fects, she says. People get irritable at 4200 meters, their judgment becomes erratic, and they tend to make mistakes. "So we had rules," says Wolff. "For example, you were supposed to breathe oxygen for 1 minute every 30 minutes." Some $120,000 was spent on a system to provide oxygen-enriched air to the control room and other places where the observers would be spending their time. "But we found out we didn't need it," she says. Instead, dormitories and a mess shack were built for the construction crew at the Hale Pohaku ranger station (the same "temporary" buildings that serve visiting astronomers today); it turned out that by spending their off hours at 2800 meters instead of sea level, the workers stayed acclimated to Mauna Kea's 4200-meter summit.

Far worse than the altitude, it turned out, was the weather. Winds of 100 kilometers per hour are not uncommon on the summit, and in the winter there are fierce blizzards. (The observatory currently operates the only snowplow in the state of Hawaii.) "I don't think the contractors quite believed it," says Wolff. "They had built highways in Alaska, but they were really not prepared for the nature of the winters on Mauna Kea. They had all the forms ready to pour the concrete for the foundations—and it snowed. It took them weeks to get the ice melted out. And then when it warmed up the wind would blow and the concrete buckets would swing around.

"Meanwhile, the telescope was sitting in Hilo," she laughs. "It had been sprayed with some kind of protective coating, and with all the delays the coating baked on. It took weeks to get it off again."

And so it went: foundations were poured, a dome was erected, and what was then the sixth largest telescope in the world was hauled up, piece by tedious piece, over a narrow, dusty, erosion-prone jeep road to the summit of the highest mountain in the Pacific. Construction took nearly 2 years longer than planned. But, despite all predictions to the contrary, Jefferies and the University of Hawaii did build their telescope. It was dedicated in June 1970 and began full-time operation that November.

Kuiper was invited to the dedication ceremony and he came, bearing equipment to make yet a few more water vapor measurements. Dale Cruikshank, who was an associate of Kuiper in the 1960's and who is now at the University of Hawaii, believes that by this time Kuiper had become reconciled to his defeat. His own projects in Arizona had kept him busy, and perhaps he had come to appreciate how difficult it would have been to run Mauna Kea from Tucson. And besides, it seemed that Jefferies did indeed know what he was doing. Kuiper examined the telescope and the observatory facilities with a sharp, professional eye, and said he was very impressed.

"Mauna Kea was a gamble, we tend to forget that," says Wolff. "Fifteen years ago things were a little more open, people were more willing to take a chance than they are now. Funding now is so tight, and the level of proof on environmental factors and so forth is so high for major projects that I don't think people will make the investment to search out new, undeveloped mountain sites. I think we really have the collection of observing sites that people will use now. I'm not sure that a project like Mauna Kea is something that will ever be done again."—M. MITCHELL WALDROP

This is the first of two articles on the history of Mauna Kea observatory. Next week: The Institute for Astronomy, and the Infrared Telescope Facility.

Brain Opiates in Mental Illness

A lack of brain opiates has been postulated to cause mental illness. So has an excess of the chemicals. There is evidence for both views.

About 6 years ago researchers discovered the endogenous opiates, brain chemicals that may have profound effects on mood and behavior. The discovery raised hopes that an understanding of how these chemicals work in the brain would provide solutions to such intractable medical problems as schizophrenia and depression. At a recent conference on "Opioids and Mental Illness"* investigators discussed their attempts to pin down the postulated link between the endogenous opiates, which are also called endorphins, and the development of mental illnesses.

At present there are two competing theories to explain how the agents might be involved. One theory holds that an excess of the chemicals is at fault, the other that a deficiency is to blame.

The clinical and other trials done to test these hypotheses during the past 5 years have yielded mixed results. They have sometimes, but not always, indicated that giving opiates to mentally ill patients could improve their condition, a finding which would support the idea that the patients do not have enough of the brain chemicals. But other studies have found that chemicals that block the actions of opiates have therapeutic benefits and thus support the opposing view.

Suggestions that opiate drugs might be useful for treating mental illness predate the discovery of the endorphins. Tincture of opium, for example, was sporadically used to treat depression for many decades. But the idea began to gain more credence beginning in the early 1970's, largely as a result of studies of heroin addicts. "The addictions," says Edward Khantzian of Harvard Medical School, "are a place where the biology and psychology of the mind meet."

Khantzian, Léon Wurmser of the University of Maryland Medical School, and other psychiatrists who treat addicts, often noted that the patients had turned to drugs as a self-medication to relieve their mental disturbances. Khantzian explains, "After sitting with many addicts I began to suspect that they craved less for euphoria, but that they craved more for relief from the dysphoria associated with anger, rage, and related restlessness that short-term narcotics seem to provide." In addition, psychotic patients who had been drug-free often experienced improvement of their symptoms when they began taking methadone, an opiate that is widely used for treating heroin addicts.

Attempts to wean addicts from drugs, whether heroin or methadone, gave further support to the self-medication theory. A small but consistent proportion, usually about 10 to 15 percent, devel-

*Sponsored by the New York Academy of Sciences and held in New York City on 28 to 30 October.

0036-8075/81/1127-1013$01.00/0

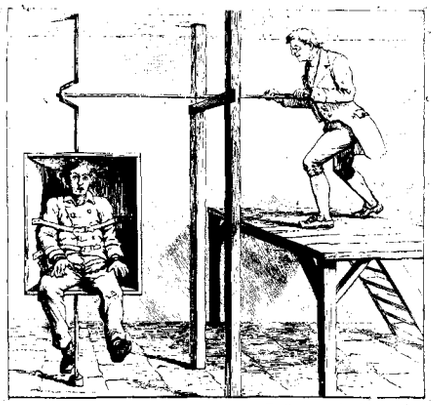
oped psychotic symptoms when the dosage was reduced beyond a certain point. According to Gerald McKenna, of the School of Medicine of the University of California at Los Angeles (UCLA), "This has been observed in three methadone maintenance programs with which we have been involved." Similar observations have been made by Herbert Kleber of Yale University School of Medicine and Mark Gold of Fair Oaks Hospital in Summit, New Jersey. The symptoms generally appear when the methadone dosage drops below 20 milligrams per day. When the drug dose is restored to about 30 milligrams per day, the symptoms are alleviated.

Suggestions that opiates be used to treat mental illness were buttressed by early experiments on the biological effects of the endogenous opiates. In particular, a report in *Science* (5 November 1976, p. 632) by Yasuko Jacquet and Neville Marks of Rockland Psychiatric Institute in Ward's Island, New York, suggested that β-endorphin, when injected into the brains of rats, produced effects resembling those of the neuroleptic drugs used to treat schizophrenia.

The first attempt to treat schizophrenic patients with β-endorphin was made by Nathan Kline of the Rockland Research Institute in Orangeburg, New York. He reported that the patients improved; they had fewer hallucinations than usual. The more rigidly controlled, double-blind studies of β-endorphin done since then have not produced impressive results, however. In a study described at the opioid conference by Don Catlin of UCLA School of Medicine, β-endorphin produced no improvement in eight schizophrenic patients. Although some of the ten depressed patients improved, the condition of others worsened. Catlin concluded, "We see no support for the use of β-endorphin as we have given it in schizophrenia; there is a modest indication for its use in depression."

Philip Berger of Stanford University School of Medicine reported that β-endorphin produced a statistically significant improvement in one measure of the condition of schizophrenic patients, but the benefit was not clinically apparent.

Lack of a pronounced response to β-endorphin does not necessarily rule out involvement of the endogenous opiates in the etiology of mental illness. There are several different endorphins. David de Wied of the University of Utrecht has proposed that a deficiency of one of the others, a γ-endorphin, might underlie schizophrenia. (β-Endorphin is a peptide containing 30 amino acids; γ-endorphin is shorter, consisting of the first 17 residues found in β-endorphin.)



Bettmann Archives, Inc.

The circulating swing

Depression therapy in 1818

Animal tests showed that γ-endorphin and two of its derivatives had neuroleptic effects. The derivative called γ-[des-Tyr^1]-endorphin or DTγE, which is formed by removing a tyrosine from the beginning of the γ-endorphin molecule, was especially active in this regard.

According to Jan M. van Ree, the Utrecht group has tested DTγE and the other derivative (designated DEγE) in a total of 40 schizophrenic patients. He says, "We saw in some of them marked antipsychotic activity that lasted in some cases longer than the treatment; others did not respond at all." Eleven patients had a marked improvement of better than 80 percent as assessed by the Brief Psychiatric Rating Scale, while 20 patients improved 20 to 80 percent. In general, patients whose symptoms were of relatively short duration benefited most, a result also found in a smaller study with DTγE by Hinderk Emrich of the Max-Planck-Institut für Psychiatrie in Munich.

Other investigators have not found such encouraging results with DTγE. John Metz of the University of Chicago reported on a small pilot study with eight patients. Only two had decreased hallucinations, delusions, and thought disorders, although six became more sociable.

Because the exogenous opiates have many of the same effects as the endorphins, some researchers have suggested that drugs such as methadone be tested in mentally ill patients. As already noted, methadone may relieve the psychotic symptoms of addicts, but testing it in nonaddicts raises an ethical issue.

Proponents of the idea note that therapy with neuroleptic agents, such as chlorpromazine and haloperidol, has helped many schizophrenic patients but is often unsatisfactory. Either the drugs do not work or they cause serious side effects, including abnormal movements like those seen in patients with Parkinson's disease and tardive dyskinesia, a condition characterized by jerking and twisting of the head and mouth. These side effects often persist even after the drug therapy is stopped.

Nevertheless, methadone has at least the potential to be addictive, and investigators who have proposed trials with it have often met resistance. Karl Verebey of the Downstate Medical Center of the State University of New York, who was the chairman of the opioid conference, complains, "Critics say there aren't enough well-controlled studies in the field. That is true, but review boards decline permission to do the studies." There were anecdotal reports at the conference of mentally ill patients who were helped by treatment with methadone or tincture of opium, although not all patients responded.

In addition, Emrich tested the analgesic buprenorphine, which mimics some opiate effects but antagonizes others, in ten patients with depression. He found that half of them responded very well to the drug, which is supposed to lack the addictive potential of morphine, and the others not at all. Emrich concludes, "Since practically all of the patients included in the study were nonresponders to conventional thymoleptic [antidepressive drug] therapy, this is a significant response."

The hypothesis that an excess of endorphins may cause mental illness is of the same vintage as the deficiency theory. In fact, the same issue of *Science* in which the Jacquet report appeared contained a report by Floyd Bloom, Roger Guillemin, and Nicholas Ling of the Salk Institute and David Segal of the University of California at San Diego on the effects of β-endorphin injection into the spinal fluid of rats. These workers concluded that the endogenous opiate produced a condition of rigid catatonia similar to that seen in some schizophrenics.

The idea that an endorphin excess could cause mental illness was appealing. "The fascinating thing about the endorphin hypothesis," says Monte Buchsbaum of the National Institute of Mental Health (NIMH), "is that if it were true, we would have a cure already in the narcotic antagonists."

Since an early report by Lars Terenius and his colleagues at Uppsala University that the opiate antagonist naloxone could alleviate the symptoms of schizophrenic patients, a dozen or so studies, most of them controlled and double-blind, have been undertaken to test naloxone's ther-

apeutic effectiveness in mental illness. According to Jan Volavka of New York University School of Medicine, those using higher doses, 6 milligrams per day or more, have generally had more positive results. For comparison, as little as 1 milligram of the drug can reverse the effects of a heroin overdose.

The largest trial of naloxone to date is a collaborative study sponsored by the World Health Organization. The WHO study, which included 32 schizophrenic and 26 manic patients at seven medical centers throughout the world,† was the first to attempt to sort out differences between the responses to naloxone of drug-free and drug-treated patients. The doses given to the patients were high, roughly 20 milligrams per day.

The project coordinator, David Pickar of NIMH, says, "The results of the WHO study were interesting. We found that schizophrenic patients concurrently treated with neuroleptic drugs showed improvement in some ratings. If they were off medication, there was some worsening, but all had indications of a lessening of their auditory hallucinations." Naloxone did not appear to benefit the manic patients.

The results of the WHO study do not support either a simple endorphin excess or deficiency theory of mental illness. Naloxone's worsening of the condition of drug-free patients would seem to support the deficiency view, an interpretation also consistent with the results of spinal fluid analyses described by Pickar at the opioid conference. The NIMH workers found that total opioid activity was decreased in the spinal fluid of male schizophrenics and unchanged in that of female patients.

The improvement observed in neuroleptic-treated patients does not fit this neat picture, however. Several investigators have noted that neuroleptic treatment raises endorphin concentrations in some areas of the brains of experimental animals. They have hypothesized, in keeping with the endorphin deficiency theory, that this effect of the neuroleptic drugs may be the way they relieve schizophrenic symptoms. In that event, naloxone ought to have decreased the effectiveness of the drugs, the opposite of what was found in the WHO study.

Pickar, pointing out that the patients helped by the neuroleptics rarely become completely normal, hypothesizes that the endorphin increases may be an unwanted side effect of neuroleptic treatment, thus accounting for the further improvement seen with naloxone. If this is the case, then either too much or too little endorphin could be causing mental disturbances. Of course, this possibility has always existed, because mental illness such as schizophrenia may have heterogeneous symptoms and origins.

In view of the large doses needed to see a naloxone effect in mental illness, there is also the possibility that the agent acts independently of the endogenous opiate system.

Several investigators have attempted to define the causes of mental illness by looking at endorphin concentrations in spinal fluid or blood. Again, the results have often been inconsistent or hard to interpret. Agneta Wahlstrom presented data obtained by the Terenius group on the endorphin content of the spinal fluid of depressed patients. These workers separate the endogenous opiates into two fractions designated I or II. They find fraction I to be increased in patients with depression, but not in those who alternate between depression and mania. The concentration of fraction II correlates positively with anxiety and suicidal tendencies in depressed patients. In contrast to the results presented by Pickar, the Terenius group has also reported that fraction I increases in patients with schizophrenia. What all this means is not clear, as the fractions have not yet been completely characterized.

There are many complications with doing and interpreting the endorphin analyses. For one, the agents comprise a mixture of substances. It is difficult to distinguish between them analytically and measurements of total activities may not necessarily reflect what is happening in the brain. Moreover, as Derek Smyth of the National Institute for Medical Research, Mill Hill, points out, "If the defect were confined to a few neuronal pathways it would be unlikely for it to show up in a change in concentration in the cerebral spinal fluid." Finally, there is an accumulating body of evidence that suggests that β-endorphin may be released in response to stress, in which case measured changes might have more to do with individual responses to stress than with the etiology of mental illness.

Buchsbaum and his colleagues of NIMH, with Glenn Davis of Case Western Reserve University, are attempting to see what is happening in the human brain itself. Lack of responsiveness to pain and inattentiveness have commonly been observed in schizophrenic patients. Using measurements of evoked potentials (EP's), which are changes in brain waves elicited by specific stimuli, the NIMH workers have shown that the two defects appear to be produced by a common mechanism—one that may be effected by endorphins. The experiments both support the endorphin excess theory of mental illness and suggest a potential method for identifying those patients who will be good candidates for treatment with opiate antagonists.

EP's provide an objective test of an individual's response to a stimulus. For the pain studies, Buchsbaum and Davis used electrical shocks of progressively increasing intensity. The EP's indicated that the schizophrenics are less sensitive to pain than are normal controls. The opiate antagonist naltrexone made the patients just as sensitive, a finding which suggests that endogenous opiates were blunting the patients' responses. Morphine injections caused the controls to be less sensitive, as expected.

The attentional task required the subject to pick out and respond to a stimulus of a given intensity, a light flash or tone, when presented in a random sequence of stimuli of varying intensities. According to Buchsbaum, attention defects were reflected in changes in the resulting EP's that were very similar to those associated with the pain deficits. He explains, "The same component of the evoked potential is sensitive to selective attention defects. It is decreased in schizophrenia and modulated by the endorphin system." Naltrexone, for example, enhanced the patients' attention responses just as it did their pain sensitivity.

Topographic mapping of the EP's over the surface of the head suggested that the schizophrenics' attentional defect may lie in the parietal lobe of the brain. The EP changes of the controls were enhanced in both the frontal and parietal lobes when they were performing a task that required them to pay attention, but the patients did not have an analogous change in parietal region EP's.

The NIMH workers are now using positron to detect changes in the metabolic activity of brain cells in response to various stimuli. "The EP's are less specific than PET scans and limited to responses from the cortical surface," Buchsbaum says. "By doing both simultaneously we may be able to determine what the EP signifies physiologically."

The most certain thing that can now be said of the relationship between brain opiates and mental illness is that nothing is settled. Despite a great deal of progress in understanding what is happening, the brain is still largely a "gray box."—JEAN L. MARX

†The seven centers are NIMH; Division of Mental Health, WHO, Geneva; Psychiatrische Universitatsklinik, Basel; King George's Medical College, Lucknow, India; Institute of Psychiatry of the Academy of Medical Sciences, Moscow; Psychiatrische Klinik and Poliklinik of the University of Munich; and University Hospital, Utrecht.