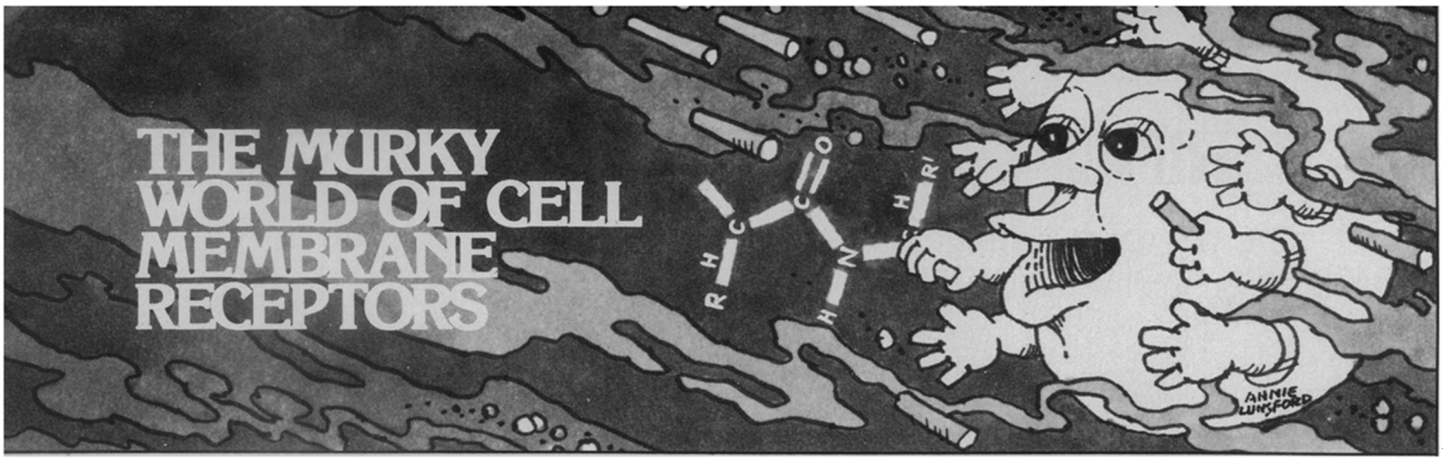


Annie Lunsford

They grab molecules that swim by. They're critical in health and disease.

BY JOAN AREHART-TREICHEL

Visualize the world of inner space—the labyrinth inside your body. Millions of hormone molecules, drug compounds, pollutants and infectious agents surge through your bloodstream at a phenomenal speed. As they zip by one cell after another, receptors on the cells' membranes attempt to intercept them. Whether the receptors manage to do so can spell the difference between health and disease.

What are these receptors? Why are they there? Do each of the 100 trillion or so cells in the human body have the same ones? How do the receptors interact with molecules and compounds? Finally, how do the receptors determine health and disease in the body? Molecular biologists can now answer these questions to some extent, as a recent international symposium on cell receptors and the medical literature reveal.

Cell membrane receptors appear to consist of protein molecules, sometimes with sugar chains attached. Progress is being made toward isolating and characterizing these receptors, according to reports at the Miles International Symposium on cell membrane receptors at the Johns Hopkins Medical Institutions. M.A. Raftery of the California Institute of Technology, for instance, has isolated and characterized the receptors for acetylcholine. Acetylcholine is one of the body's crucial chemical transmitters, passing electrical impulses between nerves and muscles. Vincent T. Marchesi of Yale University reports that the virus receptor best characterized so far is the receptor for the flu virus. It consists of 131 amino acids and 16 sugar chains.

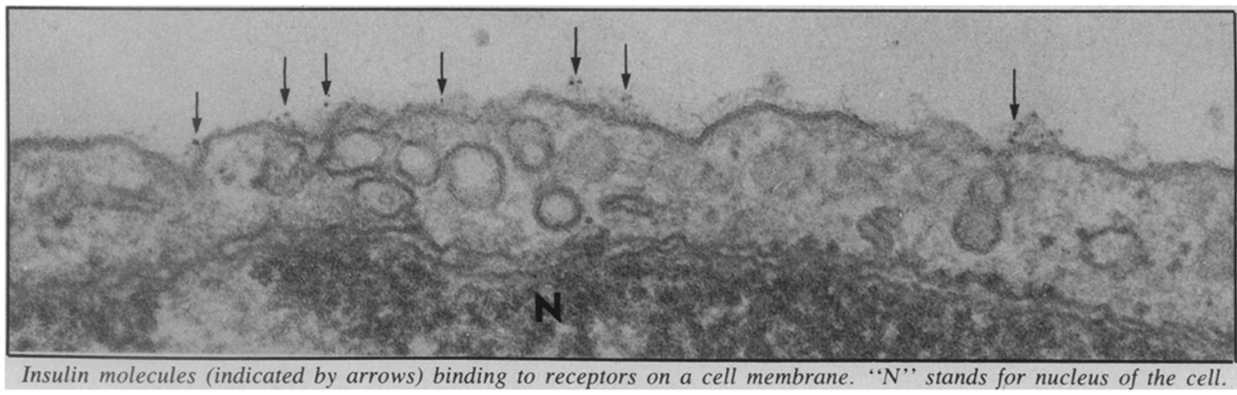
The reason that the receptors are present on cell membranes is obvious in the case of natural body molecules. If the target cells with which hormones interact didn't have receptors for the hormones, the hormones would be totally ineffective. The same situation holds for the immune system. If B and T cells (the major cells of the immune system) didn't have receptors for antigens (threatening foreign molecules), they couldn't recognize the sinister invaders and combat them. But how about receptors that allow deadly infectious agents, such as viruses, to penetrate cells? Lennart Philipson of the University of Uppsala, Sweden, replies: "It seems hard to believe that a cell would have a specific mechanism to take up a virus that could destroy it."

Purnell W. Choppin, a virologist with Rockefeller University in New York City, agrees: "Even if viruses adhere to certain receptors, it's unlikely that the receptors are there only for the viruses." In other words, the receptors probably have some other function besides "grabbing" viruses, just as purse snatchers don't devote their time solely to purse snatching.

Does each cell in the body have identical receptors? Cell receptor investigators doubt it. One of their reasons is theoretical. If a cell had receptors for all possible natural molecules and manmade compounds, its load would probably be in the millions—a stupendous burden of receptors for a chemical factory thousands of times smaller than the head of a pin. There is also scientific evidence against the notion that each cell contains an infinite number of receptors. Kenneth Melmon of the University of California at San Francisco has found that if cells are passed through a column containing the hormone epinephrine and the compound histamine, some of the cells attach to epinephrine and others attach to histamine. The reason: Some cells have epinephrine receptors, others histamine receptors.

So if cells are selective about the receptors they contain, how do they select them? Undoubtedly their genes do, and there is evidence for this, according to Richard L. Crowell of Hahnemann Medical College in Philadelphia. Robin A. Weiss of the Imperial Cancer Research Fund Laboratories in London agrees. Mendelian experiments, he says, show that genes code for receptors, and those genes may not necessarily be on the same chromosomes.

As for receptor actions, molecular biologists are learning some intriguing things about them. For one, receptors appear to be specific, and this specificity depends on whether they and passing molecules can fit together chemically like locks and keys. Each kind of hormone has its specific receptors, each kind of chemical transmitter its receptors, each kind of virus or drug its specific receptors, and so on. What's more, receptor binding is rapid and reversible, according to Robert J. Lefkowitz of Duke University, at least for



Leonard Jarett, Washington Univ. School of Medicine

Insulin molecules (indicated by arrows) binding to receptors on a cell membrane. "N" stands for nucleus of the cell.

the class of chemical receptors known as the catecholamines.

Once a receptor "mugs" a passing molecule, however, its subsequent actions become more devious. In the case of most protein hormones, say glucagon, the receptors may pass a message in the hormone to the membrane enzyme adenyl cyclase. This enzyme then activates the intercellular messenger cyclic AMP. According to Martin Rodbell of the National Institute of Arthritis, Metabolism and Digestive Diseases, whether adenyl cyclase is part of the receptor or not is still not known. And after receptors intercept viruses, they may also turn "rapist" as well by stripping the protein coats off viruses until all that remains of them are naked cores of genetic material. The cores (virions) might then be able to slip unobtrusively into a cell and infect it.

Although the role of receptors in health and disease has scarcely been tapped, enough evidence is emerging to suggest that it is a crucial one. For instance, C. Ronald Kahn, an endocrinologist at the National Institute of Arthritis, Metabolism and Digestive Diseases, has found that insulin binds to the membranes of target cells only half as well in fat persons as in nonobese persons, leading to high levels of sugar in the bloodstream. This decreased binding is due to a deficiency in insulin receptors on the target cells (SN: 10/19/74, p. 248). And as Kahn points out, "The problem seems to be a decrease in receptor number, not in receptor function. The receptors are perfectly normal but there are too few of them."

Does the decreased numbers of receptors actually cause obesity? Jesse Roth, also of the NIAMDD, believes not. "If obese patients are put on a diet," he says, "their insulin levels go down, and their receptor number returns. So it looks as if the receptor defects are a result, not a cause, of obesity."

A related condition that actually appears to be caused by receptor defects, Kahn points out, is a rare kind of diabetes that leads to extremely high levels of insulin and sugar in the bloodstream, but not a gain in body weight. Patients with this disease do not have a defect in the number of receptors for insulin, but insulin cannot get at the receptors to hook up to them. The reason insulin molecules cannot "cozy up" to receptors, it appears, is that antibodies usurp their place on the receptors. So the condition may be an autoimmune phenomenon. And then there is another disease, Roth says, that appears to derive from a hormone receptor being blocked by antibodies. It's Grave's disease, a condition characterized by overproduction of thyroid hormones, overactivity, nervousness and weakness. Patients with the disease have antibodies that compete for the receptors on thyroid cells which usually intercept thyroid-stimulating hormone. In this case the antibodies stimulate the cells, releasing an overproduction of thyroid hormones.

As for receptors actually abetting disease, Weiss points out that some chicken cells are able to resist a cancer virus because they lack certain cell receptors. This finding implies that if the receptors are present, they help the cancer virus get into the cell. Such a traitorous agreement also appears to exist between cell receptors and bacteria. D. Michael Gill, a Harvard University biologist, has found that the cholera toxin links to receptors on a susceptible cell, then manages to pass messages to cyclic AMP inside the cell (SN: 7/26/75, p. 58).

So, from the body's vantage, are receptors good or bad? Obviously, they're good when they let helpful, natural body molecules fulfill their functions, and when they help immune cells fight off threatening infectious agents. And they're harmful when they assist infectious agents in getting into cells. Crowell sums up the situation nicely: "We need to learn much more about how receptors function."

Meanwhile, most fascinating about receptors are their hara-kari acts. After they zero in on passing molecules and compounds for a while, they consume themselves, or at least disappear. And the only way they can be regenerated is for protein to be added to cells. Says Lefkowitz: "We are currently studying the effects of protein synthesis inhibition on the receptors." □