Mental Disorders: A New Approach to Treatment?

For generations, medical students have been taught that the brain is special, that it is metabolically set apart from the rest of the body. It was thought that as long as the brain was supplied with oxygen and glucose it would make whatever it needed, independently of the metabolic and nutritional status of the body.

In this context, medical scientists were taken aback by the discovery, a few years ago, that the activity of certain brain neurons varies in response to normal fluctuations in diet (*Science*, 2 April 1976, p. 41). Richard Wurtman, John Fernstrom, and their associates at the Massachusetts Institute of Technology reported that diet supplies the blood with precursors for various neurotransmitters, which conduct signals between nerve cells. And the rate that the brain synthesizes these neurotransmitters changes in accordance with changing amounts of their precursors in the blood.

This discovery is rapidly being put to clinical use and in particular has already led to the first successful treatment of a serious disorder known as tardive dyskinesia. Investigators are particularly impressed by the speed with which work has progressed. It has been only $2^1/_2$ years since Wurtman and, independently, Dean Haubrich of Merck Sharp & Dohme Research Laboratories in West Point, Pennsylvania, reported that the rate at which the brain synthesizes one neurotransmitter, acetylcholine, can be increased by increasing the amount of choline (acetylcholine's precursor) in the blood. But already dozens of groups of investigators have tried to use this information to devise treatments for patients whose neurological disorders may arise from a lack of brain acetylcholine.

At a December symposium in Tucson, researchers got together to discuss the evidence that choline or lecithin (the dietary source of choline) might be useful in treating a number of disorders. Although they agree that their only unquestionable success so far is in treating patients with tardive dyskinesia, they are hopeful that patients with several other kinds of disorders may be helped by choline or lecithin treatments.

Tardive dyskinesia is the side effect that psychiatrists worry about the most when they prescribe antipsychotic drugs such as the phenothiazines and the butyrophenones, according to John Growdon of Tufts University and the New England Medical Center in Boston. It is a disfiguring disorder that often continues indefinitely even after patients discontinue the drugs. Patients have involuntary twitches of their facial muscles, including rolling tongue movements, lip smacking, lip puckering, and rapid eye blinking. About 40 to 50 percent of patients in state mental hospitals have tardive dyskinesia, Growdon says. Reports that these patients improve after they are treated with choline are the first indication that the condition can be ameliorated.

Psychiatrists have suspected for several years that the antipsychotic drugs may cause tardive dyskinesia by creating a relative lack of acetylcholine in the brain. They based this suspicion on the observation that, when patients with tardive dyskinesia are given a drug (scopolamine) that blocks acetylcholine receptors and thereby prevents cells from using acetylcholine, the disorder worsens. On the other hand, when patients are given the drug physostigmine, which increases brain acetylcholine concentrations by preventing the breakdown of this neurotransmitter, the patients' symptoms often improve. Physostigmine cannot be used to treat tardive dyskinesia, however, because it must be injected, it is only effective for 1 hour, and it causes severe side effects, including intestinal cramps, abnormal heart rhythms, and excessive secretion of mucus in the lungs.

A Clinical Success

Within 4 months after Wurtman and his associate Edith Cohen announced that acetylcholine synthesis in rat brains increases when the animals are fed large amounts of choline, Kenneth Davis, Philip Berger, and Leo Hollister of Stanford University gave large doses of choline to a patient with tardive dyskinesia and reported that the patient improved. A few other reports of uncontrolled studies with choline were soon published, and they all indicated that choline alleviates tardive dyskinesia.

To decide whether choline is truly efficacious, Growdon and his associates carried out a double-blind crossover study of 20 patients in a state mental hospital. They found that choline improved the condition of nine patients, worsened it in one, and did not affect the condition of the remaining ten. Moreover, choline did not interfere with the actions of the antipsychotic drugs. These results were soon confirmed by other investigators, including Davis and his associates and Andre Barbeau and his colleagues at the Clinical Research Institute of Montreal.

Growdon suggests two possible explanations for the finding that not all patients with tardive dyskinesia respond to choline. First, the patients in the study were "back ward" patients—people who had been taking antipsychotic drugs for years. The severity of tardive dyskinesia is related to the amount of time the drugs are taken. Thus many of these patients may have been too badly affected by the drugs to be helped by choline. A second reason is that some of the patients may have had a form of tardive dyskinesia associated with senility rather than with antipsychotic drugs. This form of the disorder may not respond to choline, Growdon says. When he gave choline to four patients known to have senile tardive dyskinesia, none responded.

Despite its apparent usefulness in treating tardive dyskinesia, choline is not an ideal substance to take because it has one unpleasant side effect: it makes some patients smell strongly like fish. This fishy odor is caused by the breakdown of choline to trimethylamine by bacteria in the gut.

The problems with this side effect can be avoided if patients are given lecithin (phosphatidylcholine), which is the dietary source of choline. Wurtman and his associates find that doses of lecithin actually cause a greater increase in blood choline concentrations than do equivalent amounts of choline and that those concentrations remain elevated for a longer period of time than they do after patients are given choline. Since lecithin is absorbed by the intestinal mucosa and is not degraded by gut bacteria, it does not cause patients to have a fishy odor. Growdon and his associates recently reported that patients with tardive dyskinesia who respond to choline also respond to lecithin.

Investigators at the conference agreed that lecithin will probably supplant choline as a treatment, but lecithin is not without its drawbacks. Commercially available lecithin is used in the food industry as an emulsifier. These "lecithin" preparations are only about 15 to 30 percent pure; the rest of the preparations

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consist of other phosphatides and fatty substances. Thus patients must consume large quantities of the commercial preparations to receive therapeutic doses of pure lecithin. These daily doses of commercial lecithin often contain as many as 700 calories.

Another problem with commercially available lecithins is that their content varies from manufacturer to manufacturer, and so researchers cannot be sure what patients are ingesting in addition to pure lecithin. Lecithin manufacturers met with the conference participants, however, and agreed to make prepara-

Speaking of Science

Prospects for Proprietary Synchrotron Radiation Research

From the point of view of industrial researchers, the price of doing experiments at federally supported facilities, but at no expense to the government, has often been too high to pay: loss of some patent rights and a requirement to publish results in the open literature. Precedents for proprietary or secret research exists in the form of, for example, the use of neutron beams from the reactors at Oak Ridge and Brookhaven National Laboratories by companies wishing to irradiate materials of commercial significance. But the popularity of synchrotron radiation and the imminent availability of new federally funded sychrotron radiation facilities are exerting pressure for a more permanent and widely acceptable policy. Some steps toward development of such a policy have recently been taken or are under consideration.

One of these is an agreement that was worked out this summer by the Monsanto Company and Stanford University and allows company researchers to carry out x-ray studies of proprietary catalyst materials at the Stanford Synchrotron Radiation Laboratory (SSRL). Thrashing out an agreement was made more than ordinarily difficult by the complex three-way set of interests at SSRL. Stanford, seeing itself as an educational institution, required in the strongest terms that all research there be published; the National Science Foundation (NSF), which supports the operation of SSRL, lacked a firm policy on proprietary research there because the issue was not one the agency has had to face previously; and the Department of Energy (DOE), which finances the source of SSRL's photons, the SPEAR electron-positron storage ring, a facility used primarily by high-energy physicists, had a regulation governing rights to patentable inventions deriving from work at its facilities. Further adding to the complications was the large demand for access to SSRL's x-ray beam lines, so that the scientific merit of any proposed proprietary work had to be sufficient to grant it priority over other researchers' proposals, according to Arthur Bienenstock, SSRL director.

Resolution of the application by Monsanto researchers Robert Friedman and B. Ray Stults to use SSRL was achieved when: (i) the company did, in fact, submit a proposal with competitive scientific merit; (ii) the company agreed to publication of results within 1 year of completion of the experiments, enough time to reap benefits from the knowledge gained ahead of competitors; and (iii) the company and Stanford agreed to a formula whereby SSRL would recover the costs of providing x-rays to Monsanto. In addition, in order to provide a means whereby the merit of the company's proposal could be judged without disclosing its proprietary aspects, a confidential third party, in this case Bienenstock himself, who would receive and hold the proprietary data, was designated.

Brookhaven will have, in late 1981, two storage rings that, unlike Stanford's SPEAR, are dedicated entirely to the production of synchrotron radiation. According to Martin Blume of Brookhaven, officials there and within DOE, which is funding the new National Synchrotron Light Source, are working hard to develop a policy for proprietary research, in part because numerous inquiries have already been received. Blume notes that at least three categories of users from profit-making organizations can be envisaged: those wanting to do purely basic research, those who, like the Monsanto investigators, want to do research involving proprietary materials or techniques, and those wanting to use synchrotron radiation in the conduct of their business. An example of the latter might be a company offering x-ray fluorescence analyses of samples submitted by its customers. Each prospective class of users brings up different issues, none of which are settled yet, although two elements of any final policy apparently will be that Brookhaven will not offer any services that could be construed as competing with those available from private facilities and that full cost recovery for proprietary research will be required.

Brookhaven has also issued a call offering guaranteed access to synchrotron radiation for nonproprietary, basic research to institutions or groups that develop instrumentation for one of the new beam lines. It has not yet been decided whether companies would be extended this opportunity, although instrumenting a beam line is such a major undertaking that only the largest firms would likely be up to the task.

Manufacturers of microelectronic circuits may, in the end, be the ones forcing a resolution of the problem of proprietary research. One of the avenues being investigated in the drive toward further miniaturization of these devices is the use of x-rays, to replace the 4000-angstrom light now used, in the photolithographic process by which the circuit patterns are delineated. But, at present, only the high intensity x-ray beams from synchrotron radiation sources are strong enough to make x-ray lithography practical. SSRL, which is slated to have exclusive use of SPEAR on a half-time basis by the end of next year and which is in the process of constructing new facilities, now has under consideration a plan whereby those interested in x-ray lithography could use one of the new beam lines for proprietary research. The new wrinkle is that access would be outside the competitive proposal process, and therefore, says SSRL's Bienenstock, because the slow evaluation step would be bypassed, access would be on a much more timely basis. Eventual publication of research results and full recovery of operating costs would continue to be required, however.—ARTHUR L. ROBINSON

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tions of pure lecithin available in the near future.

Although tardive dyskinesia is the first disorder to respond to choline treatment, researchers are optimistic that it will not be the only one. Among a number of other disorders they are now trying to treat with choline are mania and senile dementia.

A number of psychiatrists believe that mania may be caused by a relative lack of brain acetylcholine. As evidence, John Davis and his associates at the Illinois State Psychiatric Institute and, independently, Kenneth Davis, Berger, and Hollister report that when manic patients are given the drug physostigmine, their mood often changes. They gradually become more and more depressed, going through a normal stage and then sinking into severe depression. When he first saw this happen to a manic patient, Hollister said, "This is the most impressive and the most dramatic thing I have ever seen."

Manic patients are usually treated with lithium, which is fairly toxic and must be closely monitored. It may be possible, however, to potentiate the effects of lithium with choline and thereby give less lithium to manic patients. William Millington and Anthony McCall of the Massachusetts Institute of Technology find that when rats are given lithium, the effectiveness of dietary choline in increasing brain acetylcholine concentrations is enhanced. They speculate that one of lithium's actions may be to inhibit the efflux of choline from the brain.

The common senile dementia known as Alzheimer's disease also seems to result, at least in part, from a lack of acetylcholine. Several groups of investigators, including Peter Davies and his associates at the University of Edinburgh, David Bowen and his associates at National Hospital, Queen's Square, London, and Robert Perry and his associates at Newcastle General Hospital have recently shown that the disease is associated with a partial loss of neurons that make and use acetylcholine as well as with a reduction in activity of the brain enzymes that make acetylcholine from choline. These biochemical changes correlate with dementia scores on psychological tests.

Nonetheless, researchers have not yet reported any unqualified successes in treating Alzheimer patients with choline. David Drachman of the University of Massachusetts Medical Center speculates that because selective arrays of neurons may not function properly in patients with this disease, a general increase in brain choline concentrations may not be sufficient to correct the deficiencies of these neurons. He suggests that treatment with both choline and a drug that prevents acetylcholine breakdown may be more effective than choline alone. Another possibility, suggested by Janice Christie of the Medical Research Council Unit in Edinburgh, is that Alzheimer patients should be treated early in the course of their disease before their neurons degenerate too much.

Although investigators still hope that Alzheimer's disease may respond to choline administration, they believe that other disorders are too complex and involve too many kinds of neurotransmitters to respond to choline treatment alone. One of these diseases is Huntington's chorea, which does seem to be related to a lack of brain acetylcholine but which also is associated with many other degenerative changes in the brain.

Choline, then, is not expected to be a panacea for all disorders characterized by a lack of brain acetylcholine. But it may herald a new era in the treatment of neurological disorders. Choline is specific, in that it is only converted to acetylcholine by neurons that are able to and need to make this neurotransmitter. And it has no serious side effects.

Already some investigators are looking to precursors of other neurotransmitters for the treatment of other sorts of neurological disorders. For example, Arvid Carlsson and Marget Lindequist of the University of Göteborg in Sweden suggest that the amino acids tryptophan and tyrosine, which are presursors for the catecholamine neurotransmitters, might prove useful in the treatment of depression.

Although it is still too soon to say how effective neurotransmitter precursors will be in the treatment of psychological disorders, increasingly many investigators are sufficiently convinced by the evidence at hand to at least try this approach.—GINA BARI KOLATA

Speaking of Science

The Great Titration Contest

Football teams from Yale and Princeton rarely get into any of the major postseason bowls. In the spirit of the season, however, Princeton chemistry lecturer Miles Pickering has devised a suitable alternative competition that is more in keeping with the academic status of those institutions—The Great Titration Contest. The second annual edition of this formidable event was held this December in chemistry laboratories on the two campuses, and Yale squeaked through with a 51-49 win, keeping the team undefeated in postseason play. Yale won the first contest by the somewhat larger margin of 53-47.

In the contest, some 450 freshman inorganic chemistry students at each institution are given a solution containing an unknown quantity of sodium oxalate. The students titrate the solution with potassium permanganate to determine its concentration. In this year's playoff, 51 percent of the Elis calculated a concentration within one percentage point of the actual value, while only 49 percent of the Tigers achieved the same feat. Pickering is pleased by the narrowing of the gap between the two schools and predicts a Princeton win next year.

Titration was chosen for the context, Pickering says, because it is an "objective test of laboratory proficiency" that provides "an excellent benchmark for the teacher" in gauging how well students are mastering basic laboratory skills. The exercise, adds his Yale counterpart Robert Crabtree, places a premium on attention to detail and ability to follow instructions. The fact that only about half the students complete the titration accurately, despite a dry run the week before, is attributed to the fact that most of the students in the class are not chemistry majors.

The success of the titration contest opens up several other possibilities. In addition to the expansion of the contest to other schools, there might also be parsing contests for grammarians, dissection contests for biologists, and creating unusual names contests for physicists. The vistas are endless, and if the contests just happen to increase motivation of the students, that will be merely a fringe benefit.—T.H.M.

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