Identifying the early warning signs of schizophrenia

For psychiatrists, diagnosing an emerging or recurring case of schizophrenia is often comparable to the task of art critics in deciding whether a painting is a masterpiece—they know it when they see it.

The canvas of schizophrenic disorders is splotchy and confusing, but the picture emerging from several research projects presented last week at the American Psychiatric Association meeting in Los Angeles is encouraging. It appears that a series of subtle symptoms, at least in some schizophrenics who have substantially recovered, can alert clinicians to an impending return of the disorder.

If these warning symptoms, which make up what researchers call the "prodromal" period, can be accurately identified, psychiatrists will be able to maintain recovered schizophrenics on low doses of antipsychotic drugs until larger doses are needed to prevent a relapse. This, it is hoped, will reduce the patients' risk of developing drug-induced involuntary movement disorders such as tardive dyskinesia.

Schizophrenia is actually a large group of severe disorders marked by disturbances of language and communication, thought, emotion and behavior that last longer than six months. Misinterpretations of reality can lead to delusions, hallucinations and bizarre behavior.

Recent data indicate that up to one-third of patients diagnosed as schizophrenic recover completely, and a significant number improve even after years of severe illness.

The new studies suggest that for schizophrenics who are well enough to be seen in outpatient clinics there are specific markers that indicate the disorder is about to get worse.

Stephen R. Marder and colleagues at the Brentwood Veterans Administration Medical Center in Los Angeles report that depression, paranoia, personal conflict and psychotic symptoms measured by two psychiatric rating scales are good predictors of relapse for schizophrenic outpatients.

Of 51 such patients, 19 became significantly worse in the two-year study period. Prodromal symptoms appeared about one week before schizophrenia flared up, says Marder. This pattern was similar for patients receiving both low and high doses of antipsychotic drugs.

"Pre-schizophrenia" symptoms often involve anxiety and depression and may be missed by clinicians, notes Marder. Even with careful monitoring, predicting a relapse is tricky.

Gauging a patient's subjective sense of whether symptoms are getting worse can make or break a prediction of relapse, says Douglas W. Heinrichs of the Maryland Psychiatric Research Center in Baltimore. He tested 50 schizophrenic outpatients, the majority of whom were poor urban blacks, and found that most report that the anxiety experienced before a relapse is different than that encountered at other times. Of 38 patients who reported prodromal symptoms, says Heinrichs, 24 knew the exact day the symptoms appeared. These patients were less likely to be rehospitalized than those who had no idea when the pre-schizophrenic period began.

In a sample of 140 schizophrenic patients and 80 family members interviewed using a specially designed questionnaire, 70 percent of the patients and 90 percent of the relatives were aware of symptom changes occurring about one week before relapse, reports Marvin I. Herz of the State University of New York at Buffalo. Again, symptoms centered around anxiety and thought disturbances. About one-third of the sample knew of a particular event leading to relapse.

At this point, however, the prodromal period is difficult to define, says Herz. Relapse is another slippery concept, he adds, since many stable schizophrenic outpatients still have symptoms that can hamper normal functioning.

There are other important questions about this research, observes John S. Strauss of Yale University, a pioneer investigator of schizophrenic relapse. Why, he asks, are the prodromal changes reported relatively small and hard to pick up without carefully monitored self-reports? When do symptoms represent a reaction to psychological or social stress, and when do they signal a recurrence of full-blown schizophrenia?

"So far," says Strauss, "a lot of the findings are noise because we don't know what the proper signal is." —*B. Bower*

Nouvelle cuisine: Bacteria's nylon feast

It has been just 45 years since the first fibers of nylon came winding off the assembly line. Yet already at least one opportunistic microorganism has adapted its palate to consume a byproduct released by nylon factories. The adaptation, which includes production of two apparently new enzymes, has led biologist Susumu Ohno to propose a special source for such "truly unique" proteins. "The swiftness with which these two enzymes have evolved is truly remarkable, for several decades are but a flash in the evolutionary time scale," he says.

Twentieth century microorganisms facing an onslaught of man-made compounds may find themselves in the same situation as organisms at the very beginning of life: Both groups need to create almost simultaneously a variety of proteins with novel functions, suggests Ohno, of the City of Hope Hospital in Duarte, Calif. The traditional explanation of new proteins is that a pre-existing gene duplicates, then one copy evolves gradually to a new form.

In contrast, Ohno suggests that new genes can arise from a genetic change that shifts the DNA "reading frame," making the same DNA sequence represent a different protein. This shift is possible because the amino acids of a protein are encoded in DNA as three-unit (three-nucleotide) "words" or triplets. If the grouping into triplets is shifted, the same stretch of DNA gives a different set of three-unit words, thus a different set of amino acids. There are a few natural examples where DNA in a single organism is used in more than one reading frame (SN: 4/22/78, p. 268).

Three of the 64 possible DNA triplets represent "stop" signals instead of amino acids. Often shifting the reading frame of a long stretch of DNA does not result in a protein because the new grouping produces stop signals in inappropriate positions. But Ohno argues that such premature terminations are much less likely if the original gene is made up of repeated sequences, preferably of a length not evenly divisible by three. He and others have suggested that all proteins were originally endowed with short periodicities, maintained to various degrees in modern genes.

This explanation fits the "sudden birth" of the nylon-byproduct degrading enzymes that were discovered last year in bacteria living in effluent from a nylon plant in Japan, where nylon has been produced commercially for about 30 years. Scientists at Osaka University found the genes in regions of repeated sequences on a plasmid, a circle of DNA, within *Flavobacterium* Sp. KI72.

Ohno now suggests in the April PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (No. 8) that one repeated sequence originally coded for a chain of about 430 amino acids, which due to its composition is not likely to have functioned as an enzyme. A simple DNA change — the insertion of one unit, the nucleotide thymidine — created a stop signal that silenced the original gene. At the same time, that change created the starting point for a new gene read in a different frame, encoding a nylon degradation enzyme, a chain of 392 amino acids.

"Gene duplication [and subsequent modification] would take too many years," Ohno says. "To change just 1 percent of the sequence takes about a million years. But genes that can be used in different reading frames generally have 20 to 40 percent differences. [The new enzyme] in one swoop has acquired the capacity to degrade man-made nylon byproducts."

—*J.A. Miller*