Nothing Could Be Finer: Nanotechnology in Medicine

by John H. Dirckx, M.D.

Ever since the Greek philosophers Leucippus and Democritus postulated, in the fourth century BC, that all matter is composed of invisibly small and indivisible particles ("atoms"), human ingenuity has been seeking ways to confirm and elaborate that notion. The development of the microscope by Antonie van Leeuwenhoek and others in the seventeenth century of our era opened the door to the fine structure of matter, including living things, and carried investigators a step closer to finding its ultimate components.

At the beginning of the nineteenth century the English scientist John Dalton published a refined version of the primitive atomic theory of the Greeks, unifying and explaining certain basic facts in chemistry. Dalton believed that all matter is composed of atoms; that the atoms of any given element are identical to one another, but different (in weight) from the atoms of all other elements; and that atoms combine, in ratios that can be expressed in small whole numbers, to form molecules (compounds). During the past 200 years, a huge accumulation of empirical data and world-changing advances in technology (including the development of nuclear weapons of mass destruction) have lent powerful support to Dalton's theory.

Meanwhile, the electron microscope, developed during the first half of the twentieth century, has improved on the resolving power of the light microscope by a factor of about 1000. That is, whereas the maximum magnification possible with lenses that refract a beam of light is about 2000X, the best electron microscopes now achieve a magnification of about 2 000 000X.

Besides revolutionizing the study of nature and permitting the exploitation of its resources for good or ill, these increasingly minute investigations have become the basis of most of the advances in modern scientific medicine. Biochemistry (from enzymes and hormones to DNA and energy metabolism), histopathology, microbiology, pharmacology, diagnostic imaging—none of these could have reached its present state without the unremitting pursuit of the infinitesimal.

Nanotechnology is a burgeoning new field of pure and applied science that studies and manipulates matter on a submicroscopic level, where things are measured in nanometers and nanograms. In the International System of Units (SI), the prefix *nano-* (from Greek *nanos* 'dwarf') signifies 'one billionth'. That is, 1 nanometer (nm) is 0.000000001 m or 1 x 10^{-9} m. We're accustomed to referring to very large figures, such as that representing the distance from the earth to a star, as *astronomical*. To give some notion of the degree of smallness of things measured in nanometers (nanograms, nanomoles):

- One nanometer (1 nm) is to 1 m as the diameter of a marble is to the diameter of the earth.
- The smallest bacterial cells are about 200 nm in length.
- A DNA molecule weighs 1 pg (picogram), or 0.001 ng, or 0.000 000 000 001 g.

In 1974 the Japanese physicist Norio Taniguchi coined the term *nanotechnology* to describe research and development in which matter is manipulated one atom or one molecule at a time. The original context for such investigations was in the field of manufacturing, where it had become possible to deposit films one molecule thick and to use a beam of ions like a drill or saw to shape extremely small products.

Although to date much of the work in nanotechnology has been theoretical, advances of commercial importance have been made in the manufacture of computer microchips and in the production of polymers and colloids to serve as protective coatings for fabrics and other materials. Examples include the use of nanoparticles of zinc oxide and titanium dioxide in paints, varnishes, sunscreens, and cosmetics, and of silver in food packaging and clothing fabrics.

Because it holds the promise of dramatic advances in chemistry, physics, engineering, and robotics, nanotechnology has swiftly expanded to incorporate and enrich all those fields. Fledgling disciplines that have progressed rapidly with newly acquired resources include interface and colloid science, supramolecular chemistry (which studies relationships and forces other than covalent bonding among molecules), and cluster physics (which studies the relationship between the number and arrangement of atoms in a material and its physical properties such as color, density, and magnetic attraction).

A central theme of work in this field is the change in the mechanical, electrical, thermal, optical, and catalytic properties of matter when it is observed in nanoscale. An isolated protein molecule has a much higher surface-to-volume ratio than a visible aggregation of billions of such molecules in the form of a crystal. At nanoscale, copper becomes transparent, gold behaves like a liquid, and chemically inert platinum acquires potent catalytic powers.

A **carbon nanotube** is a cylindrical molecule composed of an extremely large number of carbon atoms. Although the diameter of a nanotube is measured in nanometers, it may be several millimeters in length. Some nanotubes have only one wall, while others have several concentric ones. A nanotube can be threaded inside a larger one. Adjacent nanotubes tend to weave themselves together to form "ropes" or "wires."

The unique interatomic bonding of such structures gives them remarkable tensile strength and unusual electrical properties. Carbon nanotubes have been detected in Damascus steel and may account for some of its celebrated strength. (Steel is an alloy of iron and carbon.) Fibers composed of carbon nanotubes have been incorporated in polymers to enhance their durability and modify their thermal and electrical conductivity.

One mode of proceeding in nanotechnology is by a series of stages in which increasingly smaller tools produce still smaller tools until a sufficiently fine scale had been reached. This so-called top-down approach to nanotechnology copies age-old manufacturing strategies but carries them out at a level requiring brand-new instrumentation.

By contrast, in the bottom-up approach, materials and devices are directed to assemble themselves from molecular components. Using as their model the replication of DNA and RNA (the basis of genetics and protein synthesis), chemists have devised systems in which certain molecules can recognize certain other molecules, with which they are directed to bond in a specific configuration. As such methods become more sophisticated, increasingly complex molecules can be assembled.

Another kind of bottom-up assembly, called molecular beam epitaxy, permits precise layers of atoms to be deposited on a surface, again with the possibility of an extremely intricate final product. This and many other items on nanotechnology's agenda may seem to pertain to the realm of science fiction (see box) rather than of the factual or the possible.

Each advance in nanotechnology calls forth an explosion of new techniques and devices. Methods of measuring the size and surface charge of nanoparticles in solution are based on microelectrophoresis, light scattering, ultrasound attenuation spectroscopy, and electroacoustics. Devices that make it possible to see structures in nanoscale include the atomic force microscope (AFM), the scanning tunneling microscope (STM), and the scanning acoustic microscope (SAM).

The tip of a scanning probe microscope can be used to maneuver nanostructures into position (a process called positional assembly). In nanolithography, an atomic force microtip can function like a pen, depositing a chemical substance on a surface in a desired pattern.

Surely You're Joking, Mr. Jones!

Historians of twentieth-century science trace the idea of nanotechnology (but not the term) to a talk given by Richard Feynman at a meeting of the American Physical Society at Caltech (The California Institute of Technology in Pasadena) on December 29, 1959.

Feynman was an American physicist best known for his work on quantum electrodynamics, for which he shared a Nobel Prize in 1965. During the early 1940s he collaborated with J. Robert Oppenheimer on the Manhattan Project, which culminated in the production of the first atomic bomb. Shortly before his death in 1988 he served on the presidential commission that investigated the space shuttle *Challenger* disaster.

Like some other Nobel laureates, Feynman was thoroughly eccentric. An inveterate prankster, he enjoyed a broad range of unrelated interests, including bongo drums, juggling, lock picking, and Mayan hieroglyphics. Besides several works of popular science, he published two semi-autobiographical books of humor, *Surely You're Joking, Mr. Feynman!* and *What Do You Care What Other People Think?*

The talk at which he broached ideas later recognized as pertaining to nanotechnology was entitled "There's Plenty of Room at the Bottom." He described a process by which the ability to manipulate individual atoms and molecules might be developed, using one set of precise tools to build and operate another proportionally smaller set, and so on down to the needed scale. He also predicted some of the changes in physical properties of matter that occur with change of scale. You can read his talk at **http://www.zyvex.com/nanotech/feynman.html**

About a decade before Feynman gave his supposedly epoch-making talk, I read a story entitled "Tools of the Trade" by Raymond F. Jones, an electrical engineer and prolific author of science fiction, in the November 1950 issue of a magazine called *Astounding Science Fiction*. A crucial element in that story is an advanced manufacturing process called the molecular spray:

"It was a means of building up three-dimensional objects of unlimited complexity by spraying on molecules in precise streams of variable constituency. The spray was keyed by an intricate matrix system that steered automatically the tool mechanism and changed the quality of the molecules from uranium to soft putty if that was called for. It was possible to leave channels, build in wiring, and assemble parts in any degree of intimacy required by design, a degree far surpassing that possible by clumsy nut and bolt or welding techniques."

Some of the changes in physical properties that occur at nanoscale have proved to be obstacles to mechanical and chemical manipulations on this level. Nanotechnicians refer to the problems of "fat fingers" (clumsiness of available instrumentation to handle ultrafine structures) and "sticky fingers" (the tendency of components to adhere to tools instead of staying where they are put).

Some observers, including investigators for the National Science Foundation, have warned that much of the work currently being labeled nanotechnology is just garden-variety materials science in which materials at nanoscale play a passive role. In contrast, the design and construction of **nanodevices** represent genuine technologic advances. A nanodevice is a machine—that is, an apparatus capable of doing work—whose dimensions are measured in nanometers.

A **transistor** is a semiconductor (a device of variable and controllable conductivity) that functions as a switch or amplifier in an electronic circuit. The operation of transistors depends on the conductive properties of a small group of elements, including silicon, germanium, and gallium, with which they are made. Transistors are components of all modern electronic devices, and without them the modern computer could never have come into existence.

The hard drive of the computer on which you are reading this article contains several million transistors, some or all of which may be smaller than 100 nm. Clearly a kind of nanotechnology is already involved in the manufacture of computers, but current efforts are directed to the fabrication of transistors less than 20 nm in diameter.

A **pair of nanotweezers** is a tool capable of grasping and manipulating objects at nanoscale. One kind of nanotweezers consists of two multiwalled carbon nanotubes so arranged that they can be brought together like the jaws of a pair of tongs when one is made electrically negative with respect to the other. With such a device, researchers have succeeded in performing simple mechanical tasks on a submicroscopic scale.

An entirely different type of nanotweezers consists of two strands of synthetic DNA that can be zipped together by a third strand under the influence of a change in chemical environment. DNA has also been used to construct a nanodevice capable of reversible angular movement, like a subminiature elbow or knee. DNA molecules, like carbon nanotubes, are rigid and have clearly understood structures and internal dynamics. Moreover, DNA sequences can be fabricated in any configuration by means of existing technology and replicated in batches of literally billions at a time.

Nanorobotics refers to the design and fabrication of self-actuated and self-directed devices at nanoscale. A robotic molecular assembler would manufacture structures by placing a series of parts into position one at a time. Devices have already been made that use robotic arms to assemble simple nanostructures in 3 dimensions while the process is monitored by scanning electron microscope.

A **biomotor** is a naturally occurring molecular structure equipped with a moving part like the rotor of an electric motor. Adenosine triphosphatase (ATPase), an enzyme used by all living cells to convert food into energy, has such a structure. Each molecule of ATPase contains an elongated protein shaft surrounded by three proton channels that function like the static coils of a motor. By modifying this molecule with nonbiological materials (nickel, silicon nitride), nanoengineers have created nanomotors fueled by adenosine triphosphate (ATP). Devices based on other molecules have been fueled by light or by captive bacteria.

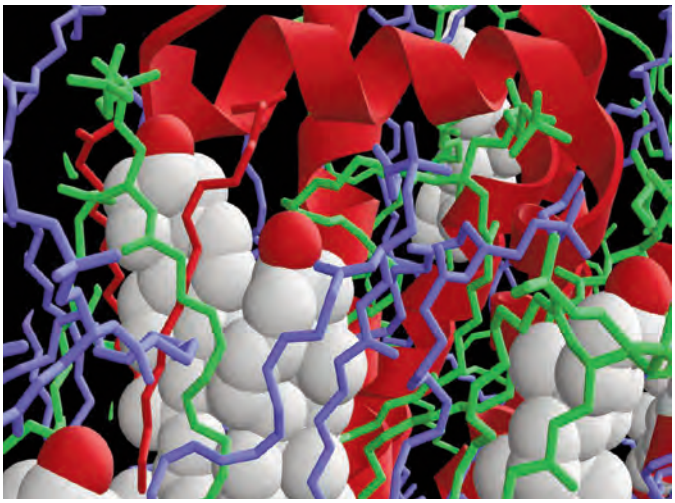
Virtually every advance and development in the physical sciences, engineering, and technology has the potential of impacting medical theory and practice. Nanomedicine is already a multi-billion-dollar industry, and further billions, including substantial contributions from the National Institutes of Health, are being spent in exploring its wider possibilities.

Despite the advanced state of sophistication that many branches of medical science have reached, current methods of **drug delivery** still leave much to be desired. The administration of drugs by the oral route can only be described as a hit-or-miss process. Current knowledge of the absorption and distribution of drug molecules is sketchy at best. For many drugs, therapeutic effects are inadequate and adverse effects troublesome because dosage forms in current use do not precisely target receptor sites.

Nanotechnology promises improvements in drug delivery through the fabrication of lipid- or polymer-based nanoparticle systems. Because of their extremely small size, nanoparticles can cross membranes and enter cells more readily than larger particles. Modification of particle size and electromechanical properties can direct drug molecules to the tissues upon which they are intended to act, keep them away from inappropriate targets, and accommodate them to the chemical environments in which they must function. Besides avoiding toxicity and adverse effects, precise targeting of drug delivery can reduce the total quantity of drug that needs to be administered to achieve its effect, lowering costs.

The term **smart drug** refers to a substance that, after entering the body, becomes pharmacologically active only under certain circumstances. For example, an antibiotic can be bound to a hydrogel molecule that renders it inactive. Only an enzyme produced by a pathogenic strain of *Pseudomonas* can break the chemical bond and release the active drug. Application of the product to a wound or ulcer leads to release of antibiotic only in the presence of *Pseudomonas* infection. Restricting the use of active drug to situations in which it is clinically indicated reduces the risk of allergic sensitization of the patient and of the emergence of strains of bacteria resistant to the antibiotic.

An immunotoxin is another type of smart drug, a hybrid molecule fashioned from a toxin and an antibody. The toxin chosen is a particularly virulent cytotoxin, capable of destroying living cells in minute dosage. The antibody portion of the molecule is designed to recognize surface features of certain types of cancer cells. Immunotoxins administered experimen-



Cholesterol illustration by Michael C. Pitman, Ph.D.

The term **nanoart** refers to two by-products of nanotechnology, both of which blend scientific interest and aesthetic appeal. One kind of nanoart consists of electron microscope scans of real objects and materials at nanoscale that have been computer printed on canvas or art paper. These are primarily art for art's sake.

Another form of nanoart is a representational process in which the intimate details of chemical compounds or organic structures are simulated graphically in three-dimensions by supercomputing. The above illustration shows the interaction of cholesterol (gray spheres) with the light-sensitive retinal pigment rhodopsin (red ribbon) in an environment of saturated and unsaturated fatty acids (blue, green, and red molecular chains). Simulations of this type provide theoretical insights and practical leads for drug design that cannot be obtained experimentally.

tally to patients with hairy-cell leukemia and Hodgkin's cell lymphoma have shown some efficacy in eradicating malignant cells.

Yet a third way in which nanotechnology may enhance the potential of pharmacology is by providing a means of xenografting functional tissue into the human body (for example, islet cells from non-human pancreas for patients with diabetes mellitus) without concerns about immune response and rejection. The alien material is enclosed in a microscopic chamber constructed of crystalline silicon and deposited under the subject's skin.

Precisely drilled pores 20 nm in diameter permit oxygen, glucose, and electrolytes to diffuse into the chamber from surrounding tissue fluids for the support of the islet cells while allowing insulin produced by the cells to diffuse outward and enter the subject's circulation. But these cells are effectively isolated from the subject's immune system, because proteins needed for the recognition and neutralization of foreign material cannot pass through the nanopores. Similarly, encapsulated neurons implanted in the brain might be stimulated electrically to release neurotransmitters to correct disorders such as parkinsonism and Alzheimer dementia.

It has long been known that pairs of large molecules in biological systems often fit together in lock-and-key fashion. This is true, for example, of hormones and their receptors as well as of antibodies and their targets. By means of nanoengineering it has been possible to fashion **artificial receptors** consisting of films of polysaccharide-like material imprinted with patterns of shallow indentations into which certain proteins, enzymes, and antibodies precisely fit. With such tailor-made receptors it may be possible to isolate and assay specific molecules, monitor drug levels, control drug release, and mimic biological receptors.

A **quantum dot** (the name Qdot is a registered trademark of Quantum Dot Corporation) is a nanoparticle of cadmium selenide that emits a quantum of light energy when it is exposed to ultraviolet light. These particles behave much like the dyes currently in use in fluorescence microscopy and fluorescence in-situ hybridization, but they glow much more brightly and yield a higher-contrast image. Quantum dots to which specific protein molecules have been bonded can seek out and fuse with specific substances (drugs, antigens, enzymes). They can be inserted into cells to monitor metabolism, drug distribution, or disease processes. They can also penetrate and label cancer cells.

Photodynamic therapy is a noninvasive and precisely targeted nanomedical method of destroying cancer cells. Nanoshells coated with a thin layer of gold and equipped with specific antibodies can be made to fuse with malignant cells that have distinctive surface proteins. Irradiation of the tumor with an infrared laser, which penetrates skin and other tissues harmlessly, causes the gold to become hot enough to destroy cancer cells without damaging other cells. Light can also be used to release a cytotoxic concentration of oxygen molecules from nanoparticles that have become bonded to tumor cells.

Another application of photodynamics is an experimental "**flesh welder**," which could revolutionize surgical technique. A suspension of gold-coated nanoshells placed at the interface of two wound edges and heated with an infrared laser can produce a virtually seamless union of tissues.

A **dendrimer** is a synthetic nanoparticle whose core supports an outer structure of intricately branched hooks. These hooks can provide sites of attachment for large molecules, such as DNA or cancer chemotherapy drugs. Unlike viral vectors currently used to deliver genetic materials inside cells, a dendrimer can enter a living cell without triggering an immune response. By mimicking mammalian cells, dendrimers can also trap and deactivate influenza virus particles.

Nanonephrology deals with the study of kidney structure and function at the atomic level, imaging methods to observe renal cell metabolism, and the use of nanoparticles to treat kidney disease. A distant goal is the construction of a nanoscale artificial kidney that can safely and effectively assume the function of kidneys in end-stage failure.

As discussed earlier, **nanopores** are apertures of precisely controlled diameter artificially created in nanomaterials. Nanopore technology offers the possibility of designing filtration

systems of advanced efficiency and exact control. The passage of materials through a nanofilter or nanosieve depends not only on pore size and shape but also on electrical charge. An artificial membrane composed of nanotubules with diameters of 2 nm and carrying a positive electrical charge will permit only negative ions to pass, and vice versa. Control of ion transport opens the door to an almost limitless range of interventions in organic and metabolic disease.

When strands of DNA are electrically propelled through an artificially designed protein channel with a diameter of 2.6 nm, the individual nucleotides can only pass one at a time. Changes in ionic current can be used to distinguish base pair sequences in roughly the same way that a Coulter counter distinguishes between red and white blood cells, or between monocytes and lymphocytes. With the ability to read as many as 1000 base pairs per second, such a device could provide a means of rapid genome sequencing.

Some objectives of nanomedical research lie farther off in the future. One of these is **neuroelectronic interfacing**, a process whereby a computer could be linked or networked to the human nervous system. Besides its obvious advantages for research and diagnosis, such a development might permit made-to-order devices to take over the functions of parts of the nervous system impaired by disease or injury

Achieving this goal calls for nothing less than the ability of a man-made machine to detect, interpret, and respond to neural signals. Although neural impulses are indeed electrical, they do not flow through nerve fibers in the same way that power flows through the wiring in a building. Formidable problems of insulation, energy source, electromagnetic interference, and biocompatibility remain to be solved.

Equally far from realization is the development of **molecular assemblers and nanorobots** to perform medical or surgical tasks within the living body. A device of this type would be injected into the circulation, which would carry it to its site of action. In order to pass through the circulatory system without being trapped in capillaries, its maximum size would be about 3 micrometers. As mentioned earlier, carbon nanotubes are the building blocks of choice for nanodevices. If these nanotubes are fashioned from atoms of C 13 rather than from the more usual C 12 isotope, their position and activity can be traced in the body by MRI.

What functions would medical nanorobots be designed to perform? Within a few decades, researchers hope to have nanomachines that can cross biomembranes, enter living cells, recognize and manipulate molecules, disassemble damaged structures, and build others anew. Synthetic nanorobots might also be programmed to mimic the structure and function of naturally occurring ones such as red blood cells, which transport oxygen and carbon dioxide; neutrophils, which attack and destroy invading microbes and dispose of tissue debris; and fibroblasts, which build or repair connective tissue by producing and depositing collagen fibers.

Each device in the first generation of medical nanobots would be programmed to perform a single task. Later machines would be more versatile, functioning as "general practitioners" with a broad repertory of skills. The ultimate goal, perhaps not altogether beyond human potential, is to free the human body from the need to correct and repair its own problems, to fight its own battles with pathogenic microorganisms and heal its own wounds, by mobilizing a workforce of nanorobots.

For more than two decades, bioengineered viruses, bacteria, and human blood and tissue cells have been used as vectors to insert therapeutic DNA sequences into the nuclei of defective human cells. A strain of salmonella organisms that has been deprived of the genes that enable it to produce purines for nucleic acid synthesis can thrive only in the purine-rich environment of a rapidly growing malignant tumor. If these bacterial cells are equipped with genes that enable them to produce proteins, enzymes, or other agents to suppress cell proliferation, their concentrating in tumor tissue can focus such effects against malignant cells.

Theoretically the genetic material of a cell could be programmed much like a computer. Chemical structures have already been designed that can operate like a toggle (on-off-on-off) switch in a computer circuit. A switch of this kind can be actuated by a change of chemical environment, and might thus become a component of a system in which the presence of a drug or chemical could turn on a specific gene.

The genomes of some microorganisms have now been fully sequenced. It should theoretically be possible to construct from scratch a stripped-down genome that, when inserted in an enucleated living bacterial cell, could direct all vital functions. This "biobot" could be programmed, in addition, to synthesize hormones, enzymes, cytokines, or other substances lacking in a given patient, or to absorb and destroy harmful substances.

The proposed construction of artificial organisms involves building a synthetic genome to order and installing it in an enucleated pluripotent (stem) cell. Similar technology may also provide a means of curing genetic diseases. A nanorobot introduced into a living cell could extract defective genetic material from its nucleus and replace it with normal chromosomes previously manufactured to order. The subject's genome would serve as a master blueprint for the replacement chromosomes and the nuclear transplant surgery.

There is no telling how soon nanomedical terms will begin appearing in medical dictation and transcription. But it probably won't be long.

1 Clinical Medicine
CE credit approved

John H. Dirckx, M.D., is the author of *Laboratory Tests and Diagnostic Procedures in Medicine* (2004), *Human Diseases*, 2nd ed. (2003), *H&P: A Nonphysician's Guide to the Medical History and Physical Examination*, 3rd ed. (2001), published by Health Professions Institute. He is an editorial consultant to the publisher of Stedman's medical reference books and medical editor of HPI publications.

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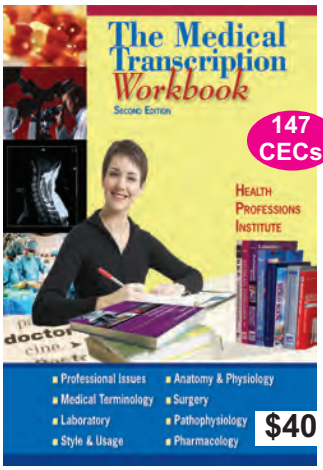

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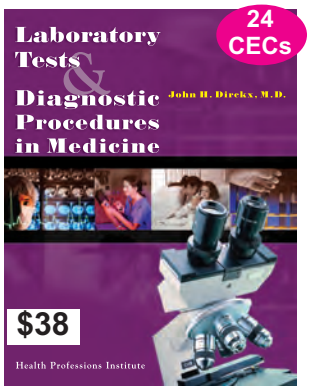

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Human Diseases, 2nd ed., covers diseases commonly encountered in dictation, including causes, symptoms, diagnostic tests, diagnoses, and treatment regimens. Dr. John H. Dirckx's clear writing and topical organization make it an easy-to-use desk reference on disease processes. It includes:

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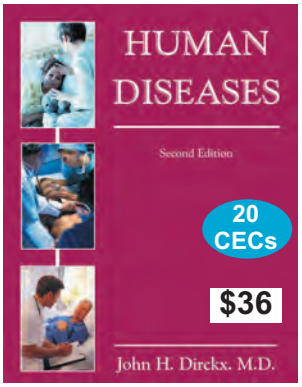
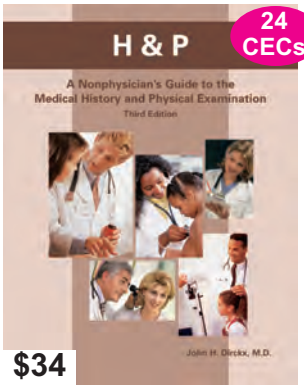


The third edition of ***H & P: A Nonphysician's Guide to the Medical History and Physical Examination***, by John H. Dirckx, M.D., aids in deciphering difficult dictation and can be used as a study aid for credentialing exams.



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