Identifying Unmet Therapeutic Domains in Schizophrenia Patients: The Early Contributions of Wayne Fenton From Chestnut Lodge

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Wayne Fenton, MD, died on September 3, 2006, while giving emergency clinical care. His leadership at National Institute of Mental Health provided a framework for therapeutic discovery. He crafted a new approach to psychosis based on poor functional outcomes and the psychopathology domains underlying long-term morbidity. His research and clinical observations during his career at the Chestnut Lodge clarified the unmet therapeutic needs in schizophrenia and provided the foundation for his vision. The results have radically changed the paradigm for discovery with emphasis on impaired cognition and negative symptom psychopathology.

Key words: psychopathology/schizophrenia/cognition/negative symptoms/Fenton

Introduction

Wayne Fenton came to Chestnut Lodge Hospital in 1984 following his psychiatric training at Yale. He was drawn to the opportunities it offered for in-depth longitudinal encounters with persons suffering from serious mental illness, primarily schizophrenia. He became involved in the Chestnut Lodge Follow-Up Study which had been underway for about 5 years, and which had recently published the first 2 reports on the design, methodology, and study sample1 and on the long-term outcome of schizophrenia and the affective disorders.2

Fenton was deeply immersed in schizophrenia, first as a clinician treating long-term patients and second as an investigator plumbing the depths of the hospital medical records to reconstruct in detail the Lodge patients admitted to the hospital between 1940 and 1975. This double exposure to current schizophrenia as a treating clinician and to past schizophrenia as an archeological phenomene-

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History Relevant to the Sample Studied by Wayne Fenton: Chestnut Lodge Hospital in Context

Chestnut Lodge Hospital (which closed in 2000) was a private, family-owned 100-bed adult inpatient psychiatric facility that opened in 1920 and was located approximately 10 miles north of Washington, DC, in Rockville, Maryland. The dual influences of Frieda Fromm-Reichman and Henry Stack Sullivan in the 1930s and 1940s led to its evolution into a long-term psychoanalytically oriented treatment facility. In the period between 1940 and 1975, the average length of stay was approximately 2 years. Each patient was housed on an inpatient ward or cottage run by an administrative psychiatrist. Each patient was also assigned a psychiatric therapist for intensive psychoanalytically oriented psychotherapy 4-5 times per week. Antipsychotic drugs were not available in America until the late 1950s; even then they were used sparingly at Chestnut Lodge until the 1970s.

The psychoanalytic culture of Chestnut Lodge placed high value on all forms of information about the patient: familial, developmental, phenomenological, diagnostic, and treatment. All these facets were regarded as potentially useful, and great efforts were extended to obtain
prior records and to record and transcribe ongoing clinical conference discussions. As an example, the patients’ admission conference did not take place until 3 months into the hospitalization in order to allow sufficient time to obtain as much information as possible. This included all records of prior hospitalizations and treatments, extensive diagnostic and dynamic evaluations of family, detailed accounts of the patient’s development and life transitions, and exhaustive descriptions of the patient’s clinical course, from prodrome to first psychosis to each subsequent relapse and intervening treatment. All this information was collected and presented by the therapist to the medical staff at a 90-minute admission conference. Subsequent observations of the patient by the therapist and hospital staff were gathered over the ensuing months and years of the patient’s hospital career, and these too were reviewed on an annual basis by the entire medical staff in a 2-hour case conference. Starting in the early 1940s, every admission and case conference was transcribed by a court reporter and typed up for key members of the patient’s treatment team and for the record room. These were the records available to Wayne Fenton for scrutiny, clinical narratives and descriptions literally averaging more than 100 single-spaced type-written pages per patient.

History Relevant to the Sample Studied by Wayne Fenton: The Chestnut Lodge Follow-up Study in Context

Details of the Chestnut Lodge Follow-up Study are available elsewhere. Briefly, the study was retrospective in design and incorporated 6 elements to ensure methodological rigor (operationally defined diagnostic criteria, adequate demographic/predictor characterization of samples, outcome measured multidimensionality, independence of follow-up data collection from the diagnostic and demographic/predictor data collection, reliability resting of all measures, and bias testing of missing subject subsamples).

Included in the follow-up study were all patients discharged between 1950 and 1975 and a smaller cohort of nondischarged inpatients from a comparable period. Selected were those without organic brain syndrome, who were between 16 and 55 years of age on admission and who were treated at Chestnut Lodge for a minimum of 90 days.

Outcome data were collected, following informed consent, an average of 15 years after discharge (range, 2–32 years) via interviews with the subjects and/or significant others. Interviews were conducted and rated by Thomas McGlashan or by research-trained social workers. The information gathered was sufficient to rate 38 outcome dimensions with an average reliability of 0.71 (κ and interclass correlations).

For baseline data, the voluminous index hospitalization medical records were transposed onto a 25-page document called the chart abstract from which each patient was rated by members of a trained team of raters on 56 demographic/predictor variables and 49 symptom variables, all with a missing data rate of 12% and with an average interrater reliability of 0.67 (κ and intraclass correlations). Using these abstracted clinical data, all patients were scored according to 8 current diagnostic systems, including the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III).

Follow-up information was obtained on 446 patients or 72% of the possible sample. A larger sample (n = 532) of clinical charts was abstracted and rated, however, to test for biases in subgroups of patients on whom follow-up was not obtained either because they refused participation or because they proved nonlocatable.

Among the larger baseline sample, 188 patients were given a diagnosis of schizophrenia based on application of research diagnostic criteria (mostly DSM-III) to the chart abstracts. The reports of the long-term outcomes of the major diagnostic groups, including schizophrenia, derived from diagnostic groups created from the chart abstracts.

Wayne Fenton’s Contributions to the Subtypes and Other Syndromal Forms of Schizophrenia

Subtypes

To explore schizophrenia in detail and depth, Fenton targeted all the patients whose diagnosis of schizophrenia had been confirmed with DSM-III criteria using the chart abstracts and the original archive of each patient. To study the classical subtypes of schizophrenia, he rated from the original records using 4 criteria sets. To study the positive and negative subtypes, he rated the records using several scales and subtype systems. The reliability of these ratings was tested between Fenton and another rater working independently on 26 cases and found to be satisfactory.

Fenton also coded 26 clinical elements that represented significant components of illness neutral history. These elements were grouped into 8 domains: genetic predisposition, developmental problems, premorbid functioning, illness onset features, early illness course, subtype stability, long-term functional outcome, and suicide risk. He compared subtype groupings with each other across these 26 illness components, thereby generating lifetime clinical profiles for each subtype. Sufficient data were available in the records to subtype 187 of the 188 patients diagnosed with schizophrenia.

His first publication in this realm involved the classic subtype criteria, ie, patients meeting operational criteria for paranoid (n = 78), hebephrenic (n = 26), and undifferentiated (n = 83) schizophrenia. Paranoid schizophrenia had an older age at onset, often developed...
rapidly in individuals with good premorbid functioning, tended to be intermittent during the first 5 years of illness, and good outcome or recovery was more often observed in this subgroup. Hebephrenia had an earlier age at onset, often developed insidiously, and was associated with a family history of psychopathology, poor premorbid functioning, and a continuous illness with poor outcome. Undifferentiated schizophrenia was also early and insidious in onset but unlike hebephrenia, it was associated with an early history of behavioral difficulties and resulted in a less deteriorated outcome.

This work validated the classical subtype distinction. In the same issue, Fenton published another article focusing upon the application of symptom domains to reduce heterogeneity in schizophrenia classification. This work replicated and extended the earlier reports of independence between symptom domains and became one of the most comprehensive trackings of the natural history of the negative symptom dimension. Fenton reported that schizophrenia with many negative symptoms was associated with poor premorbid functioning, insidious onset, partial or no remission during the first several years of illness, and in most cases a progressive course leading to permanent disability. Schizophrenia with few negative symptoms was associated with good premorbid functioning, acute onset, intermittent early course, and a better prognosis. Positive symptoms predicted future hospitalizations but were less powerful and less specific as indicators of differential illness history, course, and long-term functional incapacity. As predictors of long-term outcome, negative symptoms were of greater value when measured at index admission several years after illness onset than at the time of first hospital admission. Multivariate analyses indicated that 2 negative symptoms (anhedonia and affective flattening) contributed significantly to outcome variance independent of their association with premorbid functioning or positive symptoms.

In addition to validating the positive/negative symptom distinction, this article suggested that negative phenomenologies were not only present premorbidly (and had prognostic value) but also developed during the immediate post-onset period. Indeed, patients with the poorest long-term outcome tended to show an increase in negative symptoms during the early years of their illness: “progressive, negative symptoms early in the course of schizophrenia may thus reflect or signal a process leading to poor long-term functional outcome.” His findings suggested that negative symptoms were more than “symptoms”, ie, they reflected something close to a core pathological process in schizophrenia.

Another publication elaborated upon this theme of the nature of schizophrenia deterioration or deficit, a topic not frequently visited since the early 20th century descriptions of the disorders. Patients with deficit and nondeficit terms of schizophrenia as defined by Carpenter et al were compared in relation to symptom progression between first and index admission, natural history and course of illness, and long-term outcome. Findings were that (1) significantly fewer patients with the deficit form of schizophrenia were married before illness onset. (2) Illness onset was often insidious for patients with the deficit syndrome; once established, the illness was nearly always continuous with few remissions and, in course, appeared unreactive to life events. (3) Negative symptoms among patients with the deficit syndrome were often present at illness onset and progressed in severity over the first 5 years of illness; thought disorder and bizarre behavior also increased in severity over time. (4) Once established, the deficit syndrome was highly stable. (5) The deficit syndrome was associated with a very high risk of poor outcome and long-term disability.

In addition to providing validation for the deficit syndrome of Carpenter et al, the longitudinal profile of the syndrome suggested that deterioration in schizophrenia not only is linked to adolescent and young adult development but also is limited to this period and plateaus in severity after about 5 years. The course profile developed in this work suggested the existence of a window of deterioration in schizophrenia with limits on the length and severity of ultimate deficit. This notion was elaborated further in another communication.

These articles, along with the works of others, reshaped thinking about the domains of psychopathology in schizophrenia that were critical to its long-term course and outcome and that required the development of new treatment strategies in order to prevent the majority of patients from chronic illness and disability.

Other Syndromal Forms: Spontaneous Dyskinesia

One of the more interesting observations in the Chestnut Lodge records concerned movement abnormalities suggestive of dyskinesia in cases where the patients had never been exposed to antipsychotic medication. He reported that among 100 neuroleptic naive patients, 28% of the records contained documentation of some form of movement disorder and 15% described oral-facial dyskinesia with sufficient detail that their presence was almost certain (see table 1, reproduced from Fenton). Risk factors for “spontaneous dyskinesia” included cognitive deficits (lower IQ), negative symptoms, more symptoms at outcome, hebephrenic subtype, and presence of the deficit syndrome. Furthermore, these movements were seldom described for drug-free patients with other psychiatric disorders in the Chestnut Lodge sample, suggesting that spontaneous dyskinesia was specific to schizophrenia and intrinsic to the pathophysiology of the disorder.

These findings were reinforced by accounts of similar phenomenologies from published evaluations of first-episode patients before the use of neuroleptics and from assessments of drug naive patients in developing
Table 1. Verbatim Descriptions of Spontaneous Dyskinesia in Patients From the Preneuroleptic Era

“Peculiar facial grimacing, especially of the mouth…twisting her mouth when talking…sometimes makes pouting motions with lips.”

“There was much facial grimacing, frowning, jutting the lower jaw forward and forming his mouth in the shape of a snout.”

“There were a fair number of mannerisms and facial movements, the most noticeable one being flipping of his lower lip.”

“She was twitching her body about, making aimless jerking motions with her arms and hands. She was sucking her lips in and out making a hissing sound.”

“Grimacing…there was considerable grimacing with sucking and protruding of her lips.”

“Ritualistic gestures with feet…holds lips in an exaggerated pout.”

Fenton also investigated suicidality in the follow-up study populations of schizophrenia, schizoaffective disorder, schizophreniform disorder, and schizotypal personality disorder (total N = 322). Over follow-up, 40% of patients reported suicidal ideation, 23% reported suicide attempts, and 6.4% died from suicide. Completed suicide cases had less severe negative symptoms at admission and more suspiciousness. The paranoid subtype was associated with elevated risk, whereas the deficit subtype was associated with reduced risk, suggesting that negative symptoms may actually be protective against self-harm.32

Evolving Psychotherapeutic Treatments of Schizophrenia

During his years at Chestnut Lodge, Fenton was a dedicated clinician who relished individual clinical encounters. He understood the techniques of intensive psychoanalytically oriented and insight-oriented psychotherapy. He also understood the limits of this work and knew that its complex demands on patients could be disorganizing. He was adept at the supportive psychotherapy practiced by biologically and pharmaco therapeutically oriented clinicians. He integrated medication with pragmatic management strategies that included defining reality, reassuring directly, giving advice, modifying expectations, organizing details of living, talking with families, and intervening with social agencies. He was also aware that supportive therapy could bring patients to a stable baseline without addressing important issues such as the loss of ambition and the abrogation of personal growth and goals. Fenton attempted to resolve this dilemma by selective utilization of aspects of supportive and investigative approaches in what he termed flexible psychotherapy. As he wrote in the Comprehensive Textbook of Psychiatry31(p1224): "Flexible psychotherapy refers to a broad and pragmatic approach to psychotherapy that relies on a variety of strategies applied flexibly depending on the individual patient’s type of schizophrenia and phase of illness. Such an approach might at various times include supportive, directive, educational, investigative, and insight-oriented activity, provided in the context of an ongoing and stable doctor-patient relationship. The quality of this relationship should be characterized by empathy and a sound dynamic understanding of schizophrenia on the part of the physician. Dogmatic or rigid adherence to a single approach applied to all patients is probably the least likely to be of value.”

In this therapeutic approach, Fenton assumed that the vulnerability-stress model represented the best integration of data pertinent to schizophrenia. Many aspects of the vulnerability consisted of genetic and biological aberrations expressed developmentally as deficits. These included deficits in neuropsychological functioning and social competence, both of which he targeted as unmet therapeutic domains in his NIMH work.

The Heterogeneity of Schizophrenia Even at Its Extremes

As noted, most of the schizophrenic patients at Chestnut Lodge were treatment resistant. Before antipsychotic drugs, treatment resistance usually meant failure to respond to talking treatments, electroconvulsive therapy, or insulin coma. After antipsychotic drugs, treatment resistance usually meant incomplete response to the drug. Despite evidence of therapeutic failure in the Chestnut Lodge and other follow-up studies, heterogeneity of course was observed. Fenton developed a prognostic scale30 for chronic schizophrenia capable of predicting variation within treatment-resistant populations based on 5 items: the highest achieved level of adaptive occupational functioning, of social functioning, family history of schizophrenia, erosion of reality testing, and preservation of affect (eg, depressed mood). The prognostic score deriving from this algorithm (using history and admission data) provided strong probabilistic statements about long-term outcome. For example, 23 chronic schizophrenic patients proved capable of sustained good outcome over an average of 15 years without medication. Retrospective data revealed them to have better premorbid social and occupational adjustment, higher levels of actualized skills and social competence, fewer hebephrenic traits, and preservation of affect as seen in depressive moods.31
Fenton wrote the clinical tasks and technical strategies of flexible psychotherapy as follows:

To treat schizophrenia the therapist must use a variety of interventions and strategies. The crucial question is which interventions are of potential value for a particular individual at a particular phase of illness. All interventions aim to minimize the effect of vulnerabilities, bolster adaptive capacities, and reduce the extent and impact of stress. The range of therapeutic tasks and associated goals and interventions can be ordered hierarchically. The strategic rosetta stone here is the therapist’s capacity to shift gears, be flexible, and change roles with all patients based on changing circumstances, always keeping in mind the goal of helping the patient accept, learn about, and self-manage what may often be a chronic and devastating illness. Consideration of the patient’s schizophrenia subtype, current and premorbid functioning, and self-defined treatment goals are all relevant to the determination of appropriate treatment tasks. For patients with severe disorganized or deficit forms of schizophrenia, for example, the most humane and practical goal may be establishing a supportive ongoing treatment within a sheltered setting that minimizes stress and provides for basic human needs for an indefinite period. For the majority of patients who reside in the community amidst varying supportive structures some degree of psychoeducation and rehabilitative tasks should be planned with the aim of minimizing acute relapses and promoting maximal functioning and quality of life. A primary focus on investigative tasks should be reserved for motivated patients who have established a good working relationship with the therapist and exhibit an interest in and ability to make constructive use of such techniques. These patients are likely to have demonstrated good premorbid functioning, intermittent and less severe forms of schizophrenia, minimal residual deficits, and retention of some capacity for self-observation, curiosity, tolerance of frustration, and humor. Attunement to psychological concerns may be particularly important for patients who have a dramatic response to new medications.

This focus on multimodal approaches and the need to remediate deficits in basic psychological and social functions was the basis for Fenton’s attempt to implement elements of Hogarty’s Personal Therapy during his tenure as a Medical Director at Chestnut Lodge. It also informed his efforts as Medical Director to create multiple “wrap around” services for patients ranging from housing to behaviorally informed day programs to clinical trials with novel medications to vocational rehabilitation programs.

Unmet Therapeutic Needs

Stover et al address NIMH accomplishments that resulted from Fenton’s leadership. In this final segment, we describe the synthesis that resulted from experience during the Lodge years, and how this resulted in a vision that has transformed therapeutic discovery for schizophrenia. The foundation for the Fenton contributions included: extensive and critical scholarship, a depth of clinical experience, personal research, passionate devotion to the well-being of mentally ill persons, and exceptional leadership skills.

During the Lodge years, Fenton was aware of a fundamental tension regarding the schizophrenia concept and the meaning of classification. On the one hand, the concept of nuclear schizophrenia was dominant, with its view that highly specific and reliable diagnostic criteria could identify a disease entity with reduced heterogeneity and predict future course. DSM-III had incorporated these concepts and had formulated these criteria that resulted in a disease paradigm with new emphasis on reality distortion phenomena and a neglect of the avolitional pathology described by Kraepelin and a reduced emphasis on the dissociative phenomena described by Bleuler. At the same time, Fenton followed the work coming from the Washington Center of the International Pilot Study of Schizophrenia, which proposed a deconstruction of schizophrenia into pathologic domains. In this alternative paradigm, each domain was distinctive in developmental history, symptomatic manifestation, future course of illness, and relationship with functional outcomes. In the disease paradigm of DSM-III, specific psychotic features such as Schneiderian first-rank symptoms were presumed to represent the latent disease structure and were critical targets in treatment and drug discovery. In fact, all drugs marketed for schizophrenia have been developed within that framework, and all are similar in mechanism of action and limited in therapeutic effects. The alternative paradigm called for treatment discovery in relation to specific domains of pathology and challenged the predictive validity of psychosis for key elements of functional outcomes. Fenton evaluated these contrasting models in his clinical work and tested them in his research.

In clinical work at the Lodge, Fenton observed patients from the perspective of psychodynamic therapist, administrative and psychopharmacologically psychiatrists, and later in a private consultative practice. He knew first hand the limitations of each treatment approach. He observed patients, who continued to struggle with interpersonal relations, vocational functioning, and cognitive challenges despite reduced and stable psychosis in response to antipsychotic drugs. When initial reports suggested that clozapine was uniquely effective for negative symptoms and cognitive function, Fenton organized a clozapine treatment program before the drug was Food and Drug Administration (FDA) approved for marketing. Here, too, he observed the shortfall in therapeutic results. Keenly aware of the unmet therapeutic needs, he practiced “flexible” or integrative treatment with practical approaches to many of life’s challenges. This depth of clinical experience informed him of the critical needs of persons with schizophrenia and the remarkable shortfall in therapeutic development. These experiences reinforced
his view that specific aspects of the schizophrenic phenotype required specific therapeutic approaches that evolved from a knowledge of new and unstudied pathophysiologic processes.

During his career at Chestnut Lodge, and even more during the NIMH years, Fenton was an advocate for the mentally ill. His work with a number of advocacy groups and rehabilitation centers was an aspect of this advocacy. The lengths to which he would devote personal time and effort to help individual patients was widely known among his colleagues and is described by Heinssen in this issue and the First Person Account in this issue. Important to understanding his effective leadership at NIMH is the combination of scientific knowledge, clinical experience, and passion for the cause of the mentally ill.

The final element was personal leadership attributes. Fenton excelled as a listener, had a talent for bringing people together to discover shared goals, and could articulate ideas and suggest actions in a manner that others found compelling. He did this with integrity and without any apparent concern for credit or personal advancement. Other commentators in this issue will take note of the uniquely effective leadership style, and how government, industry, and academic scientists and leaders worked together with unprecedented success in pursuing the work essential to the Fenton vision.

The Fenton Vision

Briefly stated, Fenton enabled the NIMH to clarify a priority and put into action, programs devoted to the following principles:

1. Schizophrenia is a major public health issue;
2. Treatment, cure, and prevention will not be addressed by a continuation of current drug discovery approaches;
3. Psychosis does not define the critical unmet therapeutic needs in schizophrenia;
4. Emphasis should be placed on long-term morbidity and poor functional outcomes;
5. While there are a number of pathologic attributes which merit therapeutic discovery, impaired cognition and negative symptom pathology are the most clearly defined by a robust relation to functional outcomes;
6. An urgent need exists to bring industry science, academic science, and the FDA together, and NIMH should use its convening power and research support mechanisms to accomplish this goal.
7. Patients, advocates, clinicians, scientists, and government should be intolerant of unnecessary delays and any failure to cooperate.

Results of Fenton’s brief leadership are profoundly important and will have long-lasting beneficial consequences. Stover et al will describe the programs put in place. Here we will note the following:

8. Successful inclusion of all relevant parties in the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) process.
9. Publication of the MATRICS cognition battery.\textsuperscript{40}
10. Publication of the preclinical workshop on drug development for cognition.\textsuperscript{41}
11. FDA acceptance of cognition as a potential indication for treatment in schizophrenia and the publication of a consensus design essential to establishing a claim for efficacy.\textsuperscript{42}
12. FDA acceptance of negative symptoms as a potential indication for treatment in schizophrenia and the publication of a consensus design essential to establishing a claim for efficacy.\textsuperscript{43}
13. Establishing the Treatment Units for Research on Neurocognition and Schizophrenia network with 7 centers committed to selecting and testing novel target compounds for cognition impairments.
14. Establishing a new center mechanism for NIMH to enable investigators to translate novel treatment development into full-scale clinical testing—the Centers for Intervention Development and Applied Research grants.

Conclusion

Much is omitted, but the above material traces some of the elements that became the foundation for a remarkable leader to articulate a vision for therapeutic discovery. The initiatives based on this vision have been outstanding, and success was established for many elements of the program. The chance that patients with schizophrenia will be substantially benefited by new therapeutic discovery is much greater now than was the case when Fenton moved from the Lodge to NIMH. The pace of discovery is accelerated and focused. In the wake of his death, there was a tremendous expression of appreciation, affection, and respect from all aspects of the field. He has left behind much of substance and value, not the least of which is hope for the future.

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