

BREAKFAST FOR THE BRAIN[®]

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Breakfast for the Brain[®] is a school-year e-mail service for science educators and others on topics in life science, biomedical research, and biotechnology, published by the Massachusetts Society for Medical Research, Inc.

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FEBRUARY 2002 – VOLUME 2 – DRUG DISCOVERY & DEVELOPMENT

ISSUE NO. 1: Friday, February 1, 2002

Opening Message & Introduction to Volume 2

Notable Quote

Breakfast for the Brain[®] Article

PHARMACOLOGY... Converting Molecules into Medicines

MSMR Announcements

Open Forum

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OPENING MESSAGE & INTRODUCTION TO VOLUME 2

Welcome to the debut issue of **Breakfast for the Brain[®]**, the newest educational outreach initiative of the Massachusetts Society for Medical Research, Inc.!

Breakfast for the Brain[®] is a school-year e-mail service (September through June) for science educators and others on topics in life science, biomedical research, and biotechnology. Topics change monthly and reflect current issues and areas of research in the life sciences. **Breakfast for the Brain[®]** features a topical article delivered on the first weekday morning of each month, followed by lesson plans, background facts and information, classroom activities, puzzles and games, announcements, and other items related to the topic delivered subsequently on varying mornings throughout the month. While topics focus on issues and events in biomedicine and biological science, **Breakfast for the Brain[®]** strives to be cross-curricular and to relate these issues and events to curricula and events in non-science, as well as science, disciplines.

To achieve these goals and make **Breakfast for the Brain[®]** a welcome addition to the classroom, subscribers are encouraged to actively participate in the content and format of this unique medium with

insights, tried-and-true lesson plans, and other valuable input. Make suggestions for future topics and features you'd like to see covered in **Breakfast for the Brain**[®]. We will incorporate your feedback into the format through the **Open Forum** section of the newsletter.

Introduction to Volume 2 – Drug Discovery & Development

For most of us in the 21st century, the prospects of living a long and healthy life have never been better. Biomedical science has effectively eliminated diseases such as polio and smallpox; vaccines keep many infectious diseases in check; surgical techniques exist to repair everything from congenital heart defects to hip and joint problems in the elderly; and transplantation makes possible the replacement of failing organs. Equally as important and exciting in the big picture of modern healthcare is the world of drug discovery and development.

This second volume of **Breakfast for the Brain**[®] will explore drug discovery and development – pharmacology, history and milestones of drug discovery, and methods used in modern drug discovery and development. We begin in this issue with an introduction to the science of pharmacology.

Please Note: Because **Breakfast for the Brain**[®] is intended primarily as a vehicle for K-12 educators, Volume 2 issues will not be released during February school vacation week (the week of 18 February).

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NOTABLE QUOTE

“Organic chemistry is the chemistry of carbon compounds. Biochemistry is the study of carbon compounds that crawl.”

- Mike Adams

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Breakfast for the Brain© ARTICLE

PHARMACOLOGY... Converting Molecules into Medicines

Pharmacology is a cornerstone of the drug discovery process. New drug candidates can arise through a number of avenues -- such as bioprospecting or laboratory synthesis by an organic chemist -- but the pharmacologist is the one who tests it for physiologic activity. Promising new drugs are studied by many science professionals, including toxicologists, microbiologists, and clinicians, but their potential therapeutic effects are first documented by pharmacologists.

What is pharmacology?

Pharmacology is the study of drugs (Greek *pharmakos*, medicine or drug; and *logos*, study), and refers specifically to study of the actions of drugs. In this context, drugs are defined as “chemicals that affect the functioning of the body,” rather than the narrower definitions such as “substances of abuse” or “medicines.”

Pharmacology studies the effects of drugs and the mechanisms by which they exert their effects. There is a distinction between what a drug does and how it acts. For example, amoxicillin is a treatment for strep throat, and cimetidine promotes the healing of duodenal ulcers. A pharmacologist asks how these drugs exhibit these properties. Amoxicillin inhibits the synthesis of a cell wall mucopeptide by *Streptococcus* bacteria, and cimetidine inhibits gastric acid secretion by antagonist action on histamine H2 receptors.

Pharmacology plays a major role in human health and society. The pharmaceutical and healthcare industries are indebted to pharmacologists, who are responsible for the discovery of thousands of drugs used in the treatment of disease and the relief of human and animal suffering.

The main tasks of pharmacologists in the search for and development of new medicines are:

- screening for desired activity;
- determining mode of action; and
- quantifying drug activity.

A brief history of pharmacology

Synthetic organic chemistry began in 1828, when Friedrich Wohler synthesized urea from inorganic compounds and in doing so, shattered the vital force theory. The beginnings of pharmacology, however, are more diffuse. In the early 19th century, physiologists performed many pharmacologic studies. In the early 1800s, François Magendie studied the action of *nux vomica* (a strychnine-containing plant drug) on dogs, and showed that the spinal cord was the site of its convulsant action. In 1842, Claude Bernard discovered that the arrow poison curare acts at the neuromuscular junction to interrupt the stimulation of muscle by nerve impulses.

Despite these developments, pharmacology was recognized as a separate science only when the first university chair was established in 1847, when Rudolf Buchheim was appointed professor of pharmacology at the University of Dorpat in Estonia, then a part of Russia. Lacking external funding, Buchheim financed his own laboratory in the basement of his home. Although Buchheim is credited with turning the purely descriptive and empirical study of medicines into an experimental science, his reputation is overshadowed by that of his student, Oswald Schmiedeberg.

Schmiedeberg (1838–1921) is generally recognized as the founder of modern pharmacology. The son of a Latvian forester, he obtained his doctorate of medicine in 1866, with a thesis on the measurement of chloroform in blood. He worked at Dorpat under Buchheim, succeeding him in 1869. In 1872, he became professor of pharmacology at the University of Strassburg, receiving generous government support in the form of an institute of pharmacology, where he studied the pharmacology of chloroform and chloral hydrate. In 1869, Schmiedeberg showed that muscarine evoked the same effect on the heart as electrical stimulation of the vagus nerve. In 1878, he published a classic text, *Outline of Pharmacology*, and in 1885, introduced urethane as a hypnotic. In his 46 years at Strassburg, Schmiedeberg trained most of the individuals who became professors at other German universities and in several foreign countries. He was largely responsible for the preeminence of the German pharmaceutical industry up to World War II.

In the United States, the first chair in pharmacology was established at the University of Michigan in 1890 under John Jacob Abel, an American who had trained under Schmiedeberg. In 1893, Abel went to Johns Hopkins University in Baltimore, where he had a long and brilliant career. His major accomplishments include the isolation of epinephrine from adrenal gland extracts (1897–1898), the isolation of histamine from pituitary extract (1919), and the preparation of pure crystalline insulin (1926). His student, Reid Hunt, discovered acetylcholine in adrenal extracts in 1906.

Today, there is a pharmacology department in every college of medicine or pharmacy.

Animal Studies

Pharmacology is dependent to a large degree on studies in animal models, although in the early days of pharmacology, people -- often the scientists themselves! -- were likely to be primary test subjects as well. Friedrich Serturmer, a German pharmacist who isolated the first alkaloid from opium in 1805, administered a large dose (100 mg) to himself and three of his friends. All experienced the symptoms of severe opium poisoning for several days. The alkaloid was named morphine, for Morpheus, the Greek god of sleep.

Although humans are no longer used as primary biological models, for obvious ethical reasons, we are essential to clinical pharmacologists. When a new drug has undergone sufficient preclinical testing in animal

models to document efficacy (potential therapeutic action) and reasonable safety on short-term administration, and the data have been reviewed by the FDA, the compound is administered to a small number of human volunteers under closely controlled and monitored conditions. These so-called *Phase I clinical trials* provide essential information about dosage and side effects.

The animals most frequently used in pharmacologic studies are mammals, rodents in particular. Mice are preferred because of their small size, ease of breeding, and short generation time. Rats, guinea pigs, rabbits, and dogs are also used. Each species has characteristics that make it optimal for certain types of tests.

Basic Techniques

Animals are essential for acute, subacute, and chronic toxicity tests that a new drug candidate must undergo, as well as for important special tests such as teratology and carcinogenicity. [See **Breakfast for the Brain** ©, Volume 1 – **Toxicology** for details.]

Pharmacologists tend to use isolated (excised) organs or tissues and animals that are surgically prepared in various ways to aid in the detection and study of target activities. During the development of pharmacologic techniques, it was found that an isolated organ or tissue remained functional for several hours in a bath containing a physiologic solution of salts through which oxygen was bubbled. The organ or tissue is suspended so that the contraction or relaxation of the muscle is mechanically transmitted to a stylet, which writes on a drum covered with smoked paper rotated by clockwork at a constant speed. This device, called a *kymograph*, graphically records motion or pressure. The effects of drug substances added to the bath can be visualized in this way. In modern pharmacology, organ and tissue movements are transmitted by force transducers to polygraph machines, which produce similar tracings, or the polygraph is replaced by computerized equipment that issues a digital record.

In the first half of the 19th century, German anatomist Arnold Berthold transplanted testicular tissue into a capon (a castrated rooster) and showed that this induced growth of the comb. This method was used in the 20th century to isolate and study male sex hormones. In a similar vein, in the early 20th century, Americans Edgar Allen and Edward Doisy used ovariectomized rats to test the action of estrogenic hormones. To study anti-inflammatory agents, an arthritis model can be induced in rodents by injection of an oily suspension of killed bacteria, called Freund's adjuvant. Drugs affecting gastric secretion may be studied in animals by forming a Heidenhain pouch—a small denervated sac of the stomach closed off from the main cavity, but with an opening through the abdominal wall.

How are new drugs discovered?

Drugs are discovered in a number of ways. Pharmacology has been practiced for thousands of years. Ancient cultures, for example, used many types of medicinal herbs, minerals and other compounds extracted from animals for healing purposes.

Today, scientists are still discovering new medicinal uses for compounds whose beneficial effects have been known for centuries from natural sources. The bark of the willow tree is the natural source of aspirin. The dried leaves of the foxglove are the plant source of digitalis. And codeine is derived from the opium poppy, as is one of the most powerful painkillers known -- morphine. Anticancer drugs have been developed from the periwinkle and from the bark of the Pacific yew tree. Cyclosporins -- used to help prevent transplant patients rejecting grafted organs -- come from fungi.

New drugs can come from other sources, too. A group of microbes found commonly in the soil -- the *Streptomyces* bacteria -- produces substances that are the basis for over 500 antibiotics, of which 50 are in everyday use.

The sea is also a rich source of natural-source drugs. Sponges and corals contain potentially useful compounds. Pharmacologists are also keenly interested in a certain type of mussel that could help in finding a new treatment for arthritis patients. Conus snails, which live by catching and eating fish, produce venoms which have a very wide range of interesting toxins that have proved to be vital tools in understanding many

aspects of cellular functions. Scorpions, snakes, and certain South American frogs have very complex venoms which are being studied to understand body processes, leading to further ideas for new drugs.

So, many researchers are actively seeking natural products that could be developed into medicines. However, finding and adapting natural compounds as drug candidates is only one aspect of pharmacology.

Targeted, rational design

Today scientists involved in drug discovery develop and test chemicals in the laboratory that act very specifically on the body. Pharmacologists have some exciting tools to aid in the discovery of new drugs. The explosion of knowledge in the fields of genetics and molecular biology have revolutionized pharmacologic research. So too, has the computer.

Computer technology aids in drug discovery and reduces the number of animals needed. High performance computing can often identify substances that may have therapeutic use, accelerating the process of new drug development. High throughput screening against selected molecular targets also uses clonal cell lines grown in tissue culture. By these means, inactive or unsuitable compounds can be discarded before preclinical studies in animals are undertaken and only those with a high potential for success are pursued as drug candidates.

Many potential new drugs fail because they cannot be absorbed or metabolized by the body, or cannot reach their target. These obstacles can sometimes be predicted from *in vitro* experiments using sensitive assay methods.

Another design approach is for pharmacologists to learn from the drug manufacturing ability of the human body itself. It was discovered not long ago that the brain produces chemicals called *endorphins*, which act as the body's natural painkillers. "Endorphin" means "built-in morphine," but unlike the morphine derived from the poppy, endorphins are not addictive. Research on endorphins has shown that these compounds can play a role in such functions as regulating appetite and controlling mood, opening a new line of pharmacological research that could result in better pain relievers, anti-anxiety drugs, and compounds to prevent eating disorders.

Screening of drug candidate compounds and studying their modes of action may focus on specific tissues, organs, or systems -- or on actions, such as antihistaminic or anticonvulsant properties. As knowledge of human biochemistry and molecular biology advances, pharmacology zeroes in more often on enzymatic action and receptors.

Captopril (Capoten), developed in the 1970s, was a milestone drug that was purposely and rationally designed to fit the active site of an enzyme—angiotensin converting enzyme (ACE). This drug, and subsequent ACE inhibitors, have been instrumental in the treatment of hypertension, saving millions of lives.

Today, knowledge of cell receptors is considered cutting edge in pharmacology and drug discovery. The concept was first proposed about a hundred years ago by Paul Ehrlich, the great bacteriologist and chemist who synthesized salvarsan for the treatment of syphilis. Based on his research on bacterial toxins, Ehrlich postulated that the body's cells possess a great many "receptors" by which they combine with the food substances in the body fluids. He theorized that the metabolic products of certain bacteria combine with the receptors of some cells, causing injury to the cells. Ehrlich visualized receptors as unfulfilled chemical side chains, a conceptualization not unlike the modern idea of receptors as domains in enzymes or other proteins, with which drugs of appropriate structure can combine.

Drugs that act on the adrenergic (sympathetic) nervous system illustrate the importance of receptor research. The adrenergic nervous system has both α - and β -receptors. Propranolol (Inderal) was the first specific β -adrenergic receptor blocking agent. Marketed in 1964, it filled a dire need for new heart medicines and soon became a major therapy for angina pectoris, cardiac arrhythmias, hypertension, and essential tremor. However, all β -adrenergic receptors are not identical, and propranolol is nonselective. Second-generation drugs such as atenolol (Tenormin) and metoprolol (Lopressor), developed in the late 1970s, have a preferential effect on β_1 receptors, which are chiefly located in heart muscle. At higher doses,

they also inhibit β_2 receptors, which are found mainly in the bronchial and vascular musculature. Blockers of the α -adrenoreceptors, such as prazosin, and α_1 -blockers, such as terazosin, were developed in the 1980s.

Summary

The discovery of a promising compound is just the beginning of the long and painstaking process of developing a new drug that can be safely used in people or animals. Pharmacologists can pursue careers at all stages of this process, from basic research and identification of novel targets through to testing in animals and humans to regulatory filing and medical information.

It is estimated that it takes on average 12 years from filing a new drug patent to the launch of a major new drug - at a total cost of up to hundreds of millions of dollars. Out of every 8,000 or so compounds discovered and investigated, on average only one reaches the marketplace. Once that compound has been identified, the development phase -- lasting 6-7 years -- begins.

Why are new drugs needed?

Drugs improve the quality of life for millions of people and prevent disease on a massive scale. It is estimated that modern medicines have added 3-5 years to average life expectancy and that antibiotics and vaccines have saved millions of lives since 1945.

Anesthetics, muscle relaxants and immunosuppressant drugs have all made new surgery possible, and new drugs have also brought about effective treatments for such diseases as diabetes, hypertension, bronchitis and asthma, mental illness, and arthritis.

But the need for new pharmaceuticals remains. Malaria affects 300-500 million people each year, killing up to three million people worldwide. Although antimalarial compounds exist, resistant strains of the infectious organism are developing all the time, so research must continue to try to keep ahead of the game. Tuberculosis is still a major cause of death, and treatments are urgently being sought for other conditions such as cystic fibrosis, Parkinson's disease, Alzheimer's disease, and of course AIDS. Cancer is one of the top killers in the developed world, and heart disease remains the number one cause of death worldwide.

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MSMR INFORMATION & ANNOUNCEMENTS

The mission of the Massachusetts Society for Medical Research, Inc. (MSMR) is to promote and enhance biomedical and biological research, including the proper care and use of animals, for the improved health and well-being of people, animals, and the environment. In furtherance of this mission, the goal of the MSMR is to improve basic literacy in and enthusiasm for life science among the public, the media, and especially future generations of citizens and scientists.

The MSMR offers a full-range of programs and materials to classroom educators on topics in biomedical science, biotechnology, and the use of animals in research and testing. Most of the MSMR's outreach

programs and materials are available free of charge to K-12 educators throughout the Northeast (New England and New York). To request a copy of the MSMR's catalogue of programs and materials, send an e-mail request to Leslie Nader, Ph.D., *Vice President for Education*, at lnader@concentric.net.

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Look for the next issue of *Breakfast for the Brain*[®], Volume 2 – **Drug Discovery & Development**, next week.

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Leslie Nader, Ph.D.
Vice President for Education
Massachusetts Society for Medical Research, Inc.
73 Princeton Street, Suite 311
North Chelmsford MA 01863

Tel. 978.251.1556
FAX 978.251.7683
e-mail: lnader@concentric.net