Adenosine: The talented messenger

The development of major psychoactive drugs has been marked by a series of fortunate coincidences, if not blind luck. For instance, the first and still widely used antipsychotic drug, chlorpromazine, was originally expected to merely sedate hyperactive patients. "Though the [psychoactive] drugs existed in 1965, we didn't know about how they acted," says Solomon H. Snyder, distinguished service professor of psychiatry and pharmacology at Johns Hopkins University. Now, after nearly two decades of scientific inquiry into the workings of the brain, Snyder says, "we know...."

Armed with the relatively new technology of the neurosciences, Snyder and others are starting to attack such problems somewhat more traditionally — by first discovering how the brain's neurochemistry systems work and *then* applying this knowledge to developing or improving certain drugs.

Among the latest and most promising work of this kind are experiments at Hopkins involving the chemical adenosine. Though adenosine has been known to scientists for many years, its function as a key modulator of a number of brain and body processes is just beginning to be recognized, say researchers. "Adenosine is right in the biochemical pathway for the major activities in the body," Snyder explains. It is now known that adenosine exists rather commonly throughout the body and that it appears to: regulate neuronal function in the brain by inhibiting neuronal firing and synaptic transmission; dilate coronary blood vessels; constrict the bronchial tree; and inhibit platelet aggregation (clotting) and lipolysis (the decomposition or splitting up of fat). "In addition," says Snyder, "it's in the pathway to production of ATP — the source of all energy."

However, Snyder's latest key finding — announced to a press gathering last week — is the discovery of two separate receptors for adenosine. While the receptors are present throughout the body, their major concentrations appear to be in the brain and, in males, the testes. The ability to distinguish between two distinct receptors means scientists may now be able to "measure specific receptors upon which a drug is acting," enabling researchers to "evaluate the potency of a drug on a receptor itself," suggests Snyder.

"Because we have found subtle differences in the two types of receptors for adenosine we should be able to tailor drugs better to prevent heart attacks and to treat asthma, thus avoiding serious side effects, such as convulsions, of theophylline," he says. Theophylline, which along with caffeine has been found to block adenosine binding to its receptors, is a major component of drugs used to treat asthma. But the treatment can produce central nervous system side effects if it dilates the bronchia too aggressively. One such advanced drug might dilate coronary arteries to prevent angina, he speculates, while another might work on different receptors in the lung without affecting the heart.

Snyder, along with Robert F. Bruns and John W. Daly of the National Institutes of Health, has already begun to experiment with adenosine analogs, one of which appears not to be metabolized in mice's bodies but does reach their brains. The effect of this drug so far, he says, "resembles [that of] Valium." Snyder says that adenosine, like prostaglandins, seems to be a "universal mediator" throughout the body; he suggests it may be a "second messenger" in the chemical transmission process between cells and adds that "we already have indications there are even more [than two] adenosine receptors." A report of the work will be published in the September PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

Snyder will chair Hopkins's newly established department of neuroscience, it was also announced by Richard S. Ross, dean of the School of Medicine. Snyder says that among other activities, he hopes to publish a neuroscience journal. □

Schizophrenia ECT: Temporary help

Electroconvulsive therapy (ECT) is a recognized, if somewhat controversial, way to treat severe depression. While moderate levels of success have been reported in ECT with depression, far more hazy results have come from the relatively few trials with schizophrenics. Now, in the June 28 LANCET, researchers from Guy's Hospital in London, England, report some success in treating schizophrenics with electroshock — however, the positive results appear to be temporary.

Twenty diagnosed paranoid schizophrenic patients were told they were to receive ECT, but only 10 actually received it. The other 10 were put through an identical pre-ECT workup, complete with anesthesia, but not given shocks. After several weeks — during which the ECT group received from eight to 12 treatments each — "both groups improved, but the improvement of patients receiving ECT was significantly greater than that of controls both after six treatments and at the end of treatment," report Pamela Taylor and J.J. Fleminger.

They found, though, that "by 16 weeks [after start of treatment] there was little difference between the two groups." The researchers suggest that perhaps a longer study with more ECT administrations might trigger more lasting improvement, or at least yield more definitive evidence of ECT's effect on schizophrenia. □

Heart implant to restore natural rhythm

You may have seen it on TV — a man clutching his chest, gesturing wildly, falls down. A medic arrives and quickly makes a diagnosis — "The patient is defibrillating." A set of large metal paddles appears. "Hands off," the medic warns, and the victim's body shudders as an electric shock is applied to jolt the heart back on course.

When a person's heart goes into ventricular fibrillation — erratic beating — death can come in three to four minutes. To help some of the people who have a recurring defibrillation problem that fails to respond to drugs, doctors at Sinai Hospital and at the Johns Hopkins Medical Institutions in Baltimore have developed an automatic implantable defibrillator (AID).

"The stricken patient would now have an excellent chance to survive the attack and live to tell about it," says Michel Mirowski, a cardiologist at Sinai and the inventor of the AID. The AID is different from a pacemaker in that it gives a large shock when the heart begins to flutter erratically, not a small one when it slows down.

The device, about the size of a cigarette package, monitors the heart continuously. When it senses an arrhythmia, the AID delivers an electric shock much as the paddles do when the shock is applied externally but with only one-eighth the energy.

The device is currently undergoing clinical testing in Baltimore. The experience with the first three patients is described by Mirowski and his co-workers in the Aug. 7 NEW ENGLAND JOURNAL OF MEDICINE. Two received their implants and were discharged in satisfactory condition; the third had to have his device inactivated because it failed to halt his arrhythmias.

Since the article was written, three more patients have received implants. Two are doing well and one has died, Mirowski reported this week. □

Shuttle aimed for March '81

The National Aeronautics and Space Administration, following an exhaustive review of the troubled space shuttle program, has confirmed its earlier plan to launch the shuttle on its first orbital flight by March of next year. This is despite the fact that on July 30, the day before the decision was made, a shuttle engine was seriously damaged by fire during a test in Mississippi, dealing the program what NASA calls "a potentially serious setback." Achieving a March 1981 launching requires a "difficult but achievable schedule," says NASA Administrator Robert Frosch. "The engine failure ...," he adds, "could affect that decision, but we will make every attempt to assure that it does not." □