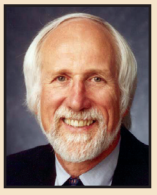
An Interview with William T. Carpenter, Jr., MD



Dr. William T. Carpenter, Jr. is a Professor at the University of Maryland School of Medicine and the Director of the Maryland Psychiatric Research Center. He obtained his medical degree from the Wake Forest University School of Medicine and undertook postgraduate training at the University of Rochester Medical Center. He began his research career with the National Institute of Mental Health Intramural Program in 1966, using neuroendocrine strategies to study the psychobiology of affective disorders. He has also been a collaborating investigator with the World Health Organization's International Pilot Study of Schizophrenia. Dr. Carpenter is the Editor-in-Chief for *Schizophrenia Bulletin*, serves on the editorial boards for numerous other psychiatry journals, and has authored over 350 publications. Dr. Carpenter is Past-President of the American College of Neuropsychopharmacology and participated in the founding of the National Alliance for Research on Schizophrenia and Depression (NARSAD) and chairs the scientific program committee. He chairs the work group responsible for psychotic disorders in preparation of *DSM-V*, and has been the recipient of national and international research awards, including the Lieber Prize from NARSAD. Dr. Carpenter was elected to the Institute of Medicine of the National Academy of Sciences in 1998.

***CS:* You are Editor-in-Chief of another schizophrenia journal—*Schizophrenia Bulletin*—and it has made a great contribution to our field. What is it like to run a journal?**

WC: I have been a fan of *Schizophrenia Bulletin* since the first issue in 1969. One of the nicest experiences that I have had with any journal was in the early 1970s when the *Bulletin's* then editor, Loren Mosher, asked John Strauss, John Bartko and me to publish what we thought we had learned in the International Pilot Study of Schizophrenia. This was a chance to think and synthesize, and in 1974 the *Bulletin* carried a series of articles wherein we proposed a paradigm shift for the study of schizophrenia. Rather than treating a heterogeneous syndrome as though it were a disease entity, we proposed that our data analyses established domains of psychopathology within the syndrome as the key targets for etiological and therapeutic discovery. The *Bulletin* provided a terrific opportunity for us, and was a focal point for the schizophrenia clinical and research communities as the field matured.

When the NIMH/NIH decided to discontinue responsibility for publishing the *Bulletin*, it had dropped in prestige and influence. In partnership with Oxford University Press, we (the Maryland Psychiatric Research Center and the Department of Psychiatry, University of Maryland School of Medicine) assumed responsibility, beginning with the first issue in 2005. The work is time consuming, but very gratifying. The field has been tremendously responsive, enabling us to publish high-quality themes, special features and original data papers receiving rapid and rigorous review. I have been thrilled as the impact factor for the *Bulletin* has advanced from #30 of 92 psychiatric journals to #6 in just two years, and to #3 of 84 social science journals.

Serving as editor has been a wonderful social experience. There is a continuous flow of informative and friendly interactions with outstanding professionals around the world. And at home, working with colleagues Gunvant Thaker, Paul Shepard and our managing editor, Janet Smith, has been deeply gratifying. Shelley Andrews was our first publisher at Oxford University Press and got us off to a terrific start—a tradition now continued with Todd Hummel.

***CS:* What did you learn early on in your career that has turned out to be important or helpful to you?**

WC: Learning to be a physician and a psychiatrist with depth in psychopathology provided the foundation. Critical additions included understanding the limitations of reductionistic models and the validity of the biopsychosocial medical model, the importance of moving from descriptive data to hypothesis falsifying scientific research, and critical appraisal of dominant ideas and paradigms.

***CS:* What advice would you give to residents who are considering a career in academic psychiatry today?**

WC: First I would say that academic medicine can provide fantastic opportunities for personal fulfillment in areas driven by idealism and intellectual challenge. And second, I would say that developing an area of expertise with passionate commitment is essential for an academic career to be gratifying. If the creative acquisition of knowledge is the basis for choosing an academic career, then early training in research with careful choice of mentors is essential. Getting there gradually without benefit of an intensive scientific learning experience often leads to disappointment.

CS: **You have mentored many of today's leaders in schizophrenia research. What, in your opinion, are the key ingredients for successful mentorship?**

WC: Mentors must be able to provide mentees with the opportunity to advance their own science and to experience maternal/paternal gratification with the independent success of their mentees. Mentors and mentees must find the mutual interest and areas of shared accomplishment that provide the glue in the relationships, without undermining the mentor's productivity or the mentee's development of independent science.

CS: **The Maryland Psychiatric Research Center (MPRC) is a premiere center with a worldwide reputation for schizophrenia research. In setting up this program, what was your vision for the MPRC and has that changed over time?**

WC: When I came in 1977 to the MPRC as Director, the institution had been moved from the state to the university for scientific administration. There were essentially no guidelines or parameters except budget and facility. Perhaps more than vision, I had a few simple beliefs and a chance to put them into practice. These principles continue to guide the MPRC. They include:

1. Schizophrenia is a lead illness for psychiatry.
2. Translational science requires excellence in clinical and basic neuroscience (and you will not have one without the other).
3. Each faculty would be responsible for peer-reviewed success of research rather than a model based on a limited number of leaders with other faculty as followers.
4. Recruitment of faculty interested in collaborations across disciplinary lines rather than selecting faculty to fill prespecified roles in a collaborative program.
5. Establishing a work environment which facilitates spontaneous collaborations and instills a sense of community across all faculty and staff.
6. Placing high value on the integrity of scientific work and deep respect for the autonomy and well-being of persons with schizophrenia who participate in research.

We have been faithful to these principles with the result of an exceptional intimacy between basic and clinical scientists. Collaborations evolve from each investigator's central interest, and this has set the stage for a number of successful "center" applications for external funding. In the process, we have been gratified by the success of postdoctoral fellows and young faculty, and by the opportunity to establish unique programs for the care and study of persons with schizophrenia and related illnesses.

CS: **In thinking about the state of treatment for schizophrenia when you started at MPRC, and comparing it to treatment today, has there been much improvement and in what areas?**

WC: Advances in therapeutics over the past thirty-two years have been very modest. There is more respect now for interpersonal therapeutics with specified goals and procedures and evidence for efficacy and/or effectiveness. Supported work programs for persons who desire these services have perhaps the largest effect size advance in the field. However, cutting edge psychosocial services are simply not available to most patients.

Advances in psychopharmacology have been even more limited. All drugs marketed for schizophrenia today initiate action at the D2 dopamine receptor. This means sixty years without producing drugs with novel mechanisms of actions. Advances since chlorpromazine are essentially broadening the range of adverse effects. The drugs are extensively similar in antipsychotic action and lack documented efficacy for negative symptoms and cognitive impairments. Clozapine, discovered before I came to MPRC, is the only drug with clearly documented superior efficacy in a subgroup of patients. But even here the profile of symptomatic relief is similar to other antipsychotic drugs and the pharmacological mechanism involved in superior efficacy is not known. The newer drugs fail to offer decisive advantage over older drugs as was clear in a critical appraisal of the early trials and confirmed in the CATIE and CUtLASS publically sponsored head-to-head comparisons. With the new range of adverse effects, the clinician has a better chance to fit the individual patient to a drug choice based on reducing the risk component of the risk/benefit ratio. Concerns about tardive dyskinesia have been joined with concerns of metabolic effects which may shorten the already remarkably reduced life span of persons with schizophrenia.

While very disappointed in progress to date, I am optimistic that the recent emphasis on cognition and negative symptoms as indications for drug development reflects a paradigm shift enabling the field to break out of the dopamine antagonist antipsychotic box and make truly innovative and novel discovery.

CS: **What has been the greatest joy in your career?**

WC: This is a tough question because there are many high points. I will answer in terms of the quality of my own life. Here it is easy. The daily pleasure, stimulation, friendship and shared goals with close colleagues. There is something special in the continuous involvement with others in thinking, learning, problem solving, and shared accomplishment.

CS: **What has been the greatest disappointment in your career?**

WC: Two things stand out. First is the failure of the field to shift paradigms and conduct more decisive scientific work by addressing specific domains of pathology rather than addressing a heterogeneous syndrome as though a distinct entity. Second is the continuous shortfall in facility and financial support. Many creative advances are not undertaken and the pressure on successful recipients of grants to do more with less is an untoward stress in the lives of investigators.

***CS:* If you knew earlier in your career the information that we now know about schizophrenia, what kind of research would you have pursued—and why?**

WC: I have spent some time on this question trying to be other than self-satisfied. Didn't work. I would do the work we just proposed (with funding success) for a new NIMH Center grant. We address critical points of missing knowledge:

- Do negative symptoms and cognition impairments emerge from the same latent structure, or are they separate pathways for drug development?
- Can endophenotypes related to cognition and negative symptoms be used to create a human model for early drug proof of concept testing for novel compounds?
- Will mapping these endophenotypes to a rat model provide a predictive screen for cognition and/or negative symptom efficacy in the human condition?
- Will novel compounds of theoretical interest for cognition and social affiliation prove efficacious in a clinical trial where subjects are selected according to endophenotype?

This brings my longstanding interest in heterogeneity reduction and domains of pathology to the practical level of novel compound selection and testing from rat to human to clinical trials models informative on the critical unmet therapeutic needs in schizophrenia.

***CS:* You are chairing the *DSM-V* working group on schizophrenia. How do you think this will influence clinical practice?**

WC: The greatest potential for change is in three areas:

- Dissociate catatonia from schizophrenia to recognize its frequent comorbidity with mood disorders and general medical disorders and increase attention to specific diagnostic and therapeutic measures which may be overlooked if considered another aspect of schizophrenia.
- Introduce obligatory dimensions parallel with categorical diagnostic class to draw specific attention to the presence or absence of potential therapeutic targets such as depression, mania, anxiety, sleep/wake disturbance, and cognition.
- Create a risk syndrome category based on recent studies identifying persons at high risk for psychoses and validation of criteria based on conversion to psychotic illness.

***CS:* What do you think are the major opportunities for schizophrenia research over, say, the next ten years?**

WC: There are many areas of promise, and I am limited in my knowledge. Nonetheless, here are a few nominees:

- Deemphasize large scale search for genes for syndromes and determine if genotype/phenotype relations are more robust and informative regarding potential pathophysiology and etiology.
- Recognize the robust contribution of environmental risk factors and explore the neurobiology of gene/environment interactions.
- Explore the contribution of epigenetic alterations to pathophysiology.
- Give emphasis to developing technologies as applied with postmortem tissue to more directly tackle the neuropathology issues.
- Given the range of animal models now developed with the potential to relate to key phenotypic manifestations of schizophrenia, establish platforms for gene/environment interactions; ascertain predictive validity of animal models for early compound screening for unmet therapeutic needs in schizophrenia.
- Determine if early intervention in advance of psychosis with compounds with efficacy for cognition and/or negative symptoms will modify onset of psychosis or alter long-term functional outcomes.
- If a new antipsychotic drug is developed without dopamine antagonism, determine if effects are additive or synergistic with dopamine antagonist antipsychotic drugs.
- Answer many less fundamental but more practical questions such as optimal integration of psychosocial and pharmacological treatment; optimal dosing of drugs and what to do if response is not satisfactory; determine most effective approach to substance abuse in schizophrenia; and, address the increased mortality rate associated with schizophrenia.
- Develop biomarkers which relate more fundamentally to pathophysiology and use these data to reconceptualize the nosology of mental illness.
- Most of all, take risk factors seriously and push translation into prevention.

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