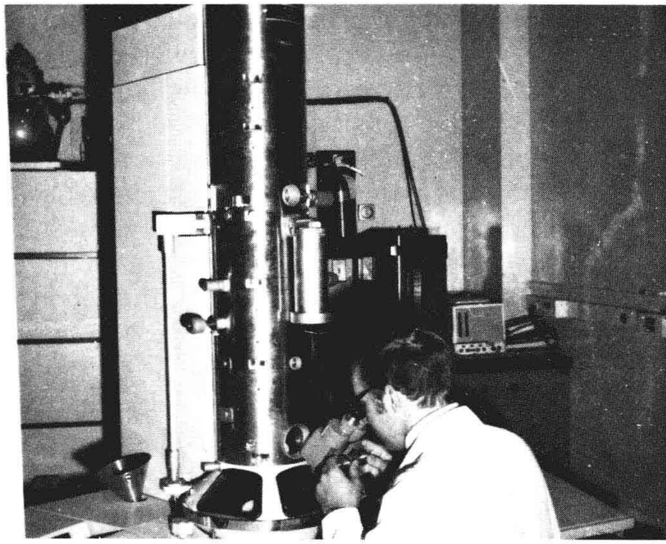
Under a light microscope, the mitochondria (M) in a mouse liver cell look like dark spots.



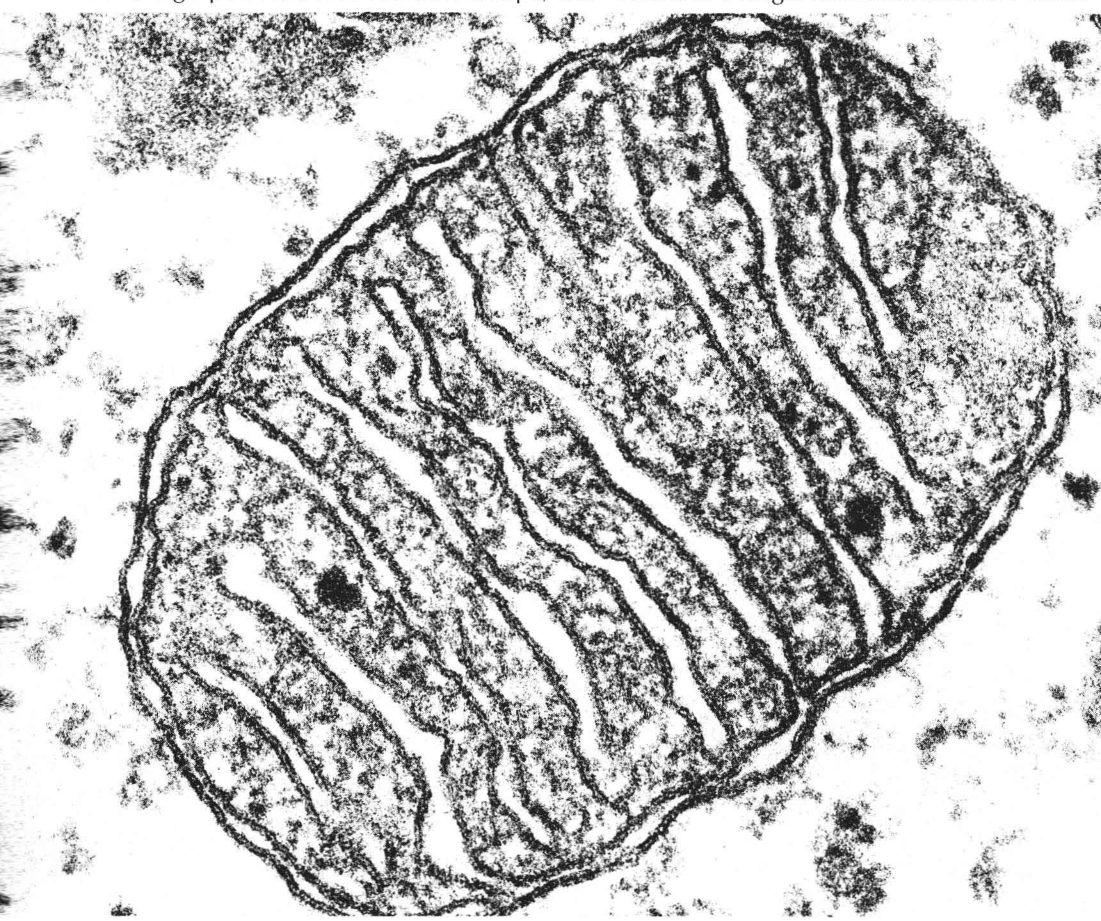
Magnification: x 3,000



ELECTRON MICROSCOPE



Under a high-powered electron microscope, the details of a single mitochondrion are clear.



Magnification: x 228,000

could pass through them. To ensure contrast between different parts of the otherwise transparent cell so as to reveal its structure, new staining techniques had to be devised, involving heavy metals; these are very dense to electrons, and different parts of the cell take them up to a different extent. The cell sections also had to be "fixed" in new ways, to preserve them, and embedded in new kinds of materials (mostly transparent plastic). Altogether, it wasn't until the early 1950's that the electron microscope was ready to make its major contributions to the study of cells.

While the cytologists (biologists who study cells) peered through their microscopes at smaller and smaller fragments of cells, in an attempt to understand their structure, another group of scientists was pursuing an entirely different, but equally important, line of research.

This line goes back to Antoine Lavoisier, the 18th-century French scientist who explained the role of oxygen in the respiration of both plants and animals, established the composition of water and other compounds, introduced quantitative methods in the study of chemical reactions, and thereby founded modern chemistry. In the 19th century, chemists isolated and identified many of the constituents of living cells—for example, hemoglobin, the red pigment of blood, and chlorophyll, the green pigment in plants. They discovered that compounds taken from animal tissue consisted of the same chemical elements as non-living materials. They isolated the nucleic acids, which are now known to govern heredity and protein synthesis. They began to study proteins, essential chemical components of living cells, and especially those proteins which control the chemical reactions that maintain life, the enzymes.

When dealing with cells, biochemists behave quite unlike the microscopists, who have enormous respect for the details of the cell's structure. The biochemists simply grind up large quantities of cells to release their contents into a solution (this is called "homogenizing" them) and then analyze the mixture (called the homogenate). This