

# Schizophrenia: New Hope From an Old Drug

Clozapine, a medication first synthesized in 1960 but not available for prescription use in the United States, appears to be an effective treatment for a substantial number of schizophrenics who do not respond to other drugs, according to a study presented last week in Chicago at the annual meeting of the American Psychiatric Association.

Clozapine rarely causes the movement disorders associated with other antipsychotic drugs, also known as neuroleptics, say the researchers. Weekly blood tests are necessary, however, to check for a potentially fatal weakening of the immune system in response to the drug.

"This is the first time that a rigorously controlled study of schizophrenics has demonstrated superior efficacy for one neuroleptic over the others," says psychiatrist Herbert Y. Meltzer of Case Western Reserve University in Cleveland. The study, conducted at 16 hospitals nationwide, was directed by Meltzer and psychiatrist John M. Kane of Long Island Jewish Medical Center in Glen Oaks, N.Y.

The ongoing project is being funded by Sandoz Pharmaceuticals Corp. in East Hanover, N.J., which will submit the data to the Food and Drug Administration later this year in an effort to gain approval of clozapine as a prescription drug. Sandoz will have a five-year patent on the drug if it gets the go-ahead from the FDA, says Meltzer.

The more than 300 schizophrenic patients in the study, who ranged from 18 to 60 years old, were among the most severe cases. They had shown no improvement for at least 2 1/2 years and no response to at least three neuroleptics. All subjects were first given haloperidol, a standard antipsychotic drug, for six weeks. Only about 2 percent improved. Most of the remaining patients were randomly assigned to treatment with clozapine or chlorpromazine, another standard neuroleptic, combined with a drug used to combat neurological side effects.

After six weeks of treatment, 30 percent of 125 patients on clozapine markedly improved, compared with 4 percent of 134 patients receiving chlorpromazine. Although standard neuroleptics usually take several weeks to become effective, some clozapine patients clearly improved in the first week of treatment. Ratings of patients' symptoms on three clinical scales were made by ward psychiatrists, psychologists and nurses.

Among patients who improved, says Meltzer, clozapine not only eased schizophrenic symptoms that respond to other neuroleptics, such as hallucinations, delusions and disordered thinking, but also lessened the social withdrawal and lack

of interest and motivation that do not usually improve with typical antipsychotic drugs.

Schizophrenia affects about 1 percent of the world's population, and approximately 300,000 people in the United States with some form of this disorder are not helped by available neuroleptics, says Meltzer. The fact that many treatment-resistant patients respond to clozapine suggests, contrary to the opinion of some psychiatrists, that such previous nonresponders do not have extensive brain damage, adds Meltzer. Clozapine does not "cure" schizophrenia, he notes, but it improves symptoms enough so that patients can function in the community and benefit from rehabilitation services.

But clozapine is not risk-free. Previous experience, both in Europe and with several hundred U.S. patients treated experimentally at several hospitals, suggests that about 1 percent of those given the drug will develop agranulocytosis, a reduction in certain types of white blood cells critical in fighting infection. Several deaths from this reaction have been reported in Europe, but none in the

United States.

Weekly monitoring of white cell counts, with discontinuation of clozapine if cell counts fall, usually reverses agranulocytosis, says Kane. No cases of agranulocytosis occurred in the new study.

"Clozapine should be available [through prescription], but it's not an unmixed blessing," says psychiatrist Jonathan O. Cole of McLean Hospital in Belmont, Mass., where about 40 schizophrenics have been treated experimentally with clozapine over the past 10 years. "There will be deaths from agranulocytosis when the drug is used in the community, because some schizophrenics will be hard to keep track of and monitor regularly," Meltzer adds that some psychiatric facilities may not have the resources to monitor white blood cell counts.

Clozapine's advantage, he says, is that unlike typical neuroleptics it rarely causes tremors, muscle rigidity, restlessness or the severe movement disorder known as tardive dyskinesia (SN: 7/20/85, p.45). Says Meltzer, "We need to understand why this drug is different from other neuroleptics." — B. Bower

## Advances reported in predicting violence

When the courts recently decided that presidential assailant John Hinckley Jr. should not be allowed to leave a psychiatric hospital to visit his family, the key piece of evidence was that Hinckley had written letters to convicted serial murderer Theodore Bundy. The question remains: If Hinckley had not written those letters, would he have been considered less dangerous to the community? Perhaps, but the fact that psychiatrists can only guess at such things points up how little is known, even among "experts"

"Psychiatrists should get out of the legal prediction system," says psychiatrist Antonio Convit of New York University (NYU) Medical Center in New York City. Perhaps because of the great fear of turning loose someone who will go on to assault or kill, behavioral scientists historically have erred on the side of "false positives" — predicting someone will become violent who, in actuality, does not. This has been a primary failing of hospital- and community-based predictive studies in recent years, according to Convit and others.

But Convit and his NYU colleagues now report violence-prediction results that he says are among the "strongest" to date. Convit is quick to point out that the studies were done in a closed psychiatric ward, where there is little contact with

outside society. Nevertheless, if this type of predictive model could be adapted to include the "risks" of the outside world, such as drugs, social stresses and homelessness, it might conceivably be applied to neighborhoods or communities, Convit suggested last week in Chicago at the annual meeting of the American Psychiatric Association.

In a three-pronged study, Convit and his colleagues first evaluated 69 patients on the "violent ward" at NYU's Manhattan Psychiatric Center and compared them with 40 nonviolent controls elsewhere in the hospital. This yielded four key "risk factors": conviction for violent crime; history of violent suicide attempt; a measurable (although not necessarily dramatic) neurologic abnormality; a "deviant" family environment, including a broken home, child abuse or a parent's substance abuse.

Then, in a preliminary predictive test, the researchers devised a scale of such factors and applied it retrospectively to 51 violent and nonviolent patients. They identified 35 of the patients correctly, Convit reports, with only eight false positives.

Finally, the researchers applied the test *prospectively* to 79 male schizophrenic patients admitted to the hospital. In a three-month follow-up of these patients

(80 percent of violent hospital incidents take place during the first three months, according to the researchers), Convit and his colleagues were correct in predicting violent behavior in 52 of the cases; the results included 19 false positives.

These results are striking, Convit says, particularly since psychiatrists have historically been right in violence prediction only 25 percent of the time; and the majority of those errors have been false positives. And of the few studies that have yielded statistics comparable to NYU's, he says, none has done so with just four

predictive variables — a great advantage in applying it to many people at a small cost. In addition, built into the NYU studies was a complex "odds ratio" factor, which takes into account the relative risk of a population — something lacking in many other studies, Convit says. There is a long way to go, says Convit, before psychiatrists can achieve the same degree of accuracy in predicting the actions of a released patient. But these studies, he says, show that "prediction of violence on a psychiatric ward can be done."

— J. Greenberg

## Highs and woes of runners' hormones

Runners who train more than 45 miles each week apparently have chronically elevated amounts of certain stress hormones — and therefore potentially harmful blood hormone profiles that are similar to those seen in patients with depression or anorexia, say scientists.

Researchers in Bethesda, Md., at the National Institute of Child Health and Human Development (NICHD), the Uniformed Services University of the Health Sciences and the National Institute of Mental Health found that certain runners maintained unusually high blood levels of adrenocorticotrophic hormone (ACTH) and cortisol, hormones that help the body adapt to stress. Data came from comparing subjects who did not exercise regularly to two groups of runners: one moderately trained by running 15 to 25 miles per week, the other highly trained at more than 45 miles per week. Blood samples were drawn from the 21 subjects — all men — during treadmill exercise, as well as at other times during the day.

While all three groups had elevated ACTH and cortisol levels during intense exercise, the levels in the highly trained group persisted at roughly 40 percent above those in the other groups. In a report in the May 21 *NEW ENGLAND JOURNAL OF MEDICINE*, the scientists say the reason for the exercise-dependent, chronic hormone elevation is unclear and may represent either "an adaptive change to the daily stress of strenuous exercise or a marker of a specific personality profile."

Although the hormonal similarities to depression and anorexia nervosa are intriguing, their significance remains a mystery. "This [study] opened a lot of new questions [about exercise and stress] we hadn't thought of before," coauthor George P. Chrousos of NICHD said in an interview. "The data will come, but we need more prospective studies where we follow the athletes through training. Until that time, we won't know for sure." He says a psychological study of 50 "compulsive athletes" is under way.

Whatever the cause, the hormones involved serve multiple functions in the body, and findings from the study may have broad implications, says Chrousos. He says elevated levels could be related to mild suppression of the immune system, because cortisol has been suspected for years of causing immunosuppression. Also, it could explain the reproductive-system problems seen in young athletes — male as well as female — undergoing endurance training. Moderation, say the authors, may be the best, since what "would be beneficial in the short term may be detrimental . . . over prolonged periods." — D.D. Edwards

## New benefits seen in vitamin A therapy

Severe vitamin A deficiency can lead to xerophthalmia (dry-eye disease), a leading cause of blindness among children in the developing world. To combat this, world health groups have for years been bringing low-cost eye exams and vitamin A supplements to malnourished regions. But new research indicates that blindness is not this deficiency's only major threat. Even those whose deficiency is not severe enough to cause blindness appear to be at increased risk of infection — a leading childhood killer in developing nations. A new test to diagnose the deficiency, along with dramatic increases in child survival where vitamin A therapy was tried, were reported last week at a congressional hearing.

Unpublished Indonesian field studies of the new eye test indicate that "five to 10 times as many children as previously believed may be suffering ill-effects of vitamin A deficiency — an estimated 25 to 50 million children every year," says Alfred Sommer, director of the Dana Center of the Wilmer Eye Institute at Johns Hopkins University in Baltimore. Sources of vitamin A include dairy products, carrots and leafy vegetables.

The test, which Sommer helped develop, involves pressing a small strip of filter paper against the white of the eye. If there are mucus-producing goblet cells on the eye's surface, some will adhere to the paper and show up when a stain is applied. The absence of such cells is not only the first symptom of developing xerophthalmia, but also an indicator of otherwise unapparent vitamin A deficiency, explains Keith P. West Jr., a Johns Hopkins nutritionist and collaborator of Sommer's.

In Sumatra, Sommer, West and Indonesian colleagues achieved striking reductions in childhood mortality through once-every-six-months administration of a high-dose vitamin A capsule. Their study, to be published next month in the *AMERICAN JOURNAL OF CLINICAL NUTRITION*, involved roughly 26,000 children under age 5 — half of whom received no capsules and half of

whom were directed to get supplements. (Any with dry-eye disease were excluded from the analysis.)

When the researchers compared mortality among children who received the supplement with that of children in the control villages, they found "an astounding 70 percent reduction in mortality" attributable to the vitamin therapy, Sommer reports.

Two related studies offer clues as to why the supplement affected mortality. One, published by Sommer and two colleagues in Tanzania in the Jan. 31 *BRITISH MEDICAL JOURNAL*, showed that among African children hospitalized with measles — a leading childhood killer in developing countries — the death rate can be halved by prescribing two high-dose vitamin A capsules in addition to standard medical care. Measles is known to deplete body reserves of vitamin A. This, the authors explain, "presumably reduc[es] the [body's] ability to resist secondary infections or their consequences, or both."

Last year, researchers at the University of Adelaide and Adelaide Children's Hospital in Australia reported that smaller supplements — equivalent to eating an extra half-carrot daily — reduce by 20 percent the number of acute respiratory infections contracted by allergic or respiratory-illness-prone children. Since the Australian preschoolers ate diets that contained — even before supplementation — what should have been sufficient vitamin A, the study suggests that a history of acute infection may increase one's need for the vitamin.

Vitamin A therapy "is inexpensive" and "may very well have the potential to reduce child mortality on an astounding scale," says Rep. Tony P. Hall (D-Ohio), who last week chaired a hearing of the House Select Committee on Hunger, where many of these findings were reported. Hall is heading efforts to increase U.S. funding for vitamin A supplementation in developing countries — from \$6 million this year, to \$8 million in the coming fiscal year.

— J. Raloff