ature for 18 hours to improve their superconducting properties. Fairbank and LaRue noticed that the five spheres that had been annealed on a niobium substrate had no fractional charges, but three that had been annealed on a tungsten substrate had charges of $+\frac{1}{3}$, 0, and $-\frac{1}{3}$. Fairbank estimates that during the annealing process, a niobium sphere could pick up about 10^{12} atoms of tungsten, which would migrate onto its surface. The implication is that if quarks have been found, they reside in the tungsten rather than the niobium. Each ball contains about 10^{17} atoms of niobium.

The tungsten connection is one aspect of the experiment that many physicists find implausible. Even if the quarks were attributed to niobium, the discovery of two in eight spheres gives an incidence of quarks many orders of magnitude greater than limits set by previous quark search experiments. If the quarks are attributed to the smaller number of tungsten atoms, then the measurement implies that there are 10^{11} quarks in every gram of tungsten. Could so many quarks go unnoticed? One point raised by critics is whether a tungsten atom with a quark would behave chemically like ordinary tungsten. Fairbanks points out, however, that most of the searches that put stringent limits on the existence of quarks were made in media that were lighter than tungsten (mass 184). There is also an argument in the literature of theoretical astrophysics that if quarks are trapped in nuclei, they are more likely to be in heavier nuclei.

The second implausibility that physicists find in the Stanford result is the fact that the negative fractional charge disappeared. Quarks would be bound so tightly in niobium that they could not be removed by chemical changes, according to the general opinion. If a quark was lost, it could only have occurred by dislodging a small speck of the ball that happened to contain the quark. The odds against dislodging the right speck of material would be extremely small unless the quark was on the surface of the sphere. Fairbank says this is one of the considerations that led them to wonder if the fractional charges might not have been transferred to the surface of the balls from the substrates used for annealing. In any event, the news that the "quark" could be lost so easily (the balls were delicately transferred in and out of the apparatus using a fine brush dipped in alcohol) caused a number of physicists who had been favorably disposed at first to be more skeptical.

Other experimenters have gotten data that appear to measure fractional charges with a high level of statistical significance, but have demurred from claiming a discovery until background effects were better understood. Klaus Ziock, at the University of Virginia in Charlottesville, found pseudo-evidence of quarks but could not eliminate background effects. He published the data, but did not claim evidence for quarks. The problem of systematic background effects is "the whole story" in this sort of experiment, says Ziock.

The most troublesome background problems are electric field nonuniformities that can be caused by crystalline inhomogeneities in the capacitor plates (the "patch" effect) and effects that would produce a dipole charge distribution on the ball (an uneven distribution of positive charges with respect to negative charges). Learning to reduce these effects is what takes years of work in such experiments, and "we think we understand all the electric and magnetic background forces," says Fairbank. "We are obviously cautious," he says, "but we wouldn't publish if we had not carefully considered all the alternatives."

Fairbank's reputation may account for the unusual degree of credence the experiments have been afforded. (Few physicists gave the monopole and superheavy element experiments better than a few percent chance of verification.) As the discoverer of the first quantization of magnetic flux and the mapper of many of the basic properties of liquid helium (^{3}He and ^{4}He), he is a highly respected experimentalist. Characterized as a "terribly clever guy" by his colleagues in the physics community, he is not known as one who by nature is conservative about publishing novel results.

If the Stanford announcement is correct, then many unsuccessful searches that have been made for quarks in myriad places—seawater, manganese nodules, and moondust—were misdirected. "I would be very pleased if quarks were discovered by Fairbank," says John P. Schiffer of Argonne National Laboratory, one of the unsuccessful quark searchers. But, says Schiffer, "I think he has a long way to go."—WILLIAM D. METZ

Hormone Receptors: How Are They Regulated?

Many obese people have high concentrations of insulin in their blood but have normal concentrations of blood sugar, even though insulin should decrease blood sugar concentrations. Pregnant women produce a great deal of angiotensin II, which increases blood pressure, but they usually do not have hypertension. Some men have tumors that secrete enormous quantities of a hormone that stimulates testosterone production, yet they do not make abnormal amounts of testosterone. These are examples of a well-recognized process whereby certain hormones seem to lose their effectiveness after a period of time.

As of a few years ago, no explanation of this phenomenon was known. Recent research, however, shows that this lack of responsiveness is due not to faulty hormones but to changes in the target cells. All of these hormones must bind to specific receptors on the surfaces of cells before the cells respond to them. It now seems likely that many cells react to persistently high concentrations of certain hormones by changing their surface receptors so they bind fewer of those hormones. Although investigators speak of "lost" receptors, these receptors may be inactivated or may disappear from the cell surface.

Now that this effect has been documented, growing numbers of investigators are beginning to look for and find it in their studies of hormones. They are beginning to realize that hormones need not cause a loss or inactivation of their own receptors only; they may also affect receptors for other hormones.

These changes in the receptivity of cells to hormones are likely to be important control mechanisms. For example, they may prevent cells from overreacting to high hormone concentrations. They may also provide a way for hormones that act in sequence to amplify or diminish cellular responses to their successors. Investigators believe that an understanding of how hormones affect their own and other receptors may lead to new ways to treat certain diseases, such as insulin-resistant diabetes.

A few years ago, Jesse Roth, Ronald Kahn, and their associates at the National Institute of Arthritis, Metabolism, and Digestive Diseases discovered that cells of obese diabetics and other insulin-resistant patients, as well as obese people who have normal blood glucose concen-

trations, have abnormally few insulin receptors. They found that this apparent absence of receptors also occurs in genetically obese rats and in rats made obese when they are fed gold thioglucose, which destroys brain cells that control eating (*Science*, 16 July 1976, p. 220).

This discovery led several groups of researchers to ask, Are there few receptors because there is a high concentration of insulin or, conversely, is there a high concentration of insulin because there are few receptors? Roth and his associates and Jerrold Olefsky of Stanford University and his associates believe that excess insulin decreases the number of functional receptors.

Roth and his colleagues can demonstrate in vitro that excess insulin reduces insulin binding. They grow white blood cells in culture without insulin. These cells then bind normal amounts of insulin. When insulin is added, their insulin binding decreases. Olefsky and Roth both find that when obese people diet, and thereby decrease their blood insulin concentrations, their cells are able to bind increased amounts of insulin. Because this occurs while the people are still quite overweight, the investigators attribute the increase in available receptors to the persistent decrease in insulin concentrations caused by the diets. Olefsky and Roth obtained similar results when they studied obese rats. In addition, Olefsky finds that increases in insulin concentrations can cause normal volunteers to lose insulin receptors. These volunteers increased their insulin concentrations by eating carbohydrates every 2 hours. Olefsky reports similar results in rats when he gives them increasing amounts of insulin.

Since the demonstration of the insulin effects, many investigators have showed that a wide variety of receptors are regulated by hormones. Some, like those of insulin, seem to be regulated only by their respective hormones. But other receptors seem to be regulated not only by their respective hormones but also by others.

The receptors of thyrotropin-releasing hormone (TRH) are regulated not only by TRH but also by other hormones. The TRH is secreted by the hypothalamus and acts on the pituitary gland. As its name suggests, TRH causes the pituitary to synthesize and release thyrotropin, which, in turn, causes the thyroid to secrete thyroid hormones.

Investigators have noted that when concentrations of thyroid hormones are high less thyrotropin is made. It was thought possible that the thyroid hormones affect the hypothalamus by preventing the synthesis or release of TRH. Alternatively, they could affect the pituitary by preventing the synthesis or release of thyrotropin. Recent results reported by Mark Perrone and Patricia Hinkle of the University of Rochester School of Medicine and Dentistry indicate that the thyroid hormones affect the pituitary cells at least in part by causing a loss of TRH receptors and a decreased biological response to TRH. These investigators studied the process in rat pituitary tumor cells, which can be grown in vitro and which respond to TRH and thyroid hormones. (These results do not rule out the possibility that TRH also affects the hypothalamus.)

Arman Tashjian and his associates at the Harvard School of Dental Medicine and Harvard Medical School find that still other hormones—the glucocorticoids—affect TRH receptors on the rat pituitary tumor cells. But unlike the thyroid hormones, the glucocorticoids increase the amount of TRH that binds to these cells. Moreover, the effects of TRH and glucocorticoids cancel each other, so that if the cells are exposed to both hormones simultaneously, they neither lose nor gain TRH receptors.

In addition to TRH receptors, receptors for gonadotropins, pituitary hormones that act on the gonads, seem to be regulated by other hormones as well as by gonadotropin. During ovulation, ovary cells respond to a variety of hormones, such as estrogen and various gonadotropins. JoAnne Richards, A. Rees Midgley, and their associates at the University of Michigan find that this hormonal response is controlled in part by changes in the numbers of receptors for specific hormones on ovarian cells. For example, when two gonadotropins such as follicle stimulating hormone and luteinizing hormone are secreted and act on the ovaries in sequence, the first hormone paves the way for its successor by increasing the number of receptors for the second hormone.

Still a third type of hormone whose receptors are regulated by other hormones is the catecholamines, which are neurohormones such as epinephrine. Robert Lefkowitz and Lewis Williams of Duke University Medical Center report that when rats are given excess thyroid hormones, the number of catecholamine receptors on their heart cells increases two- to threefold. Lefkowitz points out that this finding seems to explain the well-known clinical effects of hyperthyroidism as well as provide a rationale for the standard treatment of patients with this disorder.

Patients who produce too much of the thyroid hormones have rapidly beating hearts and palpitations. These are symptoms that would be expected if the patients produced excessive amounts of catecholamines, since these hormones increase the heart rate. Moreover, the symptoms of hyperthyroidism can be relieved when patients are given propranolol, which binds to and blocks catecholamine receptors on heart cells. But hyperthyroid patients were found to produce normal amounts of catecholamines. The results of Lefkowitz and Williams suggest that thyroid hormones increase the heart rate when they increase the number of catecholamine receptors on heart cells. This increase in receptors makes the heart more responsive to catecholamines.

Most hormones studied seem to produce the same effect on their receptors in all cells sensitive to them. Insulin, for example, causes a loss or inactivation of its receptors in liver cells, fat cells, and white blood cells. But at least one hormone—angiotensin II—seems to affect receptors on different cells in different ways. Kevin Catt and his associates at the National Institute of Child Health and Human Development find that angiotensin increases the number of its receptors in cells of the adrenal cortex and decreases the number of its receptors in smooth muscle cells. This finding, they believe, may explain some seemingly perplexing effects of angiotensin on blood pressure.

Control of Blood Pressure

Smooth muscle cells, such as those of small arteries, respond to angiotensin by contracting and thereby causing an increase in blood pressure. Adrenal cells respond by producing the hormone aldosterone, which causes an increase in blood volume and thus contributes to an increase in blood pressure. In some circumstances, such as sodium deprivation or pregnancy, people make a great deal of angiotensin and aldosterone but rarely have high blood pressure. According to Catt, these effects may be due in part to a decrease in the number of the receptors for angiotensin on smooth muscle cells (which decreases their tendency to contract in response to this hormone) and an increase in the number of these receptors on adrenal cells.

To truly understand the effects of hormones on their receptors, rather than just document them, investigators would like to know how hormones affect their receptors, what happens to lost receptors, and how the receptors return when hor-

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mone concentrations drop. It is of some clinical significance to understand this process, since an understanding may lead to the development of drugs to prevent the loss of receptors and thereby control disorders involving diminished responses to hormones.

At first glance, the different hormones appear to affect their receptors through similar mechanisms. All must bind to their receptors in order to regulate them, but binding alone is not sufficient. For example, analogs of these hormones that cause the cells to respond also cause receptors to be lost in proportion to their capacity to provoke cellular responses. Apparently, some action of the hormone-receptor complex on the cells controls the loss of receptors.

Several possible mechanisms of receptor loss have been proposed. The receptors could be degraded, or they could change their conformation so they no longer bind hormones, or they could sink into the cell membrane to reappear later. It now seems likely that different hormone receptors are lost in different ways. Investigators have evidence that receptors for some hormones may change their conformations so they no longer bind added hormones and that receptors for others may be degraded.

More is known about the events that take place inside cells after catecholamines or prostaglandins (hormone-like substances that affect all tissues and organs) bind to cells than about events that take place after other hormones bind. Investigators have used their knowledge of these events to discover that receptors for these hormones may undergo conformational changes that inactivate them and to understand what step in the responses of cells to catecholamines and prostaglandins is associated with the conformational changes.

When catecholamines or prostaglandins bind to their receptors, an enzyme that resides in the cell membrane is activated. This enzyme, an adenylate cyclase, catalyzes the synthesis of cyclic AMP, which then serves as a cellular regulatory agent. Two lines of evidence now indicate that the activation of this enzyme by the hormone-receptor complex may be all that is necessary for the hormones to inactivate their receptors.

One indication that the activation of an adenylate cyclase is linked to the inactivation of these receptors comes from work with mutant cells. Paul Insel, Kenneth Melmon, and their associates at the University of California at San Francisco used mutants of a mouse cell line that are blocked at various stages in their response to catecholamines. For example, in one mutant, the adenylate cyclase is not activated when the hormones bind. In another, the adenylate cyclase is activated, but the next step in the response to cyclic AMP is blocked. These investigators used these mutant cells to show that cells exposed to catecholamines must activate an adenylate cyclase before hormone binding decreases and that no further steps in the utilization of cyclic AMP are necessary.

The results of Insel, Melmon, and their associates are supported by results of Chhabirani Mukherjee and Lefkowitz, who found that membranes isolated from frog erythrocytes inactivate their catecholamine receptors in response to catecholamines. Similarly, isolated membranes inactivate prostaglandin receptors in response to prostaglandins. These membranes contain the hormone receptors and the adenylate cyclases but no other components involved in the cell's responses to catecholamines or prostaglandins.

From their studies with isolated membranes, Lefkowitz and Mukherjee have evidence that the inactive receptors are unable to bind added hormones because they have not yet released the hormones that they originally bound. It appears likely that the interaction of the hormone-receptor complex with the adenylate cyclase alters the conformation of the receptor so that it only slowly releases the hormone. Once the catecholamines or prostaglandins are released from the inactive receptors, the receptors return to their active form. Lefkowitz believes that this explanation of how isolated membranes lose their responsiveness to these hormones may also apply to whole cells, but that receptors in whole cells are likely to be changed in other ways also. For example, the receptors may undergo a conformational change when they interact with the cyclase and then may be degraded by the cells. Another possibility is that the initial conformational change is followed by an additional chemical or conformational alteration of the receptors.

Tashjian and his associates believe that calcitonin, which is chemically unrelated to catecholamines and prostaglandins, may cause its receptor to be inactivated in a similar way. Working with newborn mouse bones grown in vitro, they found that salmon calcitonin decreases calcitonin binding by the bones. The hormone is radioactively labeled, so Tashjian and his colleagues can ascertain that it remains bound to the bone when receptors for calcitonin are lost. Whether mouse calcitonin (which is not yet available for research) causes a loss of hormone binding in the same way is not known. These investigators find that, as human calcitonin, which also decreases the number of binding sites in bone, does not bind as tightly to the cells as salmon calcitonin, it may cause this effect by a different mechanism, such as degradation of receptors.

Are Receptors Degraded?

It is becoming popular now to speculate that many hormone receptors are degraded when cells lose their ability to bind the hormones, but only one group of investigators has direct evidence for this hypothesis. Gordon Niswender, J. H. Abel, and their associates at Colorado State University have autoradiographs showing gonadotropins bound to receptors on the inside of ovary cells. These hormone-receptor complexes are in the lysosomes of cells, which is where degradation takes place. These results are causing a stir among other investigators because they fly in the face of current dogma about the action of gonadotropins and other polypeptide hormones. Most researchers previously believed that such hormones never entered cells.

Evidence that receptors for other hormones are degraded is much less concrete. It relies on reports that the loss of some hormone receptors takes place when protein synthesis is blocked but that the receptors do not return when the hormone concentrations are decreased unless protein synthesis is permitted. The presumption is that the hormones cause the receptors to be degraded, and so no receptors can return to the cell surface unless they are synthesized anew. Maxine Lesniak and Roth, for example, found that growth hormone receptors do not return without protein synthesis. Consistent with this reasoning that a dependence on protein synthesis indicates that receptors are degraded is the observation, by Lefkowitz and his associates, that protein synthesis is not required for either the loss or return of catecholamine receptors, which are presumably not degraded.

The current deluge of results indicating that hormones regulate their own and other receptors is, in the opinion of many investigators, an indication of the importance and generality of these observations. Researchers believe that further studies of the effects of hormones on their receptors will lead to a new understanding of how hormone actions are controlled and new treatments for many clinical disorders.—GINA BARI KOLATA