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The Pioneering Contributions of Irving Gottesman: An Appreciation

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Abstract

Irving Gottesman was one of the leading psychopathologists and behavior geneticists of our time, greatly influencing our basic conceptualization of the transmission of schizophrenia and other major mental disorders in ways that impacted research programs around the world. Here we highlight his landmark twin studies of schizophrenia, his introduction of the concept of endophenotypes, and his role in providing the conceptual base for vulnerability/stress models of schizophrenia. His ability to influence our basic assumptions about the nature of genetic factors, environmental factors, and their interaction in the onset and course of major mental disorders was truly remarkable.

Irving I. Gottesman, Ph.D., was one of the most influential psychopathologists and behavior geneticists of our time, making contributions that focused on the genetics of schizophrenia but that also spanned scholarly contributions on intelligence, delinquency, violence, and alcoholism. I was fortunate to know Irv Gottesman during my graduate school days at the University of Minnesota and stayed in regular touch in the years since that time, so I am honored to be able to comment on his many achievements and influences on clinical science.

The landmark twin study of schizophrenia based on the Maudsley twin series, published in detail in the 1972 book by Gottesman and Shields (Gottesman & Shields, 1972), remains a model of methodological rigor and intellectual achievement. This twin study was so rigorous and thorough during a period in which the debate about the genetic vs. environmental origins of schizophrenia still raged that only those unyielding to clear data could then deny the strong genetic component in the transmission of schizophrenia. At a time that there were controversies over the breadth and boundaries of the diagnosis of schizophrenia, Gottesman and Shields solved the problem by submitting case summaries of each twin to a panel of six judges from the U.S., U.K., and Japan. In this way, they were able to calibrate the breadth of the diagnosis to show that, while the monozygotic:dizygotic (MZ:DZ) ratio based on diagnoses for each of the six judges supported an important genetic factor in schizophrenia, a middle-breadth diagnostic construct yielded the highest MZ:DZ ratio. This early study was followed by a later demonstration (Gottesman & Bertelsen, 1989) that the risk for schizophrenia in the children of an unaffected co-twin of a MZ twin with schizophrenia was

not different than that in children of the MZ twin with schizophrenia. Thus, they concluded that the unaffected MZ twin had an unexpressed genotype that nevertheless transmitted genetic vulnerability to the children.

The data from this Maudsley twin study of schizophrenia, as well as examination of data from previous research, led Gottesman and Shields (Gottesman & Shields, 1967, 1972) to propose a multifactorial polygenic theory of the transmission of schizophrenia that departed markedly from the dominant theories of the genetics of schizophrenia at that time. Instead of a single major gene for schizophrenia with “incomplete penetrance” (Slater, 1958) or one that leads to schizotypy (Meehl, 1962), Gottesman and Shields drew from the quantitative liability models of Falconer (Falconer, 1989) to posit that many genes of small influence together lead to a continuous dimension of vulnerability to schizophrenia. This polygenic model could accommodate the lack of any clear Mendelian pattern to transmission of schizophrenia, the rapid reduction in risk for schizophrenia as one moved from MZ twins to first to second degree relatives of probands with schizophrenia, and the allowance for environmental as well as genetic factors in liability to schizophrenia (which MZ concordance rates around 50% also indicated). The polygenic model of schizophrenia has now become the widely accepted one, bolstered by evidence from genome-wide association studies indicating that more than 100 genes contribute to the predisposition to schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics, 2014). The 1972 book was published while I was in graduate school at the University of Minnesota, where the opportunity to hear Irv Gottesman discuss it in person was a major influence on me and my fellow grad students, as it showed the impact that the combination of rigorous empirical research and creative, broad-reaching modeling could have on the field.

Irv Gottesman also introduced to clinical science the concept of “endophenotypes” (Gottesman, 1991; Gottesman & Shields, 1972). Displaying again his scholarship that ranged well beyond clinical psychology, Gottesman drew from concepts of basic genetics (John & Lewis, 1966) to hypothesize that clues to the genetic factors in schizophrenia could be found in underlying abnormalities that are closer to DNA than the clinical syndrome of schizophrenia. These endophenotypes were hypothesized to have several characteristics, including presence in first-degree relatives of schizophrenia probands to a greater extent than in the general population, heritability, and continued presence in clinically remitted states in individuals with schizophrenia (Gottesman & Gould, 2003). The endophenotypes could be cognitive, neurophysiological, neuroanatomical, biochemical, or endocrinological in nature, but many of the most thoroughly investigated candidates for schizophrenia have been cognitive and neurophysiological ones (Gur et al., 2007; Turetsky et al., 2007). The search for productive endophenotypes has resulted in thousands of articles and led to the formation of a consortium across multiple universities to allow large samples of individuals with schizophrenia and their biological relatives to participate (Braff, Freedman, Schork, & Gottesman, 2007; Calkins et al., 2007). Indeed, this approach has extended to another consortium to examine the extent to which endophenotypes relevant to schizophrenia and bipolar disorder are similar versus different (Ivleva et al., 2014; Tamminga et al., 2014). Promising evidence of the relationship of several endophenotypes to genes relevant to susceptibility to schizophrenia has recently been found (Greenwood et al., 2011; Greenwood et al., 2013).

Another major contribution of Irv Gottesman was the conceptual base that led to an emphasis on vulnerability/stress or diathesis/stress models of schizophrenia (Gottesman & Shields, 1972; Gottesman & Shields, 1982). While these models arose from several intellectual traditions, the multifactorial, polygenic model of the transmission of schizophrenia provided a strong quantitative foundation for the search for vulnerability factors that interacted with psychosocial and biological stressors during development to impact the onset and course of schizophrenia (Nuechterlein & Dawson, 1984; Zubin & Spring, 1977). Subsequent developments sought to identify and show interrelationships among individual vulnerability factors within individuals and stressors in their environments (Jones & Fernyhough, 2007; Nuechterlein et al., 1992; Nuechterlein et al., 1994; Walker & Diforio, 1997).

In addition to his impact through ground-breaking empirical and conceptual publications, Irv Gottesman had a remarkable talent to influence the field through his many emails. In recent years, I and many of his other colleagues and collaborators regularly received his emails pointing out alternatives to our scientific views and also new developments in related fields that we should take into account. His amazingly broad scholarship and incisive wit brought to our attention issues that piqued our curiosity and greatly enriched our research programs. Irv Gottesman will be sorely missed.

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