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Magic Molecules: How Drugs Work

THE BOOK

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> *...A GOLDMINE OF INFORMATION ...[some] topics covered in the book include antibiotics, hormonal drugs, cardiovascular drugs, painkillers, anti-cancer drugs, drugs for treating mental disorders, vitamins, minerals and herbal drugs, and gene-based medicines. Some chapters are illustrated with appropriate diagrams for better comprehension. Magic Molecules is a goldmine of information about the myriads of medicines we use and ought to be a must read for not only clinicians and those in medical profession but also for anyone who wants to be informed about the fascinating world of drugs...*

Editor's recommendation — this book carries the editor's "must buy" recommendation.

Magic Molecules: How Drugs Work *by* Susan Aldridge, Hard Cover, 6" x 9".
Cambridge University Press, 32 Avenue of the Americas, New York, NY 10013-2473. . . Publication Date September 1998. 284 pages, ISBN-10: 0521584140. ISBN-13: 9780521584142. Price $50.00

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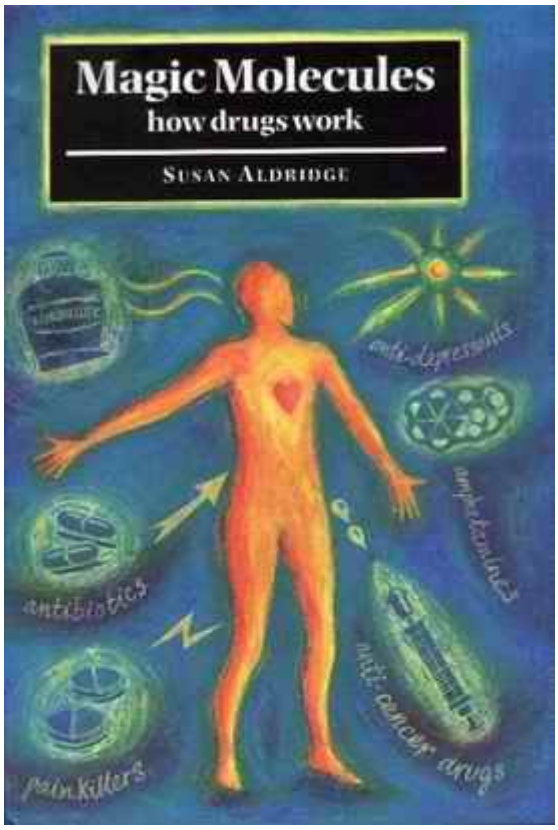

There'd be hardly any person, young or old, in this world who has never used a medicinal drug to seek relief from some health problem. And drugs come in myriads of forms meant for treating myriads of diseases. Many traditional drugs have been used by man for thousands of years and new drugs are coming into the market all the time. There are now effective treatments for diseases like AIDS and multiple sclerosis, where none existed before. While a majority of drugs are still available only on doctor's prescription, the range of medicines available over the counter is rapidly changing. Even with prescribed medicines, patient non-compliance not only comes in the way of achieving the desired results but also often leads to serious consequences such as development of drug resistance. In many cases self medication leads to more harm than good. Many of these irrational uses of medicinal drugs are the result of a lack of general awareness in the public about drugs and the way they work in the body. Susan Aldridge's *Magic Molecules* can certainly go a long way to change the situation. She explains the complexities of drug action - not only of medicinal drugs but also of a few of the non-medicinal and addictive drugs used for pleasure - in her inimitable style that anyone with a little knowledge of science should be able to understand.

It is common knowledge that some drugs can be taken by mouth while others have to be taken through painful injection. Few of us perhaps have ever bothered to find out why it is so. *Magic Molecules* gives us the answer; and the answer is quite simple. If we take a drug by mouth it has to withstand the onslaught of the acid and digestive enzymes of our stomach. Small molecules like aspirin can easily clear this hurdle and enter the small intestine from where it is readily absorbed into the bloodstream. But a larger molecule like the hormone insulin used to treat diabetes isn't so lucky; it is broken up and made useless by stomach acids. That's why it has to be administered by injection. Of course, researchers keep trying to overcome the hurdles and often come up with viable solutions. For example, the antibiotic penicillin once had to be administered only by injection, but now oral penicillin is available that is as effective.

> *...Aldridge devotes a full chapter to 'How drugs work.' Drugs work in a variety of ways. Aspirin relieves headache by blocking the production of pain-producing substances known as prostaglandins, and are then swept away by the general circulation. All the aspirin is cleared from the body within 24 hours. Some drugs act by interfering with the way in which an enzyme or a receptor functions and thereby influencing body function...*

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Click here to read interview with Susan Aldridge, the author of *Magic Molecules: How Drugs Work*.

The action of an enzyme depends on its shape, which acts like a lock into which a key can fit. The chemical, which the enzyme transforms into a product, called the substrate, fits snugly into the active site like two pieces of a jigsaw. Thus joined, the enzyme can get to work - by snipping a chemical bond in the substrate, or creating a new one between two different substrates to make a larger molecule. Finally, the product molecule gets detached from the enzyme, which now gets ready to act on another substrate molecule.

Some drugs, called enzyme inhibitors, are designed to prevent the enzyme from latching on to the substrate and thus blocking its action. For example, the common drug aspirin prevents the release of substances known as prostaglandins that are responsible for the sensation of pain, by inhibiting the action of an enzyme called cyclooxygenase. Many other drugs, such as angiotensin converting enzyme (ACE) inhibitors used to treat hypertension, certain antidepressants, penicillin, and some drugs for the treatment of AIDS, act in the same way.

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There are other ways in which drugs can act. Some drugs such as ion channel blockers act by interfering with the normal traffic of substances in and out of cells. Calcium blockers, for example, can reduce the workload on the heart in a heart patient by blocking the ion channel on heart muscle cells, which reduces the strength of the muscle contraction of the heart.

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very careful with drugs with a small therapeutic index because with these drugs the onset of toxic effects appears fairly quickly after the minimum effective dose. For example, the antibiotic gentamicin has a therapeutic index of only 3; that is, if three times the minimum effective dose were prescribed accidentally, it could prove fatal. In contrast another antibiotic, benzylpenicillin, has a therapeutic index of over 100. So here, if the patient does not respond to a lower dose the physician can increase the dose without much worry.

Sometimes, even if the dose is correct, the patient does not get the desired effect of a drug. This is often due to non-compliance by patients rather than inefficacy of a drug. People on medication for high blood pressure, asthma, depression, schizophrenia, and epilepsy have a strong tendency to reject their drugs. Some of the reasons, says Aldridge, are rooted in human psychology; patients fear addiction, are absent-minded, or fail to appreciate the seriousness of their condition. She says better communication between doctor and patient can improve compliance. And she may be right, as seen with the 'directly observed therapy', or DOT for TB patients in India and elsewhere.

> *...One of the major reasons why many patients are reluctant to continue with a drug is the side effect it sometimes produces, which may range from stomach irritation and acidity to allergies. Fortunately, many side effects are predictable from the way the drug acts and the patient may be told in advance about them. Sometimes, if a patient is taking more than one drug at a time, their mutual interaction may cause problems...*

One of the major reasons why many patients are reluctant to continue with a drug is the side effect it sometimes produces, which may range from stomach irritation and acidity to allergies. Fortunately, many side effects are predictable from the way the drug acts and the patient may be told in advance about them. Sometimes, if a patient is taking more than one drug at a time, their mutual interaction may cause problems. Fortunately, such drug-drug interactions are often predictable and can be avoided by careful prescription.

The number of drugs available today runs into several thousand, and new drugs are being created routinely. Discovering and developing new drugs is a costly business. It may take 12 years and cost upward of $350 million to bring a drug into the market from its initial discovery. Besides basic research to identify the lead molecule, every drug has to go through several stages of clinical trials before it can be considered safe for regular human use. The high cost of drug development arises from the enormous rate of failure. Most candidate drugs don't make it to the phase III clinical trial, which is the last stage before the drug can be released for general use. Typically only one in 5,000 compounds evaluated in the initial stages actually make it to the market.

> *...Nearly half of the world's drugs come from natural sources; of this about half come from plants traditionally used in healing. But there still remains huge untapped potential in the natural world. For example, of the estimated 0.5 to 10 million animal species only some 500 species of marine animals have been shown to contain substances that can kill cancer cells...*

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A serious problem that is coming to the fore in many countries is the overuse of antibiotic drugs, which has led to the appearance of many drug-resistant varieties of bacteria that do not respond to

even some of the most advanced antibiotics available today. According to the World Health Organization, "more than 90% of some bacteria species in Asia have developed strong immunity to frequently administered antibiotics such as penicillin and ampicillin." Yet, a recent report in *Time* says that in countries like China patients often coerce doctors to prescribe antibiotics at even the slightest symptom, thereby multiplying the opportunities for stronger strains to flourish and making infections harder to suppress. Aldridge discusses at length the problem of drug resistance and suggests simple measures to solve it.

The other topics covered in the book include antibiotics, hormonal drugs, cardiovascular drugs, painkillers, anti-cancer drugs, drugs for treating mental disorders, vitamins, minerals and herbal drugs, and gene-based medicines. Some chapters are illustrated with appropriate diagrams for better comprehension. *Magic Molecules* is a goldmine of information about the myriads of medicines we use and ought to be a must read for not only clinicians and those in medical profession but also for anyone who wants to be informed about the fascinating world of drugs.

-Biman Basu



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Biman Basu is a prominent writer of Asia, having written more than 15 books on various subjects. He has reviewed a number of books for various journals. He has been associated with Anil Aggrawal's Internet Journal of Book Reviews since its inception. He can be contacted at basu_biman@yahoo.com. More information about him can be had by clicking here.

Comments from Editor-in-Chief Dr. Anil Aggrawal and Excerpts from the book:

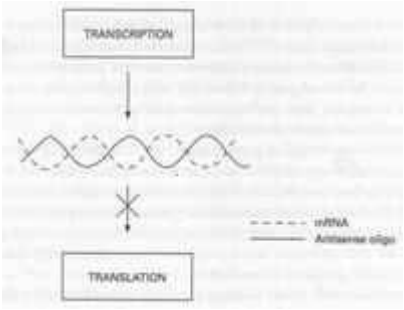
This highly informative book by Susan Aldrige deserves to be read by all and sundry. The board of editors - after much deliberations - decided to run some excerpts from this book so readers can get

some idea, how easily and effortlessly Aldridge explains even complicated concepts to the lay reader. Here on pages 252-3, she explains - with the help of a diagram - what antisense drugs are all about.

MAKING SENSE OF ANTISENSE (pages 252-3)

In 1978, Paul Zamecnik of Harvard University demonstrated that the DNA to protein machinery could be interrupted by the use of small synthetic stretches of DNA called oligonucleotides (oligos for short). He used an oligo with a sequence complementary to an mRNA molecule which Rous sarcoma virus (which causes tumours in chickens) needs to reproduce itself. This oligo bound to the mRNA and so stopped it moving on to the ribosome for translation. Such oligos are known as antisense oligos, because they have the same sequence as the antisense or template strand of the corresponding DNA (see Fig. 11.5).

Fig. 11.5. How antisense oligos work. Transcription produces a single strand of mRNA which would normally go through to translation. However, a comp¬lementary strand of antisense DNA will create a double helix, as shown, which cannot he translated, so gene expression is turned off. Note that the oligo must have the same sequence as the antisense or template strand of the original DNA; it is complementary to the mRNA which, in turn, was complementary to this strand of DNA. (Click to enlarge)



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Now Zamecnik's brilliant idea is being transformed into a range of specific DNA drugs against cancer, viral infection and Crohn's disease (an inflammatory condition of the bowel). By turning off the expression of genes active in disease, the oligos nip the disorder in the bud or stop its progress (so the theory goes). After some technical problems during the early devel¬opment stages, there are now 12 antisense drugs well on their way. In leu¬kaemia, for example, Alan Gewirtz at the University of Pennsylvania has treated 15 patients with chronic myelogenous leukaemia by removing some of their bone marrow and exposing it to an antisense oligo against a gene called c-myb. This is just one of the many genes involved in abnormal cell division (see also Chapter 7). Turning it off in these patients had a dramatic effect; once the treated bone marrow was returned to their body, their remission rates increased by 50 per cent. Better still they experienced no toxic side effects (compare that to the suffering that conventional cancer chemotherapy causes).

There are two small US biotech companies which specialized in antisense drugs - Isis and Hybridon. It seems likely that a drug created by Isis, fomivirsen, which treats the cytomegalovirus infections occurring in AIDS, will be the first drug of this type on the market; it is currently doing well in phase III clinical trials.

If there is a major problem with recombinant and antisense drugs, it is in how to deliver them to their targets. Currently, proteins cannot be taken by mouth because they will be digested in the gut before they reach the bloodstream. Even in the blood, they may be degraded by enzymes before entering cells. And as large molecules, they do not diffuse through cell membranes in the way small, conventional, drug molecules do. Instead they are taken in by a process called exocytosis, in which the membrane folds in on itself to form a small cavity which then engulfs the protein molecule, taking it into the cytoplasm. All these problems currently mean that high doses have to be given to allow therapeutic doses to reach their target - which pushes costs up. However, new developments in inhalation technol¬ogy for drug delivery (see also the discussion on drug delivery in Chapter 2) promises to make recombinant drugs a more practical and affordable option in the near future. Many of the same problems apply to oligos, which are also quite a bit larger than conventional drug molecules. These have to be delivered to the nucleus of the cell, which is where they act on mRNA. With oligos, which are synthetic - rather than recombinant - molecules, the delivery problems may be addressed by modifying the chemistry of the drug molecules.

The book is full of interesting facts such as these. We are sure our readers would enjoy the book as much as we at the journal office did.

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-Editor-in-Chief