



## Monte S. Buchsbaum and the Genain Quadruplets

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### ABSTRACT

The Genain Quadruplets, a genetically identical group of sisters, all developed schizophrenia by their early 20s. Beginning in the 1950s, under the direction of David Rosenthal, they have been studied extensively with a number of neurobiological, neuroradiological and neurobehavioral measures at the Intramural Program of the National Institute of Mental Health (NIMH). A major focus of research interest has been the fact that they varied greatly in the severity of their illness. The present report emphasizes the important role that Monte Buchsbaum had in their evaluation, especially with respect to neuroradiology, during their second period of study at NIMH in the 1980s. It is of special interest that Buchsbaum et al. (1984) concluded “No strong relationship is shown between these (radiological) measures and illness severity or drug responsiveness.” The inference, therefore, is that the differences in illness severity among the sisters were not readily attributable to differences in the amount of damaged brain, at least as could be determined by the imaging methods available in the 1980s. The current report also summarizes the results of the other studies performed on the sisters in the 1980s, to which Monte Buchsbaum contributed.

It is with nostalgic pleasure that I recall the earliest interactions with Monte, in relation to our shared interest in the Genain Quadruplets. But first, I will describe my first contact with the Genain family, and the earliest test data I obtained from them.

The Genain Quadruplets were a group of identical quadruplets, all of whom developed schizophrenia, in varying degrees of severity, by the age of 20. Their existence was brought to the attention of the scientific public by David Rosenthal, a psychologist at the National Institute of Mental Health (NIMH) in Bethesda, Maryland. Rosenthal estimated the probability of their occurrence as one in one and a half billion. He had been informed of their existence by a “Dr. Grant,” who remains anonymous. In 1963 Rosenthal published “A Case Study and Theoretical Analysis of Heredity and Environment in Schizophrenia: The Genain Quadruplets.” This volume consisted of a series of articles by 25 scientists and clinicians who had evaluated the Genains and their parents during their first visit to NIMH. The sisters were at NIMH or at nearby facilities for three years during the 1950s. Rosenthal coined the name “Genain” meaning “dreadful gene” from the Greek. He also gave them pen names corresponding to the institute, the NIMH, where they were studied: Nora, Iris, Myra and Hester. This followed a tradition, as their real names were derived from the initials of the hospital where they were born.

My first encounter with the Genains was in 1958 (as I recall) when I had the opportunity, thanks to David Rosenthal, to administer, or try to administer, the continuous performance test (CPT-Rosvold et al., 1956) to the sisters. I estimated the date from age information presented in various chapters in Rosenthal's book, as I was one year older than the Genains. We had little data on patients with schizophrenia on the CPT at that time. However, the results, some of which are summarized in

Table 1, mirror their clinical status as reflected in many examples in Rosenthal's book.

I had been at Boston University from 1961 to 1980, and returned to NIMH in 1981, as chief of the Laboratory of Psychology and Psychopathology. At the urging of David Rosenthal, who was still active at that time, we invited the Genain sisters to return to NIMH for a follow-up visit. The goal was to reevaluate them with the new technologies that had been developed during the 20+ year interval from 1958 to 1981. At that time the sisters were in their early 50s, and had been on antipsychotic medication for some time. This provided the opportunity to test them on and off their medication to evaluate the effects of the drugs. Some of those data are presented in Table 2. In addition, we could retest them with some of the same measures we used in the late '50s to ascertain whether changes, if any, had occurred. We eventually published the following three articles, from studies done on the Genain sisters at NIMH during the early 80s, based on work done by 32 NIMH scientists and research assistants. As you can be seen, Monte led the electrophysiological, PET and tomographic studies, cutting-edge technology at the time. Lynn DeLisi led and coordinated the diagnostic and biochemical studies. I do believe that this concentrated, unified effort, to evaluate a highly unusual genetic phenomenon (one in one and a half billion?) was, and still is, unique.

This is a brief summary of Monte's paper: “The findings were consistent with those from other groups of patients with schizophrenia and showed great similarity within the quadruplets. CT scans revealed uniformly small lateral ventricles. PET scans replicated earlier findings of relatively low glucose use in the frontal lobes, but did not show strong familial concordance.” From the Discussion: “No strong relationship is shown between these measures and illness severity or drug

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**Table 1**  
CPT Scores of the Genains, circa 1958\*.

Name	% Correct CPT X Task	% Correct CPT AX Task
Myra	89	73
Nora	29	28
Iris	1	3
Hester	Untestable, CPT X Task	

Myra's scores are comparable to those of normal IQ subjects, whereas the scores of Nora and Iris resemble more closely those of brain-damaged defective persons (Rosvold et al., 1956), or of patients with severe idiopathic generalized epilepsy (IGE-Landsdell and Mirsky, 1964). The latter resemblance is suggestive of similar pathophysiological brain mechanisms in schizophrenia and IGE (Mirsky and Duncan, 2015). Hester could not be persuaded to take the test, despite my (AFM) superb clinical testing skills.

\* From Rosenthal, 1963. Rosenthal, 1963

**Table 2**  
CPT Scores of the Genains, circa 1981\*.

Name	% Correct CPT X Task	% Correct CPT AX Task
Myra	82 (79)*	31 (36)
Nora	98 (25)	81 (22)
Iris	98 (65)	80 (57)
Hester	81 (27)	42 (13)

\* The figures in parentheses are the scores off medication. Note the highly significant drop in the scores of all the sisters, except for Myra. This is another indication of the different, more benign (?) expression of the disorder in Myra, as compared to the other three sisters. From Mirsky et al., 1984.

responsivity. This suggests that the abnormalities seen in off-medication patients with schizophrenia are not easily explained by institutionalization or social functioning effects" (Buchsbbaum et al., 1984, p. 108).

Lynn DeLisi's findings were summarized as follows: "A substantial number of biochemical measures were assayed in the Quadruplets and in some of their close relatives. The findings of elevated urinary phenylethylamine excretion, decreased plasma dopamine-B-hydroxylase activity and increased a-adrenergic receptor concentration in all Quadruplets warrant further genetic studies" (DeLisi et al., 1984, p. 76).

The following is a summary of the neuropsychological results: "We conclude that the Genains are functioning about as well as they ever have in their adult lives. This is probably due to the medication (primarily neuroleptics) and other supportive treatments they have received over the years. With respect to the varying degrees of illness, scrutiny of the data of these three studies leads to speculation that certain unique biochemical findings interacting with differing types and

amounts of cerebral pathology constitute a major cause of the variable expression of the schizophrenic diathesis" (Mirsky et al., 1984, Table 5).

By the time these studies were completed at NIMH, Monte had moved to UC Irvine, where he was Professor of Psychiatry. I had moved to Boston University. Monte was involved in a 25-year follow-up publication of the Genains (see references), although most of the data had already been published. These publications were Monte's last official contact with the Genains, although he and I and Lynn DeLisi have had occasional informal communications about them over the years.

I have kept in touch with the sisters during the past 60 years, visiting them on several occasions, and always remembering to bring them a box of chocolates. We have continued to publish the results of these contacts, and I have listed them in the References section. On one visit I was able to reward their participation in the seemingly endless interviews and tests with a check for \$1000—as "payment for their services." Myra, the sole surviving quadruplet (age 88 as of this writing), recently wrote and published a book about the history of her family, "The xxxxxx Quadruplets: The Alphabet Sisters." She used the true family name in the title of the book, but in keeping with the Rosenthal tradition, I will not reveal it. In the book she thanked me again for the chocolates and the check. It is of interest that although she is quite open about the harsh, even brutal treatment the sisters received from their father, there is no mention of the illness, or of the frequent hospitalizations the quadruplets endured over the years.

Myra has mastered the internet and usually remembers to send me a birthday greeting by email. For me, the contact with the Quadruplets has been the most meaningful and dynamic exposure to schizophrenia that I have had, and their story emphasizes how little we still know about the causes of the disorder.

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