strated that EXAFS can determine the structure of transition metal complexes immobilized on polymer surfaces. Strictly speaking, this is not an example of the ability of EXAFS to probe catalyst surfaces because it is the complex that acts as the catalyst, not the surface. The immobilized complex consists of a transition metal atom surrounded by several organic ligands and is called a heterogenized homogeneous catalyst. In experiments with one complex, bromo tris(triphenylphosphine) rhodium, Joseph Reed, Eisenberger, and their colleagues at Bell Laboratories observed the change in the local environment of the rhodium as the amount of cross-linking in the polystyrene support was varied. At low cross-linking, the polystyrene was so flexible that nearby rhodium complexes could form dimers, but at high cross-linking, the polystyrene became more rigid and only monomer complexes formed. Dimerization had been proposed as one explanation of the lower catalytic activity of immobilized, as compared to unbound, complexes.

All of the EXAFS studies of surfaces used x-rays from the Stanford Synchrotron Radiation Project (SSRP), located at Stanford University, which uses the SPEAR electron-positron storage ring as a source of synchrotron radiation. Synchrotron radiation, which is the light emitted by charged particles orbiting in curved paths, is much more intense than ordinary x-ray sources if the particles are electrons moving with relativistic energies (up to 4 Gev in SPEAR), is almost 100 percent plane polarized, and is emitted over a continuous range of photon energies. All of these properties make synchrotron radiation a seemingly ideal x-ray source, although researchers can obtain EXAFS spectrums in the laboratory with conventional equipment, if they are willing to wait long enough. A rule of thumb has been that 1 hour at SSRP is worth 2 weeks or more in the laboratory.

One major limitation of EXAFS as applied to surfaces is that many low atomic number elements cannot now be examined directly. Lytle and his colleagues, for example, could see oxygen by studying the EXAFS spectrum of ruthenium with a nearby oxygen neighbor but could not obtain an EXAFS spectrum for oxygen. Similarly, Stern could get EXAFS spectrums from bromine but not from carbon. In many cases, especially those involving catalysts, researchers want to be able to see such typical adsorbed species as carbon monoxide, nitric oxide, and hydrocarbons, all of which involve light elements. The problem is that there exists no adequate x-ray monochromator for the energy range from about 300 ev to 2 kev in which the inner shell absorption edges of the low atomic number elements reside. This purely instrumental difficulty may soon be solved, as it is receiving attention around the world, but for now it is a limiting factor in the usefulness of EXAFS.

So far, EXAFS has been applied to only a few surface problems. Surfaces are notoriously difficult to characterize, and observers think it premature to be too optimistic this early. Right now, however, the technique is causing a lot of excitement.—ARTHUR L. ROBINSON

Drug Design: Developing New Criteria

Physicians and their patients sometimes encounter difficult decisions concerning whether or not to use certain drugs. The difficulty lies in the fact that the side effects of some medicines are as bad as or worse than the conditions the drugs are supposed to ameliorate. For example, spironolactone is used to lower blood pressure. This drug can cause impotence, lack of sexual libido, and breast growth in men. Hypertension, in contrast, is largely without symptoms, although deadly.

Drug companies often search for drugs with fewer side effects than existing ones in a random, hit-or-miss way. Now, however, a rational basis for the design of one class of drugs is available. This method of drug design provides a way to find drugs that would be expected to have minimal side effects as well as maximal effect for their designated purposes. The method is applicable to the class of drugs that mimic or block the effects of steroid hormones on cells. This includes drugs that structurally resemble steroid hormones and may also include some drugs like aspirin, whose structures do not resemble those of steroid hormones. The new design criteria for these drugs are an outgrowth of studies of how steroid hormones act on cells.

During the mid-1960's, investigators discovered that all steroid hormones seem to have a common mode of action. These hormones enter cells and bind to specific receptors in the cytoplasm. Then the hormone-receptor complex moves to the cell nucleus where it affects gene expression. Each steroid hormone has its own receptor and was at first thought to be able to bind only to that receptor. Then, a few years ago, investigators began to realize that different steroid hormones can bind to each other's receptors, although with lower affinities than they bind to their own.

If hormones can bind to each other's receptors, investigators reasoned, it is likely that drugs that mimic or that block particular steroid hormones can also bind to receptors for other hormones; and perhaps side effects might be caused in that way. Drugs that mimic steroid hormones were found to bind to hormone receptors and act on the cells the same way as the hormones do. Drugs that block the actions of steroid hormones were found to bind to the hormone receptors but to have no other effects on the cells. However, by tying up the hormone receptors, the drugs prevent naturally occurring hormones from acting on the cell.

Most of these drugs that mimic or antagonize steroid hormones are given in large doses compared to the concentrations of naturally occurring hormones found in the blood. Thus, even if these drugs have fairly low affinities for the "wrong" hormone receptors, the drugs might still be present in sufficient quantities to bind to significant numbers of the "wrong" receptors. One of the first indications that this possibility may be realized comes from studies of hormone receptors in the kidney, which were carried out by John Funder, who is now at Prince Henry's Hospital in Melbourne, Australia, David Feldman, who is now at Stanford University, and Isidore Edelman of the University of California at San Francisco. They found that glucocorticoid hormones, such as cortisol, bind to mineralocorticoid receptors in the kidney. Mineralocorticoids, such as aldosterone, cause salt and water retention and, probably, thereby increase blood pressure. Edelman and his associates also found that mineralocorticoids bind to glucocorticoid receptors.

Feldman points out that the binding of glucocorticoids to mineralocorticoid receptors may explain why some patients who are given cortisol retain salt and water. With the advent of synthetic glucocorticoids, this side effect was diminished. According to Feldman, there are two reasons that the synthetic compounds produce fewer side effects. First, the synthetic compounds, fortuitously, bind less well to mineralocorticoid receptors than the naturally occurring glucocorticoids do. In addition, the synthetic compounds bind better than the

natural ones to the glucocorticoid receptors. For this reason, lower doses of the synthetic compounds are needed and side effects are further diminished.

About 2 years ago, two groups of investigators simultaneously reported that the side effects of spironolactone could be due to its binding to the "wrong" hormone receptors. The investigators were Julio Pita, D. Lynn Loriaux, and their associates at the National Institute of Child Health and Human Development, and C. Bonne and J. P. Raynaud of the Centre de Recherches Roussel-Uclaf in France.

Spironolactone acts as a diuretic. It is prescribed for patients with hypertension and is thought to be effective because it decreases salt and water retention and thus reduces blood volume. The drug produces its diuretic effects by binding to mineralocorticoid receptors and antagonizing mineralocorticoid hormones. The two groups of investigators found, however, that spironolactone also binds to testosterone receptors of rat cells and antagonizes the effects of testosterone. They reasoned that, if the drug binds to testosterone receptors of human cells, this binding could explain the estrogenic side effects of the drug, such as breast growth and impotence. Since estrogens and testosterone have opposing effects on cells, a drug that blocks the action of testosterone may have estrogenic effects.

Raymond Menard and his associates at Rhode Island Hospital in Providence had previously found that, in rats, spironolactone blocks the action of an enzyme needed for testosterone biosynthesis. They postulated that a similar effect occurs in humans and attributed the estrogenic side effects of spironolactone to this action of the drug. But Loriaux and his associates found that people given normal therapeutic doses of spironolactone had no changes in their plasma estrogen and testosterone concentrations but did exhibit estrogenic side effects. Now, Safa Rifka, Loriaux, and their associates report that spironolactone binds to human testosterone receptors in vitro; the binding constants of the drug are such that normal doses of spironolactone could cause estrogenic effects by binding to testosterone receptors in vivo.

Loriaux points out that recognition of the fact that spironolactone binds to testosterone receptors in vitro may make it possible to develop derivatives of this drug that antagonize mineralocorticoids but do not bind to testosterone receptors. He reports that there is at least one example of two closely related drugs that differ in their abilities to bind to the "wrong" hormone receptors; namely, digitoxin and digoxin. These two drugs are used to treat congestive heart failure. Digitoxin acts like an estrogen in humans, causing breast growth in elderly men, for example. Digoxin does not seem to cause these side effects. Rifka, Loriaux, and their associates find that digitoxin binds to estrogen receptors and acts like an estrogen in rodents whereas digoxin does not. Loriaux believes that some of the differences in side effects between these two drugs may be due to this difference in binding to estrogen receptors.

Structures May Be Deceiving

Researchers have sometimes been surprised to find that certain drugs bind to receptors of steroid hormones that do not appear to resemble drugs in structure. For example, Charles Nugent and his associates at the University of Arizona were asked by Mead Johnson & Co. to test the drug melengestrol acetate, which is a progesterone-like steroid that was used to treat people with rheumatoid arthritis. Nugent and his associates found that, although this drug does not at all resemble cortisol, it acts like cortisol. For example, people given the drug decreased their production of cortisol, just as they would if they were given this hormone. Nugent says the most likely explanation of his finding is that the drug binds to glucocorticoid receptors of human cells and acts like a glucocorticoid on those cells. Others had shown previously that the drug acts like a glucocorticoid when administered to animals.

Other drugs that have surprised investigators with their ability to bind to steroid hormone receptors are some of the nonsteroidal anti-inflammatory drugs (NSAID). This class of drugs includes aspirin, phenylbutazone, and indomethacin. They are known to block the synthesis of prostaglandins, which are hormone-like substances that exert numerous effects on cells. Their anti-inflammatory properties are generally attributed to this action, but they have also been reported to have some other effects that resemble those of steroids. For example, they can cause salt and water retention, antagonize the effects of spironolactone, and sometimes improve the condition of patients with Addison's disease, a condition in which too little glucocorticoids are made. Feldman and Chaiyapon Couropmitree report that some of the NSAID's bind to mineralocorticoid receptors, and they speculate that this may explain why some NSAID are more likely than others to cause salt retention. Moreover, they believe it possible that the drugs also bind to glucocorticoid receptors. Such binding might at least contribute to their anti-inflammatory properties (since glucocorticoids prevent inflammation) and might also explain the effects of the drugs on people with Addison's disease.

Now that the binding of a diverse group of drugs to the "wrong" steroid hormone receptors has been documented, researchers believe that many more examples will be discovered. An important implication of the work is that it provides criteria that can be used in designing drugs. Drugs can be screened in vitro to see whether they bind to the "wrong" receptors and mimic or antagonize hormones. If so, derivatives of the drugs can be tested to find those that would be predicted to have minimal side effects. It should be possible to decide what aspect of a drug's structure is responsible for the desired actions and what aspect is responsible for the side effects.

Some research along these lines has already been reported from Edelman's laboratory. For example, Funder and his associates tested derivatives of the spirolactones, a group of mineralocorticoid antagonists that includes spironolactone. They determined how alterations in the drug's structure affect its ability to bind to mineralocorticoid receptors. These studies were extended by Carolyn Sakauye and Feldman, who showed that knowledge of the binding of spirolactones to mineralocorticoid receptors is not sufficient to predict their biological activities. Some of the compounds that bind the most avidly to mineralocorticoid receptors also act like weak mineralocorticoids on the cell. Others that bind less well have no mineralocorticoid actions. Loriaux and his associates are now testing spirolactone derivatives to find those that antagonize mineralocorticoids but do not bind to testosterone receptors. According to Loriaux, they have already found such a compound but have not yet shown that it is as effective in vivo as it is in vitro.

Needless to say, drug companies are extremely interested in these lines of research. Frederick Radzialowski of G. D. Searle & Co., for example, says that his company is testing receptor binding by drugs in order to find those with diminished side effects. (Searle manufactures the spirolactones.) No one claims that this sort of testing will replace animal tests; the effects of a drug depend on its absorption and metabolism at least as much as on its effects on cells in vitro. But the receptor binding techniques are now providing a way to rapidly screen drugs and to rationally decide which drugs should be most effective in animal tests.—GINA BARI KOLATA