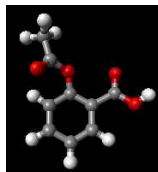


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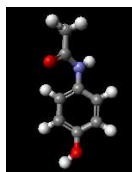
## THOUSANDS OF LOCKS AND KEYS

As we have seen in the previous sections, living entities are intricate arrangements of macromolecular order and disorder. Each protein is built from the blueprint of an organism's genetic code. Proteins convert food molecules into energy, assist in the transmission of information through the organism, and defend against invading parasitic cells. The molecular arrangements which constitute life are highly complex and highly interdependent. Governing these constituent processes is a difficult task involving extensive chemical communication. Electrical nerve impulses are triggered by the molecular mediation of small molecules known as neurotransmitters. Less pressing chemical messages are carried by fluctuations in the concentrations of hormone molecules in the blood stream controlling growth and the sudden release of energy required in the flight from an enemy, for example.

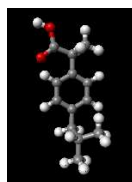


*Aspirin*

As humans have evolved they have learned that, in addition to providing food, some of the molecules made by plants and animals have important effects on the body. Alcohol, for example, known for thousands of years (an early product of the biotechnology industry), variously prized and despised for its effects on us, interacts with the normal passage of nerve impulses in the brain. We call any chemical which influences an organism a drug. Some drugs effect the mood and behavior of their recipients and others interact most strongly with invading organisms, killing bacteria, for example, and leaving the human healthy. Drug molecules interact with enzymes and receptive molecular sites within an organism to provoke or inhibit a particular response. The required response might be the destruction of a bacterium, as in the case of an antibiotic, or the inhibition of nerve transmission in the case of a sedative. Understanding the similarities between different molecules which achieve similar effects can be a profitable way of exploring new medicinal opportunities.

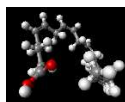


*Paracetamol*

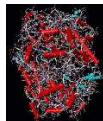


*Ibuprofen*

The structure of the aspirin molecule is shown above with the structures of ibuprofen and paracetamol. Aspirin is derived from a compound found in the bark of the willow tree and was discovered in 1899. The source of its pain killing power is now known to be its interference with the synthesis of a class of molecules, prostaglandins, which cause inflammation in a variety of tissues, leading to pain. The image above shows the three pain killing molecules aspirin, ibuprofen and paracetamol, in a spacefilling representation. We can see the structural similarities of these molecules. All three have a six membered ring structure, which tends to avoid the polar environment of water and a comparatively small appended group of atoms which are able to bond to part of their receptor molecule. The similarity in the structure of these molecules is clearly evident and from their similar pain killing actions we can deduce that they can fit into similar active sites even before the details of their active sites have actually been determined. This information can then be used to both understand the activity of related compounds and also to help design new compounds to analyze experimentally. In fact, the structure of one of the receptor sites of these three analgesic molecules has recently been determined using the techniques of protein crystallography. Prostaglandin H2 synthase-1 as this structure is known is a gigantic molecule. It contains around five thousand atoms and converts a long acid molecule, arachidonic acid, into inflammatory prostaglandin with its two distinct active centers. The crystal structure of the receptor reveals that the painkilling drugs need their common ring structure to reach the active site of the molecule from the non polar environment of the cell membrane. Once in the active site the pain killers achieve their inhibition of the formation of pain causing molecules through differing interactions with the amino acid side chains of the channel leading to the active site.

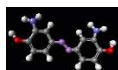


*Arachidonic acid.*

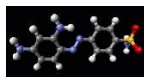


*Prostaglandin H2 synthase 1*

The early realization that synthetic chemicals could be exploited in medical applications grew out of the use of newly discovered molecular dyes in staining medical specimens. These synthetic organic dyes, which had revolutionized the textile industry, turned out to be valuable in highlighting the differing regions of a cell in microscope slide preparation. If dyes bound differently to differing biological materials perhaps, then, certain dyes and related compounds could target and destroy bacterial cells. The impetus for a search for compounds able to kill bacteria came, then, not from deep conviction in Fischer's lock and key hypothesis, but from pragmatic empirical observation. Paul Ehrlich was the first chemist to pursue successfully this line of investigation and through extensive preparative chemistry and testing produced, in 1910, the arsenic based drug Salvarsan, effective against diseases such as sleeping sickness and syphilis. Although Salvarsan was used with success in the treatment of a number of bacterial illnesses, the majority of bacterial infections were still without effective treatment. In the late 1920s the German dye company I.G. Farbenindustrie (later to become BASF, Bayer and Hoechst) employed Gerhard Domagk to investigate the possible exploitation of its dyes in medical applications. In 1932 Domagk discovered that one particular dye, Prontosil, developed to stain leather, was effective in curing mice infected with streptococcal bacteria, and importantly, did not appear to harm the animals, as many previously tested compounds had. Domagk realized the importance of his discovery when his own daughter contracted a streptococcal infection from a simple puncture wound and was close to death. Injections of Prontosil were effective in treating the disease. Domagk reported his work in 1935 and sulphur based drugs, as drugs of the Prontosil type became known, were soon widely used. One early success was the treatment of Franklin D. Roosevelt, Jr. the son of the President of the United States.

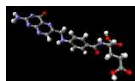


*Salvarsan*

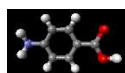


*Prontosil*

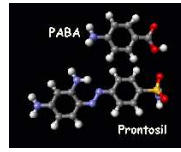
Like Ehrlich, Domagk decided to employ dye-like molecules in his search for antibacterial drugs because dyes exhibited differential staining properties, leading to their routine use in microscopy, implying that certain regions of an organism, could be targeted at the molecular level. Indeed, Domagk himself referred to the synthetic drugs that he developed as 'magic bullets', able to target selectively and kill a particular cell within a complex living organism. How do such drugs achieve their remarkable effects? The sulphonamide drugs inhibit bacterial reproduction by interfering with the synthesis of folic acid which then halts the production of the bacteria's DNA, preventing the replication of the bacteria. Bacteria unlike mammals must synthesize their folic acid molecules in situ and this is achieved by building up from para-aminobenzoic acid (PABA). Comparing the structures of Prontosil and PABA shows that a part of the drug molecule closely resembles the natural feedstock chemical, and indeed the drug works by binding permanently with the active site which might have catalyzed the production of folic acid. Thus the bacteria's synthesis of folic acid is blocked and consequently bacterial reproduction grinds to a halt. Folic acid is also vital for the human organism. However, folic acid is not synthesized by humans, instead it is a required part of our diets, it is a vitamin. Bacteria cannot synthesize folic acid when Prontosil is present, and they cannot make use of folic acid which might be present in their host environment because bacteria have not evolved a method which can transport folic acid across their cell walls. Thus the sulphur containing drug can kill the bacteria and leave the human unaffected - a precise set of chemical interactions underlying the magic of the medicinal bullet.



*Folic acid*



*PABA*



[Tasting the Shape of Molecules](#)