

## Getting to the Source of Schizophrenia

**T**here is nothing more terrifying than losing one's mind.

Schizophrenia is a terrifying brain disorder that affects one in 100 Canadians – and causes this very problem.

Three hundred thousand Canadians suffer from schizophrenia at one point in their lives, and their problems include disorganized thinking, paranoia, hallucinations and social withdrawal ([www.schizophrenia.ca](http://www.schizophrenia.ca)). While drugs have been available to control this disorder since the 1950s, the origins of schizophrenia are still a mystery.

For the bulk of my career, I have devoted myself, as physician and researcher, to uncovering the mysteries of this disorder, so that we might understand it, treat it – and maybe even cure it.

### DOPAMINE SENSITIVITY

The origins of schizophrenia remain unclear. Some scientists believe it may arise from abnormalities in brain structure or inappropriate connections of neurons. A common view is that genetics has an important role, and it is currently assumed that only a few altered genes create a predisposition to develop schizophrenia.

Thanks to a CIHR-funded international study involving 16 researchers from eight universities, including the University of Toronto, Emory University (in Atlanta, GA), McGill University, McMaster University, Oregon Health and Science University, Duke University (in Durham, NC), the University of Kuopio (in Finland) and the University of Washington, we have come to the conclusion that many altered genes can lead to dopamine supersensitivity, making an individual vulnerable to psychosis. (Dopamine is a neurotransmitter that allows people to move, think and feel.) Although this work was done with rats, the principle readily applies to humans ([www.pnas.org/content/vol102/issue10/](http://www.pnas.org/content/vol102/issue10/)).

### For years, researchers have been trying to discover the altered genes

In the mid-1970s, when I discovered the antipsychotic receptor now known as the dopamine D2 receptor, I also discovered that these receptors are elevated in 50% of patients who have schizophrenia. Brain imaging of living schizophrenia patients show elevated levels of D2 receptors in some cases, but not all.

Because most individuals with schizophrenia are supersensitive to dopamine, we looked for evidence of supersensitivity in the D2 receptors themselves, and this is exactly what we discovered in rats with various altered genes. Our international team showed that, in essence, when various genes are altered, the brain is provoked to try and protect itself. Compensation for this abnormality takes the form of readjusted supersensitivity of the dopamine D2 receptors, which account for movement and thought. A supersensitive dopamine system can, in turn, cause the recurrence of hallucinations and delusions that schizophrenics regularly suffer.

### NEXT STEPS

For years, researchers have been trying to discover the altered genes that could bring about schizophrenia. Our discovery offers new directions for research, including a method to detect such altered genes. In fact, genes that are altered but that do not lead to supersensitivity can be ruled out as likely to trigger the disease.

Schizophrenia has traditionally been difficult to diagnose. Some of its characteristics resemble those of bipolar disorder (or manic depression). Our discovery should lead to improved diagnoses using brain scanning to assess the supersensitive state of these receptors – work that is now in progress.

Earlier specific diagnosis and treatment could provide considerable savings to the Canadian healthcare system. As it stands, schizophrenia costs Canadians more than \$2.3 billion in direct healthcare costs and an additional \$2 billion in indirect costs ([www.schizophrenia.ca](http://www.schizophrenia.ca)).

Most importantly, if we find the mechanism that triggers dopamine receptors into their supersensitive state, we can find new drug treatments. If we control that mechanism, we may be able to put an end to a disorder that has been caught up in mystery for centuries.

### About the Author

Dr. Philip Seeman is a Professor in the Departments of Pharmacology and Psychiatry at the University of Toronto. He holds a medical degree from McGill University (1960) and a PhD from Rockefeller University (1966). Dr. Seeman's groundbreaking work in the fields of schizophrenia and neuroscience has led to fundamental contributions to the understanding of dopamine receptor systems in the brain, systems now known to be involved in a variety of diseases including Parkinson's and schizophrenia. He has received innumerable awards, including the Prix Galien (1994), the Isaak Walton Killam Memorial Prize in Medicine (1996) and the Order of Canada.