Molecular medicine—
Designs in drug research

What happens to the living cell when substances like hormones and drugs impinge on it? Long an area of guesswork and conjecture, answers are now coming from an NRC group capable of observing the processes at the molecular level.

For certain of modern medicine's drug-mediated treatments, it is often said that the cure is worse than the disease itself. Because the drugs are not site-specific to the malady, they can do as much damage to the healthy parts of the body as to the diseased areas. The reason for this lies in the nature of drug research, which in many cases involves studies of chemicals at the gross or whole animal level. Simply put, promising chemicals are administered to diseased test animals, which are then observed to see if their condition improves. As one clinical chemist puts it, the approach is a bit like medical roulette. The kidneys may be saved at the expense of the liver.

In recent years, however, this research area has been invaded by scientists with sophisticated techniques that enable them to dip below the surface character of disease conditions, providing them with a view of the disorders at the cellular level. One such scientist is NRC's Dr. Ian C.P. Smith, a former theoretical chemist who sees in his methods a way of getting at the molecular nature of certain diseases. This kind of detailed information may enable scientists to fashion drug structures to counteract specific molecular aberrations underlying diseases, an approach that has already been tagged "molecular medicine". During the last six years, Smith and co-workers Dr. Keith Butler and Dr. Roxanne Deslauriers have focussed their attention on the thin, bi-molecular "skin" that surrounds the living cell, and the compounds that interact with it. The proper functioning of this complex membrane is critical to the health of the cell and, ultimately, to that of the organism as a whole.

Called the plasma membrane, it maintains the basic integrity of the cell, permitting needed materials to enter and ensuring that metabolic wastes are transported out. The external surface, ribbed with protective antigen structures that act as chemical identity tags, is the face that the cell presents to the outside world.

"We are just now beginning to understand the organization of this skin," explains Dr. Smith, "particularly the way its molecular components, mostly fat-like compounds and proteins, interact with one another. Before we can appreciate what happens to it in diseased states we need to know what its healthy condition is like."

One of the molecules that has come under intensive study by the group is cholesterol. "Though the hazards of excess cholesterol are well known," continues Smith, "forming plaques in arteries, stiffening blood vessels and so on, the substance is extremely important to the proper functioning of mammalian plasma membranes. Over the years we have used special techniques to study the location and effects of cholesterol within the lipid-protein matrix of the membrane, and we now have a fairly good idea of its function."

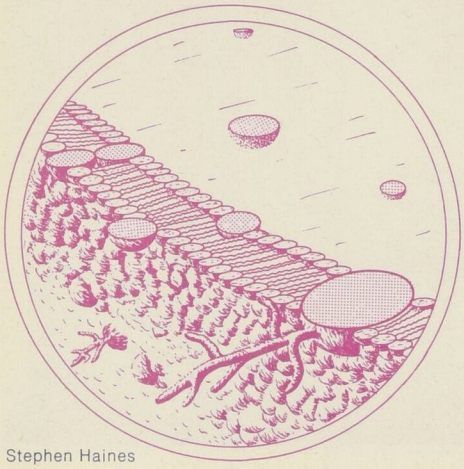
It turns out that cholesterol regulates the packing and motion of stacked, chain-like molecules (fatty acids) that make up much of the membrane's internal milieu. "In other words, it determines how 'fluid' the system will be," says Dr. Smith. "Under normal conditions, the membrane is more like a liquid than a solid, but too much cholesterol causes it to stiffen or become wax-like, thereby forming a less penetrable barrier to substances that normally pass through. As well, the protective antigens on the outer surface become less mobile, and no longer able to shield the cell against harm from the outside. Clinicians who fight cancer by mobilizing the body's immunological defences against infection are now seriously considering the effects of cholesterol levels on their treatments."

On the other hand, too little cholesterol may make the membrane too fluid, reducing its natural selectivity to molecules that pass through. The biological edict of food-in, wastes-out is thereby disregarded.

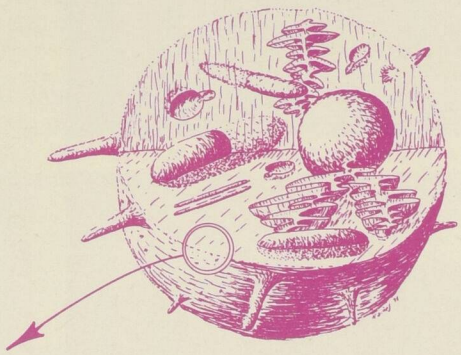
The analytical techniques used by the group go under the somewhat abstruse names of Electron Spin Resonance (ESR) and Nuclear Magnetic Resonance (NMR) spectroscopy. Although the machinery and attendant terminology are complex, basically the method involves attaching magnetic "labels" to molecules like cholesterol and inserting them into test membranes. This renders the environment surrounding the label "visible" to the machine, permitting the observers to follow membrane changes in a very detailed way, particularly important changes like fluidity.

Although the group now applies its techniques to living cells (the membranes of human leukemia cells have recently been shown to be vastly different from normal white blood cells), much of the work has been done on so-called "model membranes", man-made systems that mimic the real thing. One such study has looked at the effects of anesthetics on nerve membrane

The enlarged area shows the plasma membrane, a thin, bimolecular sheath that surrounds all living cells. Made up of a double layer of fat-like compounds and protein (the balls are proteins) this skin is critical to the healthy functioning of the cell. Not only does it regulate the substances that enter and leave, but it also serves as the site of action for chemicals like hormones, anesthetics, opiates and other drugs.



Stephen Haines



La partie agrandie montre la membrane plasmique, mince gaine bimoléculaire qui enveloppe toutes les cellules vivantes. Constituée d'une double couche de protéines et de composés semblables à des lipides (les boules sont des protéines), cette peau est indispensable au bon fonctionnement et à la santé de la cellule. Elle assure non seulement la régulation des substances qui y entrent et qui en sortent mais elle sert également de site d'action à des substances chimiques comme les hormones, les anesthésiques, les narcotiques, et d'autres substances médicamenteuses.