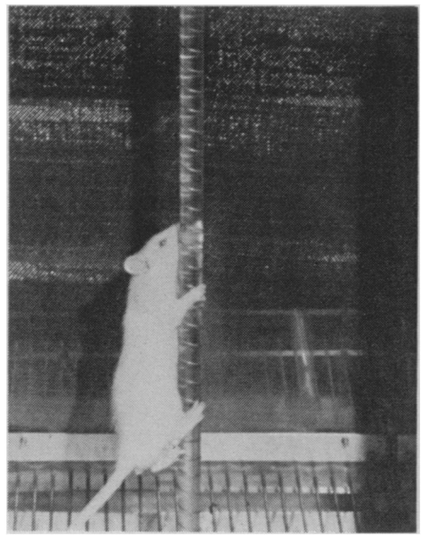
The role of hormones in learning, memory and behavior

The first chemical involved in learning and memory was isolated from brain extracts in 1970. Now the origin of some learning and memory chemicals has been traced to the brain's pituitary gland



DeWied

Hormone shots quicken rat's climb.

by Joan Arehart-Treichel

This is the third in a series of articles deriving from the author's recent reporting tour of European medical laboratories.

Most endocrinologists concern themselves with the isolation, sequencing and synthesis of hormones, and with their clinical application. A handful of scientists, however, are moving in another direction. They are trying to show that the pituitary hormones are not just necessary for the body's many physiological processes, but are intimately involved in learning and memory, and therefore in behavior. Such possibilities are intriguing. The pituitary gland is only about the size of a quarter, tucked away at the base of the brain.

David DeWied, director of the Rudolf Magnus Institute for Pharmacology in Utrecht, Holland—a leading pharmacology research center in Western Europe—has evidence for the pituitary gland's role in learning and behavior. It is that not only melanocyte-stimulating hormone (MSH) can influence behavior in rats—Abba Kastin of the Veterans Administration Hospital in New Orleans also found such evidence recently (SN: 1/29/72, p. 78)—but also that adrenocorticotrophic hormone (ACTH) and vasopressin can influence behavior too. The peptides from all three pituitary hormones that influence behavior appear to be separate from the chemical parts of those hormones that control straight physiological processes. In fact, DeWied has found other pituitary peptides that influence learning, memory and behavior. Some are related more to ACTH and MSH, others more to vasopressin.

The Utrecht pharmacologist does not care to speculate on whether any of these pituitary peptides might turn out to be the first known memory chemical, scotophobin, which was isolated and sequenced from crude brain extracts a year-and-a-half ago (SN: 11/6/71, p. 308). But scientists at his institute are now examining synthetic scotophobin and making comparisons.

The story DeWied tells SCIENCE NEWS from his European center is provocative, and with more immediate clinical applications than most people would suspect. Work DeWied has carried out over the past decade, with the assistance of fellow scientists in the United States and Europe, has led him to his present confirmations.

Back in 1957, there were some scientific indications that removal of the pituitary gland from rats prevented their learning how to respond to stimuli, such as a light, buzzer or mild shock, by scurrying through a shuttlebox, leaping up a pole and so forth. There were also suggestions that injections of ACTH restored the rats' ability to learn or to make conditioned responses.

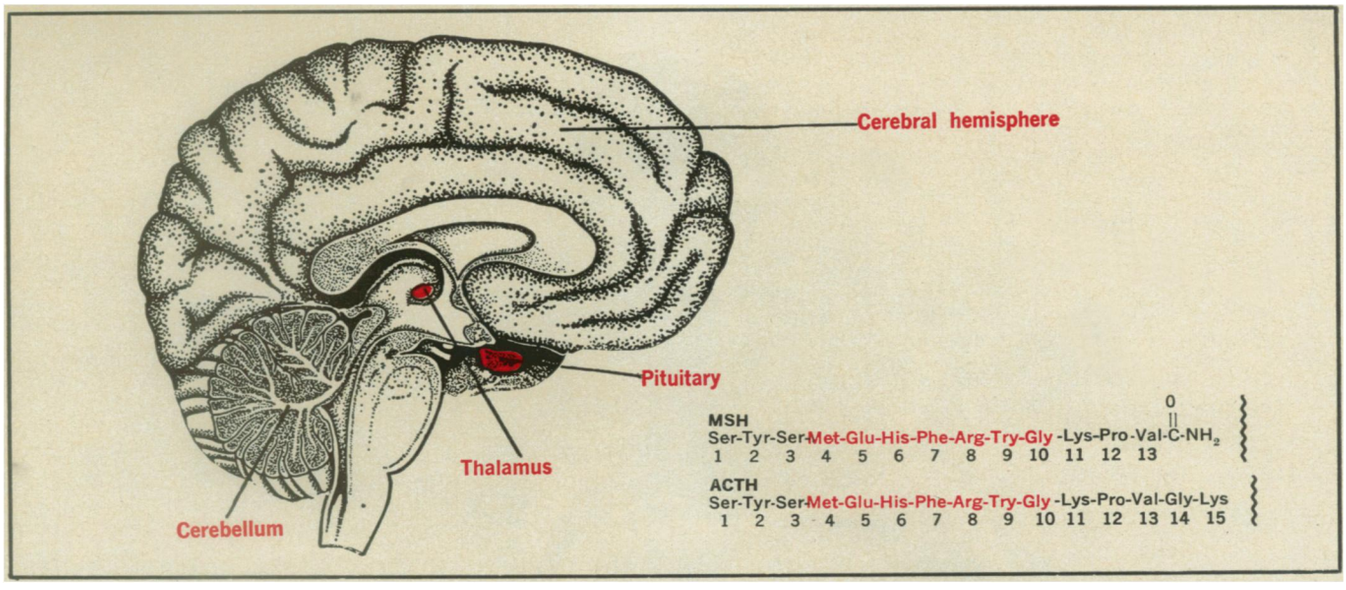
DeWied became interested in this problem when working with Arthur Mirsky and Robert Miller of the University of Pittsburgh in 1958. They injected ACTH into rats and found some positive effects on memory. Back in the Netherlands, at first in Groningen, but since 1963 in Utrecht, DeWied injected ACTH into rats whose pituitaries had been removed. By 1964 he had found that the ACTH injections almost restored the rats to normal responses, but not quite, compared with control rats whose pituitaries had not been removed. He also found that giving the rats without pituitaries injections of adrenal cortex steroids—target hormones controlled by ACTH—did not restore normal responses or behavior. He concluded that the effect of ACTH on behavior was not mediated by the target gland of ACTH, the adrenal cortex, but was triggered directly by ACTH.

Then in 1965, DeWied took another pituitary hormone closely related to ACTH chemically, MSH, which has no effect on the adrenal cortex, and injected it into rats without a pituitary. He found the MSH restored normal behavior. "Which proved," DeWied recalls, "that we were dealing with not only an extra-target effect of ACTH, but of MSH." This discovery came in 1967, and, in fact, provided Kastin with a take-off point for his work on MSH and behavior.

"So then," DeWied says, "we wanted to see whether we could get the same effect with still smaller peptides than the total protein hormones, ACTH and MSH." Because the first 13 amino acids of ACTH and MSH are the same, the active part of the molecule on behavior had to reside in these first 13 amino acids. Accordingly, he asked Henk Greven from the Organon Co. in Holland, who had experience with peptide synthesis, to synthesize peptide sequences ACTH 1-10, 2-10, 3-10, 4-10, 5-10, etc. The sequence ACTH 4-10 was found to be the smallest chemical entity capable of restoring normal behavior in rats without pituitaries.

In 1968, then, DeWied had ample evidence that the pituitary is crucial for conditioned responses in animals, and that the pituitary chemicals that seemed to be influential were the amino acid sequence 4-10 of ACTH and MSH. To reinforce this evidence he took rats with a pituitary, and injected them with the ACTH 4-10 peptide. The injections helped the rats remember what they had learned for a longer period than control rats. Here, DeWied points out, he was probably dealing with memory as well as with learning.

Thus DeWied had learned that taking away the pituitary induces a defi-



Thalmus is target of behavioral chemicals. The identical amino acids 4 to 10 of MSH and ACTH are critical.

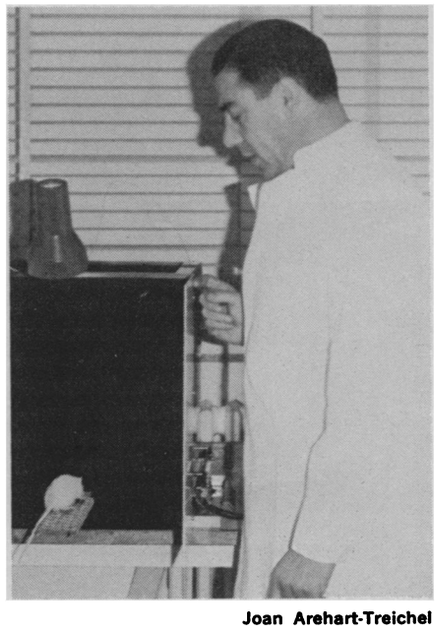
ciency in behavior that can be restored by a crucial peptide, and that this peptide also enhances learning and memory in animals with pituitaries. In view of these findings, he postulated that maybe the pituitary manufactures peptides related to ACTH and MSH, which are released from the pituitary whenever an animal has to learn or remember. He then embarked on a long and exceedingly difficult course of trying to isolate such peptides from crude pituitary extracts.

Saul Lande, a biochemist at Yale, had done a number of isolation studies of peptides from hog pituitaries. Lande provided DeWied with 17 fractions of the peptides. DeWied injected them into rats without pituitaries and found that four of the 17 had strong effects on learning. One of the four active fractions was sent to Lande, who purified it further into 16 subfractions. Upon injecting them into rats without pituitaries. DeWied came up with six potent subfractions.

"Then we chose one of the most active of these subfractions of the lowest molecular weight," DeWied says, and our peptide chemist at the Rudolf Magnus Institute, Albert Witter, purified it. The crucial material turned out to contain seven amino acids. Lande came up with the same thing about the same time. The peptide was dubbed desglycinamide 8 lysine vasopressin, because to the investigators' surprise, it was closer to part of the amino acid sequence of still another pituitary hormone, vasopressin, than to the 4-10 amino acid sequence of ACTH and MSH. This discovery was not a complete sleeper, though, DeWied stresses. Previous scientific research had suggested that vasopressin might have some effect on behavior—more of a long-term effect, though, than the short one that ACTH, MSH and their analogues have.

DeWied gave the desglycinamide 8 lysine vasopressin to rats. Their learning and memory responses were the best DeWied had obtained so far. "We knew," DeWied declares, "that we were dealing with the most important chemical yet as far as learning, memory and behavior are concerned."

Last year DeWied and Lande continued to isolate still other crucial behavior peptides from crude pituitary extracts. Some are related more to ACTH and MSH, others more to vasopressin. The isolation of the desglycinamide 8 lysine vasopressin was recently reported in the JOURNAL OF BIOLOGICAL CHEMISTRY. They are now trying to determine the exact chemical structures of other pituitary peptides. They have also just found that desglycinamide 8 lysine vasopressin is devoid of the classical physiological activities of vasopressin, such as vasopressin's effects on water retention and blood pressure in the body. Details of these findings will appear soon in the BRITISH JOURNAL OF PHARMACOLOGY.



Joan Arehart-Treichel

DeWied with his rat performers.

The target of these various pituitary learning and memory peptides appears to be the thalamus of the brain, as Bela Bohus, from Pecs, Hungary, who is presently working in the Rudolf Magnus Institute, has found, after two challenging years of research. It it far too early, however, to show exactly how crucial learning and memory molecules might act at the cellular or subcellular levels of thalamic tissue or other brain tissue.

DeWied's hypothesis, based on biochemical work carried out by Willem Hendrik Gispen and Peter Schotman, also at the institute, is that learning and memory chemicals, produced in the pituitary, may alter the permeability of the membranes of nerve cells. As a result, one nerve cell might synapse with another nerve cell, thus passing along crucial learning and memory experiences that ultimately alter behavior. This theory is attractive because it bridges two hotly opposing views on the physiology of learning and memory. One view is that learning and memory are contained solely in protein or peptide molecules. The other view is that learning and memory are exclusively nerve cell transmissions.

Clinical studies with the pituitary behavior peptides are just getting under way. The implications are thought-provoking. DeWied declares: "It is quite possible that disturbances in pituitary hormones may underlie certain behavior disorders, and that injections of the crucial pituitary peptides might bring relief from such disorders." □