NEUROCHEMISTRY

Clues from a chemical

PCPA's effects on the brain amine serotonin are stimulating new research

by Louise Campbell

"We must hurry," Sigmund Freud once said to his colleagues, gathered for their weekly meeting in his Vienna flat above a grocery store. "The men with the hypodermic syringes are on our heels."

Freud believed that science would someday demonstrate the biochemistry of mental illness. But listening to neurotic women painfully recall forgotten sexual wishes—recollections that sometimes removed such hysteric symptoms as paralysis of an arm or failure of vision—Freud came to believe that conflicts about the deep instinctual drive of sex caused much mental illness. He also found that by describing their dreams, patients could bring back feelings of rage and shame associated with the repressed sexual wishes. Experiencing these feelings seemed to aid recovery.

The chemistry of the brain is still a mystery. But the profession of psychiatry has continued to build on the triad the Viennese explorer first linked—sex, dreams and mental illness. Perhaps no medical hypothesis has aroused more controversy than Freud's view that derangement of the sexual drive is the basic cause of neurosis.

This view, like most of the diverse psychiatric explanations that have followed it, was based on observation. Psychiatrists do not have an experimental method. Many have hoped that the current brisk study of brain biochemestry would bring psychiatry closer to an exact science.

In this perspective, laboratory study of an experimental drug's effects on the sexual behavior of certain animals is arousing interest among investigators in many fields. The drug also produces insomnia in some animals and changes the part of sleep—rapid-eye-movement (REM) sleep—that workers in this field think is associated with dreaming in both humans and animals. (Even birds have fleeting moments of REM sleep.) And, in one of its most puzzling effects, the drug evokes intense rage in some cats, affection in others.

The drug, para-chlorophenylalanine (PCPA), is not new, but its effect on the animal brain was discovered only a few years ago by Drs. B. K. Koe and Albert Weissman of the Pfizer Research Laboratories in Groton, Conn. These researchers reported that the drug sharply reduces the level of a naturally occurring neurochemical, serotonin, in the brain of rats, mice and dogs. They noticed no effect on the behavior of the animals and said that their ability to perform simple experimental tasks to get food rewards was unimpaired. Other workers soon confirmed the serotonin suppression, and began to find some behavioral effects. Rats, for instance, showed an aversion to alcohol after taking the drug (SN: 7/13/68, p. 37).

Serotonin (5-hydroxytryptamine), first found in human blood by Dr. Irvine Page and workers at the Cleveland Clinic, is now known to be secreted by the pineal gland (once a third eye on the way to mammalian evolution) and to be present in many parts of the human nervous system. It is also found in the venom of wasps and cobras and is one of the compounds whose oxidation makes bananas turn brown.

Little is known about how serotonin acts in the brain, and investigators quickly recognized that PCPA could be used to study this brain chemical. PCPA is the first experimental drug that makes

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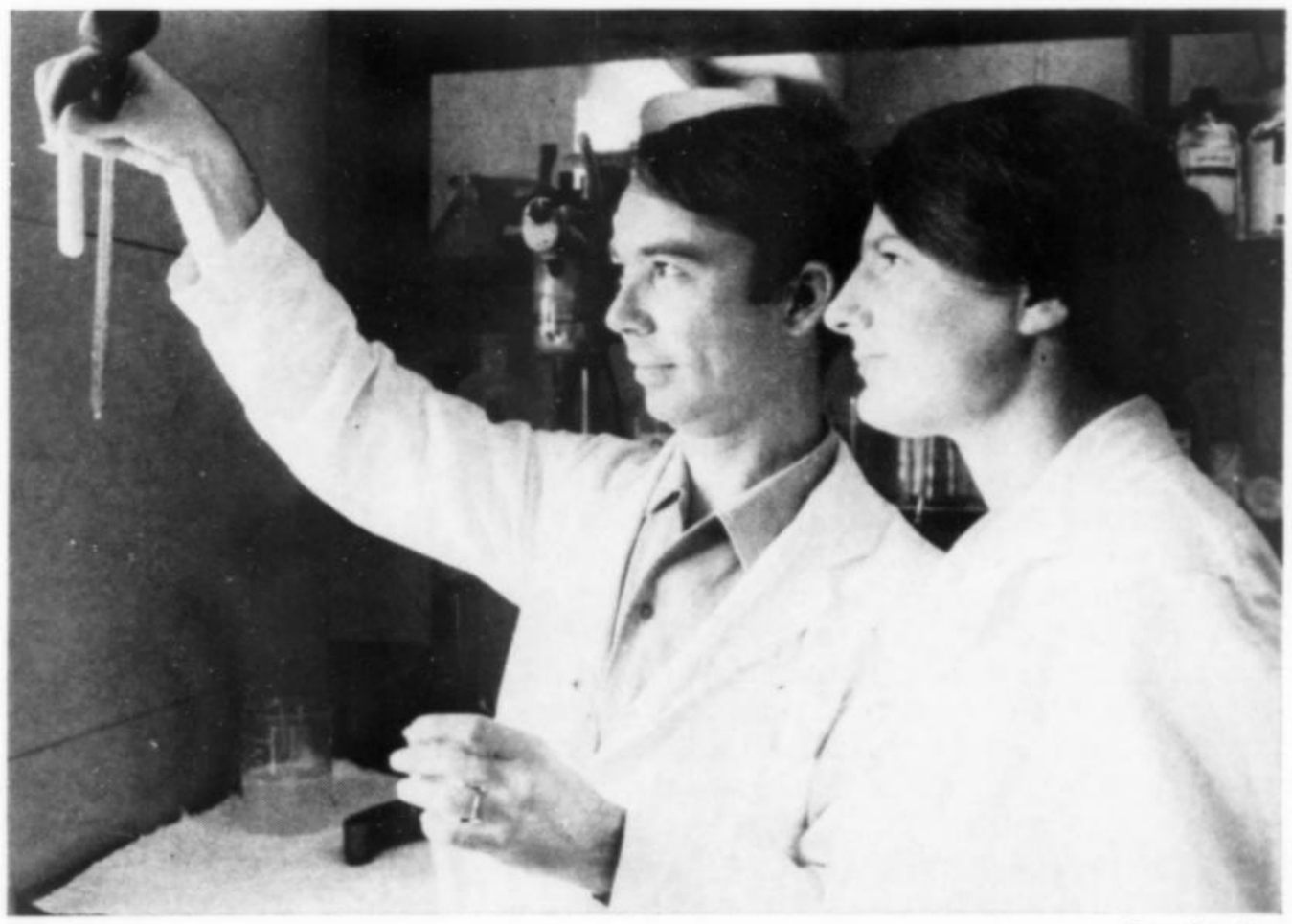
Dement looks for dream mechanisms.

it possible to separate the effect of serotonin from the effects of two other known brain amines (compounds that carry nitrogen on their carbon rings).

Other compounds are known that reduce brain serotonin—reserpine, one of the first-discovered tranquilizers, is an example—but these also reduce the levels of two other important brain amines—norepinephrine and dopamine. Thus these nonselective depressors were not much help to researchers seeking to learn something about how each of these three brain amines act. (Other neurochemicals are known to be present in the human brain—acetylcholine, transmitter of the peripheral



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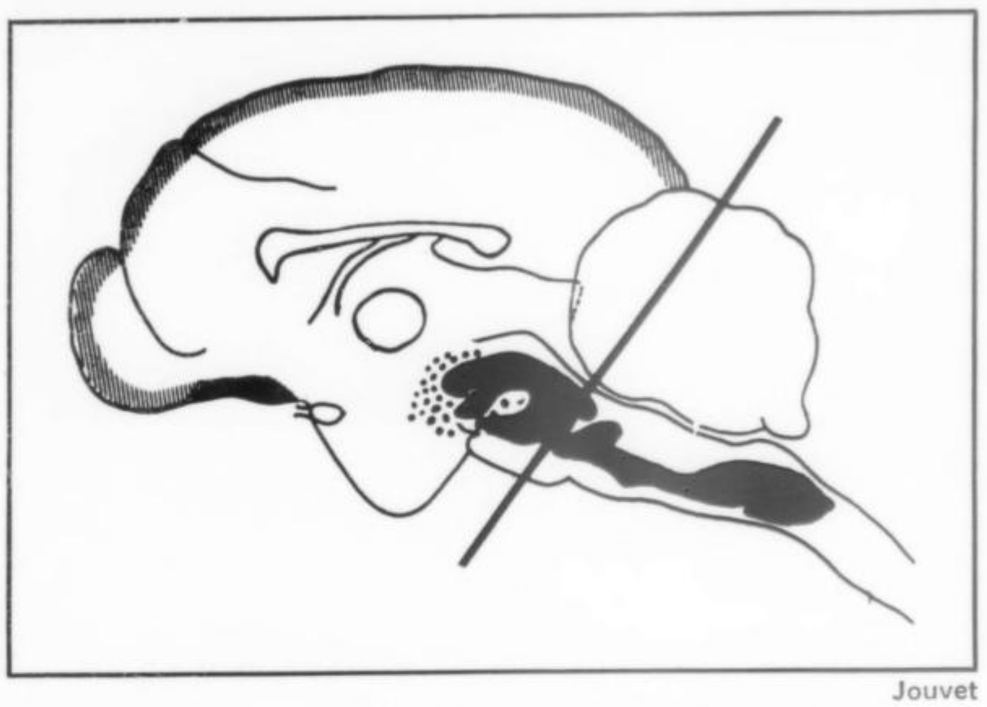
Tagliamontes hope drug may help psychiatrists relieve sexual disability.



Jouvet

Center in cat's brain (right) produces sleep.

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PCPA produces hyperactive sexual behavior in rats.

parasympathetic nervous system is one —but ways to examine them are even less developed.)

The three brain amines are synthesized in body biochemistry from essential amino acids. PCPA reduces brain serotonin by linking to and blocking a key enzyme necessary in the synthesis of serotonin. The enzyme blockage is not reversible, but in 7 to 10 days the body regenerates the enzyme.

Sleep researchers were especially interested in PCPA. They already had some experimental evidence that serotonin is necessary to sleep and they quickly devised experiments to see if PCPA, by reducing brain serotonin, would also produce insomnia. They found that it did. And they confirmed the effect of serotonin reduction by showing that sleep could be restored by giving a serotonin precursor. The precursor, 5-hydroxytryptophan, crosses the blood-brain barrier (serotonin does not) and in one chemical step is converted to serotonin in brain cells.

A French sleep researcher, Dr. Michel Jouvet, chairman of the department of experimental medicine at the University of Lyons, showed that PCPA produces sleeplessness in cats. As a result of his earlier work, Dr. Jouvet was able to trace the PCPA effect on sleep to particular nuclei in the midline of the brain. By precise surgical removal of these midline nuclei (the raphe nuclei), Dr. Jouvet had earlier produced cats that never sleep. He then used a fluorescent technique invented by Swedish researchers to show that serotonin is present in high levels in the cells of these nuclei. (Formaldehyde makes brain amines fluorescent, and norepinephrine, dopamine and serotonin each show a different fluorescent color and spectrum.) Dr. Jouvet used the same technique to demonstrate that PCPA removes serotonin from these specific brain nuclei.

Dr. Jouvet, and Dr. William Dement of Stanford University, are particularly interested in the effect of PCPA on REM sleep. Both have studied rapid-eye-movement sleep for more than a decade by recording the electrical activity of the eyes and various parts of the brain.

Both believe that while their work has shown serotonin to be the chemical agent of the "deep wave" sleep not accompanied by dreaming, other biochemical agents of the sleep associated with dreaming have yet to be found.

Neither worker has experimented with PCPA on humans as yet. Dr. Karl Engelman of the National Heart and Lung Institute, who has been using PCPA to reduce intestinal diarrhea in some cancer patients, did observe some effects of the drug on sleep. His patients did not become insomniac, he reports, but they no longer had REM sleep—the sleep associated with dreaming.

Although these effects on humans were different from the effects noted by Drs. Jouvet and Dement in cats, the discrepancy, at the present pioneering state of the investigation, is neither surprising nor particularly disquieting to the researchers. One reason so little is known about brain biochemistry is that human brains, with fully developed cerebral cortexes, differ markedly in function from those of any lower mammals. And each of the experimental mammalian species used differs from others in both brain anatomy and brain function.

Dr. Jouvet suggests that there are three keys to dreaming—serotonin, norepinephrine and acetylcholine—each acting on a different brain center in a given sequence.

"It is like a fail-safe system," Dr. Jouvet says, "that prevents intrusion into [the] waking [state] of the hallucinatory processes involved in dreaming." Dr. Dement, who also practices psychiatry, has suggested that in schizophrenia the normal "fail-safe" system has broken down.

The sleep researchers also noticed that PCPA produces extreme sexual excitement and compulsive sexual behavior in mice, rats, rabbits and cats. Popular folklore has looked for this sort of effect in compounds ranging from the mandrake root to absinthe. When news of the aphrodisiac effect of PCPA in animals came to public attention about 10 months ago, a scientific controversy erupted.

Administrative officers at Pfizer, for example, show little enthusiasm for this possible effect. They have given the company's public relations department the job of trying to persuade reporters not to write about the sexual-excitant effect of the drug. Pfizer officials say they fear amateurs may try to make PCPA, as they have made LSD (lysergic acid diethylamide), an amine with powerful and dangerous effects on the human brain.

A group of Italian researchers now working at the National Heart and Lung Institute—including Drs. Gian L. Gessa and Alessandro and Paola Tagliamonte—believes that this experimental compound has an important future in treating human sexual disabilities. They plan to begin work with humans when they return to their own university in Sardinia at the end of this year. But clinicians who have used the drug (it is available only for experimental use in relieving diarrhea in patients who have a rare intestinal cancer, and in treating schizophrenia, for which it has not been useful) say they have not found the slightest indication that PCPA acts as a sexual stimulant in humans, and believe there is no possibility of such development.

The Italian researchers, who have been experimenting with PCPA in the National Heart and Lung Institute laboratory of Dr. Bernard Brodie, one of the pioneers in the study of brain sero-