ing Upjohn, are interested in identifying such inhibitors.

A final intriguing finding suggests that the leukotrienes may have a role in the nervous system. Murphy and Barry Hoffer, who is also in Denver, find that very low concentrations of LTB_4, LTC_4, and LTD_4 cause prolonged excitation of some brain neurons. Murphy says, "They increased almost irreversibly the firing rate of Purkinje cells and cells in the basal ganglia. . . . We were surprised that they were that active."

Murphy and Hoffer do not yet know what, if anything, this means; the leukotrienes have not yet been detected in brain. But they note that the agents stimulate contraction of guinea pig ileum (intestinal smooth muscle), a point of resemblance between them and many known or suspected neurotransmitters, including acetylcholine and the endogenous brain opiates. They suggest that the leukotrienes may serve as long-term regulators of nerve excitability during allergic reactions and possibly under normal conditions. More work will be needed to test this idea, but with pure preparations of leukotrienes now available, this and the other lines of research should progress far more rapidly than did SRS research during the first 40 years of its history.—JEAN L. MARX

New Theory of Hormones Proposed

Hormones appear to be far more universal than anyone imagined, occurring in flies, worms, and even bacteria

A group of endocrinologists at the National Institutes of Health (NIH) have proposed a substantially new theory of what hormones are and how they work. The theory, as it is currently formulated, explains a number of biological mysteries, ranging from the question of why many cancer patients act as though their cancers are overproducing hormones even though no excess hormones can be detected in their bodies to the question of why some plants make substances that bind more specifically to animal hormone receptors than do animal hormones.

When the NIH group first began to work out the implications of their data on hormones they had to overcome considerable resistance within themselves. "As endocrinologists," explains Jesse Roth of NIH, "we were shackled by outmoded concepts, many of them deriving from experiments done more than 50 years ago. There is a philosophical problem. We have a general concept of how we understand hormones but a lot of the original data are buried in the literature. Only the conclusions remain fresh in our minds."

The tradition in endocrinology had been to think that only highly specialized glands make hormones. Then, about 10 years ago, evidence began accumulating that cancer cells, and even nerve cells, can make hormone molecules. But, says Roth, endocrinologists, rather than questioning their entire dogma, modified it so these findings fit in. They tended to believe that hormones are made only by glands, cancers, and nerves, and did not ask whether hormone synthesis might be far more widespread.

Roth, with Jana Harran Kova and other NIH colleagues, in the meantime, was looking for insulin receptors in the brain. "We're basically insulin receptorologists," he remarks. "We found insulin receptors all over the brain and they were absolutely the classical insulin receptors. We were struck by several things. First, the receptors were present in lots of areas of the brain and they had different distributions in different areas. Second, the receptor levels didn't change under conditions of hyper- and hypoinsulinemia. [In the rest of the body, more receptors show up when there is too little insulin around and fewer appear when there is too much insulin.] Third, insulin has little access to the brain. If you inject an animal with insulin, little of it gets to the brain." These observations led Roth to believe that the brain might be making insulin and that it might be using the hormone in very different ways than the rest of the body.

After looking for, and finding, insulin in the brain, Roth and his colleagues decided to see where else in the body it might be. Roth, with James Rosenzweig and other colleagues, found insulin in the testes and liver.

"When we found insulin in these other cell types, we began to think that perhaps other cells besides those of the pancreas and the brain can make insulin. We began to break the monopoly of the gland," says Maxine A. Lesniak, one of Roth's associates. A few years ago, William Odell of the University of Utah had come to similar conclusions in his work with another hormone, human chorionic gonadotropin. Says Roth, "We asked how far back in evolution does the ability to make hormones go? And we decided to try to reach bottom. We got flies, worms, and unicellular organisms and looked for insulin production."

"We started with flies and worms and we looked at the heads and bodies of the flies and the internal organs and skins of the worms," says Derek LeRoith, a member of Roth's research team. "We found material similar to insulin. Then we jumped to protozoa and once again we found material that looked like insulin. We tried fungi and *Escherichia coli* and came up with the same result."

LeRoith, Roth, and their associates characterized the material from fruit flies, earthworms, protozoa, and *E. coli* by determining that it reacted with insulin antibodies, it was the same size as insulin, it promoted glucose oxidation in isolated fat cells (this is a standard insulin assay), and its action on fat cells was abolished if it was first allowed to react with insulin antibody. In short, the material appeared to be insulin or more like insulin than any known substance.

Next, LeRoith and Roth in collaboration with colleagues in Bethesda, New York, Cincinnati, Dallas, Los Angeles, and La Jolla began looking for other peptide hormones in primitive organisms and found evidence that a long list of hormones, including ACTH, β-endorphin, somatostatin, cholecystokinin, calcitonin, glucagon, and arginine vasotocin, may be there.

Working with Dorothy Krieger of Mt. Sinai School of Medicine and Candace Pert of NIH, Roth and his associates characterized β-endorphin and ACTH in protozoa. The evidence for endorphin is its size, its reactivity with anti-endorphin antibodies and opioid receptors, and its physical-chemical characteristics in high-performance liquid chromatography. The evidence for ACTH is its size, immunoreactivity, and biological activity.

In addition, Krieger found some high

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molecular weight material in protozoa that is very similar to a large molecule in mammals that serves as a precursor for ACTH and β-endorphin. This large molecule in the protozoa reacts with both the ACTH and the endorphin antibodies.

What does it mean if hormones are so widely present, made even by unicellular organisms? Roth proposes that hormones are an evolutionarily ancient form of cell-to-cell communication. He notes that, in at least two instances, other investigators have found evidence that unicellular organisms may respond to hormones in the same way as animals do—through specific receptors.

In 1972, Z. Rosenweig and S. H. Kindler of Tel Aviv University reported that the hormone epinephrine activates the enzyme adenylate cyclase in protozoa and that this effect is eliminated by propranolol, which specifically blocks epinephrine receptors. In 1979, J. O. Josefsson and P. Johansson of the University of Lund reported that opioid peptide and plant alkaloids that mimic these hormone-like peptides alter the feeding behavior of amoebas. Naloxone, which blocks one class of opioid peptide receptors, eliminates this effect.

Roth suggests that cell hormones and neurotransmitters began as what cell biologists call tissue factors—substances that stimulate cells to grow or come together or otherwise react biochemically. Only when animals evolved to have extreme cell differentiation and cellular organization did glands evolve to overproduce these hormones so the animals could use them in more clever and sophisticated ways. This theory explains why it is that many mammalian hormones are also tissue factors. For example, insulin and glucagon, in addition to their roles as hormones, act locally as tissue factors on cells within the pancreas.

"We would also argue that exocrine and endocrine functions overlap," says Roth. "At the level of unicellular organisms, there is no difference between exocrine and endocrine functions." The distinction between exocrine and endocrine functions occurred late in evolution, he proposes. This hypothesis explains the finding that many classical messenger molecules, such as prostaglandins, nerve growth factor, and the hormones luteinizing hormone releasing hormone, gastrin, and prolactin are found in exocrine fluids such as saliva, intestinal secretions, milk, and semen.

The NIH group postulates further that cells contain a number of genes for each hormone and that which gene is expressed by a given cell type is arbitrary. For example, he and his colleagues find that guinea pigs produce two different insulins. The normal guinea pig insulin is made in the animal's pancreas. But in the brain and other organs, guinea pigs make a distinctly different insulin like the one made by rats and pigs. Other researchers have found that the rat expresses two insulin genes and that the anglerfish expresses two different glucagon genes.

> "We're at the stage now where the theory can encompass everything."

If there are indeed many closely related genes for each hormone, only one of which is ordinarily expressed in a particular cell, some perplexing behaviors of cancers may be explainable. Cancer cells frequently secrete hormones that can sometimes cause severe metabolic disturbances. For example, lung cancers often make vasopressin, which causes water retention to such an extent that patients can suffer convulsions or go into comas. Other lung cancers seem to be secreting something that causes water retention but no known hormones are apparent.

In these cases, says Roth, the tumor may be making a water retention hormone that is just different enough from vasopressin to be missed by radioimmunoassays for these hormones. For example, they may make arginine vasotocin, which is the water-retention hormone of birds, fish, and lower animals.

Similar situations occur with other hormones. Insulin can be made by tumors of the pancreatic islets. A number of other cancers, including liver and adrenal gland cancers, make insulin-like growth factors, substances that act like insulin but are not detected by the radioimmunoassay for insulin. But, says Roth, "In one-half to two-thirds of the non-islet cell tumors, we don't know what the devil they're making. People have not looked for hormones not usually present in humans. Maybe we should look more widely for hormones like guinea pig–type insulin in these patients."

Since Roth believes that hormones appeared in evolution before plants and animals diverged, it follows that plants and animals should make similar hormones. There are substances similar to neuropeptide hormones in plants, Roth points out. But there also are plant alkaloids, which do not have molecular structures at all like those of hormones, but which bind extremely well to animal hormone receptors. Some of these alkaloids, in fact, have a greater specificity for animal hormone receptors than the hormones themselves do. For example, pharmacologists distinguish between two kinds of receptors for the neurotransmitter acetylcholine—muscarinic receptors and nicotinic receptors. They make this distinction by seeing whether the plant alkaloid muscarine or nicotine binds to the animal receptors; acetylcholine binds equally well to both receptor types.

Plant alkaloids, when they bind to animal hormone receptors, can cause specific physiological effects. The alkaloid glycyrrhetinic acid in licorice can cause high blood pressure by mimicking the hormone aldosterone. Men can get enlarged breasts from smoking marihuana because the alkaloid tetrahydrocannabinol binds to estrogen receptors.

"People always said these specificities were accidental. We would argue that the specificities developed because plants had hormones and receptors like animal hormones and receptors. Then, as the plants evolved, they got fancier and made alkaloids that don't look like peptide hormones but that fit into the hormone receptors," Roth remarks. He suggests that some plants learned to markedly overproduce these alkaloids and to use them as insecticides. The alkaloids kill insects by blocking insect hormone receptors. "This isn't all chance," Roth says.

A number of researchers who are familiar with Roth's theories are enthusiastic. "Jesse can be incredibly compelling. I think his hypothesis is fantastically interesting," says Krieger. "Conceptually, I'm delighted with the hypothesis," says Wilbur Sawyer of Columbia University's College of Physicians and Surgeons. "It's a wonderful idea. It's very persuasive," says Lydia Villa-Komaroff of the University of Massachusetts Medical School.

As for Roth, he is enthusiastic but is well aware of how speculative some of his ideas are. "Clearly, the theory is at an early stage of organization so a lot of things will fit. We're at the stage now where the theory can encompass everything. Later, it will be more refined and more restrictive," he says.

—GINA KOLATA