

DR. SOL SNYDER: CREATIVITY IN PSYCHOPHARMACOLOGY RESEARCH ... WITH THE SPARK OF A TRUE MENTOR

As a young man deciding upon his future career, Dr. Sol Snyder reached one of the defining moments of his life when he realized he had to choose between becoming a classical musician or a doctor. Fortunately for the field of neuropsychopharmacology, he chose to pursue science and medicine – and he now believes that the medical research he conducts is even more creative and inspiring than playing the classical guitar.

Nearly 50 years after that decision, Snyder has become one of the world's most preeminent neuroscience researchers. His decades-long career has focused primarily on neurotransmitters – the chemicals that act as messengers between neurons in the brain. His lifetime of work has laid the foundation for the numerous prescription medications that have been developed in the past three decades to treat various forms of mental illness. And the techniques pioneered in his laboratories have revolutionized drug development in every therapeutic category, permitting earlier, faster and more accurate testing of a chemical's effectiveness in treating mental disorders.

Snyder's first career-defining moment came while he was giving classical guitar lessons to a research associate at the National Institutes of Health (NIH). The music student invited Snyder to work with him over the summer at NIH before Snyder entered medical school in the fall. That serendipitous invitation introduced Snyder to the world of neuroscience research. After spending a summer at NIH, Snyder realized that medical research could be a truly “creative experience, more akin to being a composer” than simply pouring through science textbooks. He spent each of his subsequent summers at NIH and, during his military service following medical school, obtained a research position at the agency which would transform his professional interests and career even further.

While in medical school, Snyder had developed a scientific interest in prescription medicines. “I saw that in medicine,” he said, “you either operate on patients or give them a drug.” At the time, little was known about how the drugs actually worked – a knowledge gap which intrigued Snyder as a researcher. During his military service at NIH, Snyder was assigned to the lab of Dr. Julius Axelrod, the man who subsequently won the Nobel Prize for his research on neurotransmitters and the drugs that affect them.

Working with Axelrod enabled Snyder to merge his interest in neuroscience with his interest in psychiatry – but it was significant for another reason as well. “Working with Dr. Axelrod was the defining event in my *scientific* life,” Snyder said. “He was the perfect mentor.” In the career that was to follow, imprinted with this strong sense of the power and value of mentorship, Snyder would become known and respected for his role as an outstanding mentor to research students.

Following his tenure in Dr. Axelrod's laboratory, Snyder eventually became a psychiatry resident at John Hopkins, while simultaneously serving on the faculty of its pharmacology department. President Richard Nixon's war on drugs in the early 1970s provided the opportunity for some of his first significant medical discoveries. Using funding available for research on opiates, Snyder's laboratory developed a novel scientific technique called “ligand binding” that involved binding radioactive chemicals to brain cells. This technique enabled his discovery of the opiate receptor in the brain, which enabled researchers to ask and answer questions on how opiates act in the body – how and why they cause euphoria, reduce pain, create physical and psychological dependence and even cause constipation.

Snyder and his team used the technique to identify the receptors for all the major neurotransmitters in the brain, including the dopamine receptor. Their research verified that antipsychotic drugs worked by blocking dopamine receptors and showed that a drug's potency in blocking dopamine paralleled its

potency in alleviating psychotic symptoms. Other highlights resulting from this use of this technique included the identification of the GABA receptor where Valium attaches; the adenosine receptor, which permits caffeine to affect the brain; and the bradykinin receptor, which is involved in pain transmission. His team also used it to identify and discriminate two subtypes of serotonin receptors, presaging the appreciation of multiple serotonin receptors and the development of receptor-subtype selective drugs such as the antimigraine triptan drugs, which were the first medications developed to actually stop the migraine attack and its symptoms.

Not surprisingly, the ligand binding technique had a dramatic impact on drug development. Prior to the mid-1970s, psychotropic drugs were tested almost exclusively in laboratory rats through injection and observation – a tedious process that required the synthesis of large quantities of chemicals and great amounts of time. Snyder's technique enabled researchers to measure of receptor targets in test tubes with only small amounts of chemicals, and to conduct hundreds, even thousands, of tests a day.

Snyder's team furthered its initial research on opiates by looking for the brain's neurotransmitters that would bind to the opioid receptors. This led John Hughes and Hans Kosterlitz to discover endorphins and enkephalins – the naturally occurring “opioids” that form the basis for feelings such as the “runner's high” – which has led to a greater understanding of their effect on our emotions and perceptions of pain.

As his career progressed, Dr. Snyder's work would go on to change the very understanding of the nature of neurotransmitters – including the discovery that a gas could serve as a neurotransmitter. In the late 1980s, after nitric oxide was identified as being responsible for blood vessel relaxation, Snyder pondered whether this gas also might have a function in the brain. After developing a novel technique to monitor the conversion of the amino acid arginine to the gas, Snyder's team identified, isolated, and cloned the gene for the enzyme that makes nitric oxide. This research led to findings of this unique neurotransmitter's true function in different organs, including its role in penile erection. Under researchers at Pfizer, this work spurred the eventual development of Viagra for the treatment of erectile dysfunction.

In the 1990s, Dr. Snyder continued to research other novel neurotransmitters, discovering that the amino acid D-serine also functions as a neurotransmitter. Snyder's team found that this chemical is not located in the brain's neurons, but in the glia – the supportive cells of the brain. Further research by Snyder's team found that D-serine acted together with glutamate. The excess release of glutamate is thought to play a role in many neurodegenerative diseases by acting upon the NMDA receptors that are crucial to learning and memory. Previous attempts to block the NMDA receptors activated by glutamate had resulted in a host of adverse side effects. By identifying the specific enzyme that converts L-serine to D-serine, Snyder's team made it possible to develop a drug – one which is now being tested in animal studies – that inhibits only that specific enzyme, resulting in a drug with potentially fewer side effects. This research has important future implications for developing better tolerated medications for the treatment of Alzheimer's, Parkinson's disease and other neurodegenerative diseases.

When Dr. Snyder began his research career almost 50 years ago, only three neurotransmitters were known to man. Today, nearly 100 different neurotransmitters have been identified – many as a direct result of his efforts. He has been honored repeatedly over the course of his career for his achievements. He is the recipient of the nation's highest scientific honor, the National Medal of Science; the highest medical research honor, the Lasker Award; as well as a host of other awards from organizations including the American Psychiatric Association, the Society for Neuroscience and the National Alliance for Research on Schizophrenia and Depression. He has been elected to membership in numerous honorific societies including the United State National Academy of Sciences, the American Philosophical Society, the American Academy of Arts and Sciences, the Institute of Medicine, and is the recipient of six honorary doctorates. Dr. Snyder was admitted as a Fellow into the American College of

Neuropsychopharmacology in 1969, and exemplifies ACNP's mission of advancing the scientific understanding and treatment of psychiatric, neurological, behavioral and addictive disorders through research and education.

In recounting the many scientific discoveries emanating from his lab, Dr. Snyder is quick to credit the students under his tutelage. Many of the students he mentored not only accomplished significant research under his guidance, but went on to become luminaries in the field of neuroscience themselves. A roll call of his students reads like a "who's who" of modern neuropsychopharmacology: Joe Coyle, M.D., Eden S. Draper Professor of Psychiatry and Neuroscience at Harvard Medical School; Anne Young, M.D., Ph.D., Chair of Neurology at Harvard Medical School, David U'Prichard, Ph.D., former CEO of 3-Dimensional Pharmaceuticals, Inc.; David S. Bredt, M.D., PhD. Vice President, Integrative Biology, Eli Lilly and Company; Stephen Strittmatter, M.D., Ph.D., Vincent Coates Professor of Neurology, Yale Medical School; Jay Baraban, M.D., Ph.D., Professor of Neuroscience at Johns Hopkins University School of Medicine. And those are just a few.

Dr. Snyder's devotion to mentorship is one the reasons the Psychiatric and Mental Health Congress recognized him with its "Teacher of the Decade" award. His brand of mentorship seeks to foster an environment of collaboration and ownership, while simultaneously helping students refine and hone the direction of their research. "The one thing students need to learn from a mentor," he said, "is strategic wisdom in selecting a problem and direction in how to solve the problem." He likens this part of the mentoring process to parenting or psychotherapy – listening, guiding, encouraging and providing unconditional positive support.

The other key to successful mentoring, according to Dr. Snyder, is creativity and inspiration – a philosophy that takes him back to his training as a classical guitar instructor. Dr. Snyder believes mentorship must be inspirational and personal because the process of "creative discovery can no more be learned from a book than you can learn to play the piano from a book." He believes each student researcher needs someone who can convey to them a creative spark. For Dr. Snyder, Julius Axelrod had that spark. Since then, he has strived to act as that spark for other.

Nearly 50 years after choosing medicine over music, Dr. Snyder continues to believe that psychiatric research is an extremely creative career. And he still finds classical music an appropriate metaphor for the research process. "Good science is like composing a symphony," he said. "It is a creative enterprise ... creating something that wasn't known before. In fact, it's more rewarding than being a composer, because who is to say that your composition is any good? In science, discoveries can be verified, and one's success isn't only subjective." But, most important, he stresses, his life's work in psychopharmacological research has had a direct bearing on treating illness and on helping others.

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Dr. Snyder is a Fellow of the American Philosophical Society, of the Institute of Medicine, the U.S. National Academy of Sciences and of the American Academy of Arts and Sciences. Dr. Snyder is also a Fellow of the American College of Neuropsychopharmacology.

*Dr. Snyder is the recipient of numerous professional honors, including:
National Medal of Science (2005)*

Goldman-Rakic Award (2002) and Lieber Prize (2001), National Alliance for Research on Schizophrenia and Depression
Sarnat Award, Institute of Medicine, National Academy of Sciences (2001)
Ralph Gerard Prize, Society for Neuroscience (2000)
Judd Marmor Prize (2000), Distinguished Service Award (1989), Special Presidential Commendation (1985), and Hofheimer Award (1972), American Psychiatric Association
Bristol-Myers Squibb Award for Distinguished Achievement in Neuroscience Research (1996)
Baxter Award, American Association of Medical Colleges (1995)
Bower Award, Franklin Institute (1992)
Taylor Award, Roberts Institute (1990)
Scientific Achievement Award, American Medical Association (1985)
Einstein Award for Research in Psychiatry and Related Disciplines, Albert Einstein College of Medicine of Yeshiva University (1984)
Wolf Prize in Medicine, Wolf Foundation, Israel (1983)
Goodman and Gillman Award, American Society for Pharmacology and Experimental Therapeutics (1980)
Taylor Manor Award (1981)
Distinguished Research Award, Association for Research in Nervous and Mental Disease (1978)
Albert Lasker Medical Research Award for Basic Biomedical Research (1978)
Research Pacesetter Award, National Institute on Drug Abuse (1977)