Chapter 4
Irving Gottesman and the Schizophrenia Spectrum

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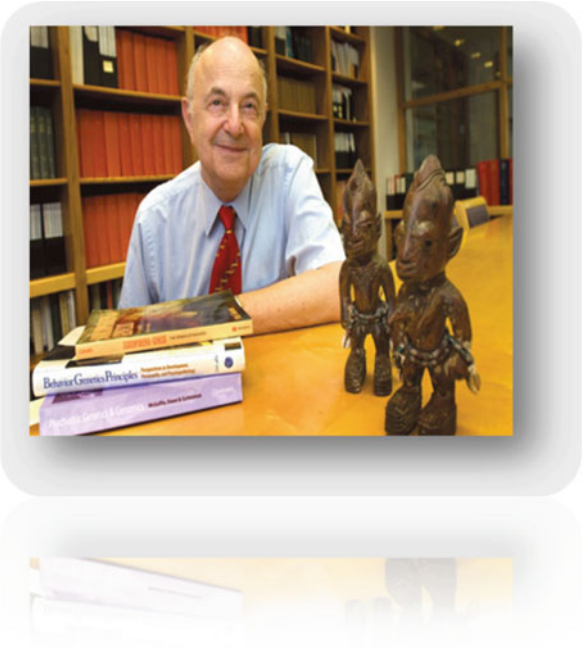

Abstract Our knowledge of the genetics of schizophrenia and its borderlands is heavily indebted to the research and writings of Irving Gottesman. In a twin study of personality assessment in adolescents with the Minnesota Multiphasic Personality Inventory (MMPI) begun in 1957 he demonstrated that certain traits were under appreciable genetic influences. In a major twin study of schizophrenia with Shields begun in 1962, using audio-taped interviews, including MMPI, and diagnosed by

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a cross-national panel of blinded judges, he demonstrated a strong genetic factor, suggesting a polygenic contribution to a multifactorial liability to the disorder. In a study on the offspring of discordant twins he demonstrated that the genetic risk was passed on from non-schizophrenic as well as from schizophrenic identical twins. Super-high-risk studies on the offspring of two schizophrenic parents (2010) showed 4 times increased risk of schizophrenia compared to offspring of only one schizophrenic parent and suggested some kind of genetic overlap with bipolar disorder. In molecular genetics his concept of endophenotypes as interforms between the genotype and its phenotypical manifestations, influenced by epigenetic and environmental factors, have inspired a large number of research studies.

Keywords Schizophrenia · Schizophrenia spectrum · Schizoidia · Schizotypal disorder · Twin-studies · Twin-offspring studies · Dual mating studies · Endophenotypes

Abbreviations

MMPI	Minnesota multiphasic personality inventory
ICD-10	International classification of diseases, 10th revision
DSM-IV	Diagnostic and statistical manual of mental disorders, fourth revision

Le hazard ne favorise que les esprits préparés (Louis Pasteur, 1822–1895)

Schizophrenia and the Schizophrenia Spectrum, including Schizotypal Disorder (ICD-10) or Schizotypal Personality Disorder (DSM-IV), Schizo-affective Disorder and Schizoid and Paranoid personality Disorder have, for the last century, been among the main topics of research in psychiatric genetics, and Irving Gottesman one of the persons who through the last half century has contributed significantly to our knowledge in this field.

Early Career

Following graduate education [1], Gottesman 1956 began his training as clinical psychologist at the University of Minnesota, which he selected because the training program was oriented towards biology, genetics and objective assessment of personality, being the home of the Minnesota Multiphasic Personality Inventory, MMPI [2]. For his dissertation he conducted a twin study of personality traits, using the MMPI in adolescent MZ and DZ twins who were school children in the area.

Heritability of Personality

The Ph.D. dissertation: “The psychogenetics of personality”, 1960, was published as a monograph: Heritability of Personality: a demonstration [3], but first in 1963, after it had been rejected by the same journal as irrelevant to psychology. The twin study

demonstrated significant hereditary components of variance for several MMPI personality dimension scales, particularly for the introversion and schizophrenia scales. This indicated that psychopathology of the psychoses had a substantial genetic component and that the MMPI might provide dimensional measures of traits observed in patients with schizophrenia and in some of their near relatives, called "schizoids" in early German genetic research. The work received considerable attention and resulted in a travel grant to the Second International Congress on Human Genetics in 1961 in Rome [1]. In Rome Gottesman was introduced to Franz Kallmann from New York and Eliot Slater from London who both had performed major twin studies on Schizophrenia [4, 5]. To Slater he happened to suggest the possibility of coming to London as a postdoctoral fellow at Slater's institute, which was met with encouragement.

The Maudsley Twin Study on Schizophrenia

In 1963 Gottesman came to Slater's Unit in Psychiatric Genetics – the "hut" – at the Medical Research Council Institute of Psychiatry on a fulltime fellowship abroad from the United State Public Health Service. He wanted to do a new twin study on Schizophrenia, based upon the Maudsley twin register, systematically ascertained in an unbiased manner from consecutive admissions to in- and outpatient services in the Maudsley, Bethlem Royal and nearby hospitals. Slater arranged that Gottesman came to work with James Shields, known from his renowned study on identical twins reared apart [6]. Gottesman wanted to improve the methodology by using the MMPI to get indicators of psychopathology and assess whether schizophrenic personality traits or schizoidia were on a continuous dimension with schizophrenia. He tape-recorded extensive semistructured interviews with the twins and presented case summaries, MMPI profiles and verbatim transcripts of the interviews to a cross-national panel of 6 diagnostic experts, leaving out information about zygosity and proband/co-twin status to get diagnostic assessments in a blindfolded way. He was in London for 1 year, came back the following year for 3 months and then every year for 2–3 weeks to work with James Shields on the analysis and the writing of papers and a book, which was published in 1972: Schizophrenia and Genetics: A Twin Study Vantage Point [7].

Apart from probandwise concordance of 58% (15/26) in MZ and 12% (4/34) in DZ twins of consensus among the 6 judges on a diagnosis of certain or probable schizophrenia, the MMPI questionnaires, obtained from the majority of the twins, showed presence of schizophrenia-like profiles in the concordant MZ and, to a lesser degree, DZ twins confirming the diagnosis. In the discordant co-twins, however, schizophrenia-like profile-scores were seen in only 3 DZ and in no MZ co-twins, disappointing the hope of finding evidence of schizoid personality traits in the discordant twins. More support was forthcoming from the blindfolded evaluation by another judge, not part of the 6 judge panel, Erik Essen-Möller from Sweden, known for his Swedish twin-study of schizophrenia [8, 9] and for his special interest in personality theory and the concept of schizoidia [10]. He coded 12 MZ probands and 7 of their co-twins as "true schizophrenia", further 2 co-twins as "possible

schizophrenia", and every one of the remaining co-twins as having characterological abnormalities of a schizoid kind. In the DZ twins he coded 19 probands and 2 co-twins as schizophrenia and further one co-twin with a schizophrenia-related personality.

The findings from the Maudsley twin study led Gottesman and Shields to genetic theorizing. Inspired by Douglas Falconer's multifactorial polygenic threshold model for diabetes and other common diseases [11], they improved the model into a diathesis-stress model with a "multifactorial" liability to schizophrenia, considered to be a continuously distributed variable determined by both genes and environment such that only those individuals whose liability exceeds a certain threshold value will manifest the disorder. Just below the threshold they expected to find a zone of schizophrenia spectrum disorders but with unknown lower border, if any, towards normality [7]. Theodore Reich and his colleagues [12] have extended the model to include two or more thresholds, for milder and more severe forms. Later, together with Peter McGuffin and Ann Farmer, Gottesman analyzed subdivisions of the twin data to look for quantitative and also qualitative differences, not finding evidence for the latter [13].

The Schizoidia Concept

Through the following years the schizoidia-related findings from the twin-study were analyzed in articles [14–16], discussing the concept of schizoidia, together with Shields and Leonard Heston, who also had been to Slater's institute in London and had performed the first adoption study in schizophrenia on adopted away children of schizophrenic mothers [17]. They discussed whether the concept implied a phenotypic resemblance and a genotypic connection to schizophrenia.

For semantic clarification they listed four uses of the term "schizoid": (1) Resembling schizophrenia, but not implying genetic connection to it, as used in "schizoid personality", meaning shy, sensitive, aloof or eccentric, shading into the normal, possibly extended to include paranoid personality and maybe also high MMPI scores on the schizophrenia scale. (2) For any disorders occurring in co-twins and other relatives of schizophrenics, whether resembling schizophrenia or not and whether occurring more frequently in families of schizophrenics than of controls. No genetic connection to schizophrenia is implied. (3) For disorders belonging to a class found more often among relatives of schizophrenics than of controls, whether occurring among relatives of schizophrenics or not. (4) For a diagnosis or behavioral traits genotypically related to schizophrenia to indicate a probable carrier of a high-risk genotype.

Disorders broadly resembling schizophrenia, schizoids and other spectrum disorders, occurring in co-twins and other relatives of schizophrenics and found more often among relatives of schizophrenics than of controls were suggested to be the most probable candidates for carriers of a schizophrenia genotype. Future twin and family studies on the relatives of probands with such disorders could possibly confirm their candidature.

Applied to the findings in the Maudsley twin study [14–16], they tried to stepwise add co-twins with other disorders resembling schizophrenia, Essen-Möller's schizoid characters, and those with high MMPI schizoid profiles, to the concordant co-twins. This, however, by each step raised both the MZ and DZ concordance rates and diminished the ratio of the rates as an indicator of "biological specificity". These co-twins therefore probably were not carriers of the genotype.

In Denmark 1972–1973: The Twin Study on Criminality

In 1972 Irving Gottesman won a Guggenheim Fellowship and went to Denmark for 1 year as a guest researcher at the Psychological Institute at Kommunehospitalet in Copenhagen [1]. Here Sarnoff Mednick and Fini Schulsinger and their team worked on high risk studies in children and on adoption studies with Seymour Kety and David Rosenthal, defining Schizotypal Disorder [18] and redefining the schizophrenia spectrum [19]. Denmark was an ideal country for epidemiological genetic research because of the existence of effective national registers, such as the Central Person Register with individual person-numbers for every inhabitant, the Central Psychiatric Register going back to 1920 [20], the Danish Twin Register, the Danish Adoption Register, the Police Register, and the Register of Causes of Death. At the institute Gottesman came to work with a Danish criminologist, Karl Otto Christiansen, on a twin study of criminality, which they did not finish because of Christiansen's death, so that only part of it has been published [21].

The Danish Dual Mating Study

During this visit he initiated a dual mating study of mental disorders in the offspring of parents who both had been psychiatric inpatients, together with Margit Fischer at the Institute of Psychiatric Demography in Århus. He had met her at a previous visit to Erik Strömgren in Århus, where she was working at a Danish twin study of schizophrenia [22]. Over the following decade Margit Fischer sorted out data from the cards in the central psychiatric register containing information about admissions of spouses, children and other relatives, and she obtained and scrutinized their hospital records for diagnostic information. After her untimely death in 1983 the author of this chapter was asked to take over her part of the project. A sample of 139 parent couples with a total of 378 children were identified. Various diagnostic parent combinations produced subgroups with offspring for evaluation of morbidity risk of same or similar disorders, but numbers were too low for statistical analysis [23].

There were no offspring of parent couples with one or both parents with schizoid or paranoid personalities. Of interest for schizophrenia spectrum disorders were the offspring of parents with reactive psychosis. According to the Scandinavian concept of psychogenic psychoses they were psychoses with acute onset as a reaction to a traumatic event, good prognosis and affective, confusional, paranoid or

schizophrenia-like symptomatology. Among the four children of two parent-couples both with reactive psychosis there were no mental disorders. Among 14 children of 5 couples with reactive psychosis versus schizophrenia was one child with probable schizophrenia resulting in a morbidity risk of 10%, which is no higher than found in children of one schizophrenic parent, suggesting that reactive psychoses did not contribute genetic liability factors to schizophrenia [23].

The Professorships and the Books

Gottesman returned to Minneapolis in 1973, where he had worked since 1966 at the University of Minnesota as professor at the Departments of Psychology, Psychiatry and Genetics and director of the Behavioral Genetics Center. From 1980 to 1985 he served at Washington University School of Medicine in St. Louis as Professor of Psychiatric Genetics at the Departments of Psychiatry, and of Genetics and Cell Biology. From 1985 he worked as professor of psychology and of clinical pediatrics (medical genetics) at the University of Virginia in Charlottesville. Following his retirement in 2001 he moved back to Minneapolis, where he took up semiretired work as Bernstein Professor in Adult Psychiatry and as Senior Fellow in Psychology at the University of Minnesota. As professor he mentored 36 doctoral students through their dissertations and 7 postdoctoral students. He was consultant on the New York high-risk prospective projects on children of schizophrenic parents, led by Erlenmeyer-Kimling and her group [24] and to a study on environmental and biological factors in identical twins by Fuller Torrey [25], in which no evidence of spectrum sub-threshold schizophrenia was revealed by a personality questionnaire in 22 non-schizophrenic co-twins. Gottesman authored or coauthored quite a number of articles and book chapters and with about 10 years interval he produced or co-produced three books of major importance: In 1982 together with Shields: “Schizophrenia. The Epigenetic Puzzle” which has become the source- and handbook of schizophrenia genetics [26]. In 1991 “Schizophrenia Genesis. The Origins of Madness”, with updated information and written for a wider audience [27], and in 2002 (updated in 2004) “Psychiatric Genetics and Genomics” together with Peter McGuffin and Michael Owen [28], the successor to the classic Slater and Cowie book on psychiatric genetics [29]. Through all these years he traveled abroad to meetings and conferences, also paying annual visits to London and Denmark.

The Discordant Twins’ Offspring Study

In the mid-1980s Gottesman took the initiative to do a follow-up study of the morbidity risk in the offspring of the discordant twins in the late Margit Fischer’s Danish twin study on Schizophrenia, assisted by the present author as his Danish partner. She had provided morbidity risk figures for the MZ schizophrenic and

non-schizophrenic twins of about the same size, but not for the DZ twins [30]. Now 18 years later it was possible to include the DZ twins in a register- and record-based follow up study, with a proper statistical evaluation of the observed difference between the risks in the offspring of the non-schizophrenic MZ and DZ twins. The morbidity risk of ICD-8/9 schizophrenia and schizophrenia-like disorders in the offspring of the schizophrenic and the non-schizophrenic MZ twins were of the same magnitude, 16.8 and 17.1%, respectively, and the same as in the offspring of the schizophrenic DZ twins of 17.4%. This is about the same as usually found in children with one schizophrenic parent. The risk in the offspring of the non-schizophrenic DZ twins was only 2.1%, significantly different from the 17.1% in the offspring of the non-schizophrenic MZ twins, and on a level expected in second-degree relatives of schizophrenics, which they actually are being nephews or nieces of the schizophrenic twins. The results confirmed that unexpressed genotypes may be transmitted to the next generation and further demonstrated that schizophrenia non-genetic phenocopies did not occur to a substantial degree to discourage molecular genetics research. The paper was published in 1989 [31] and was awarded by the Kurt Schneider Prize, first time given to other than German scientists.

The New Dual Mating Study

During the last 20–30 years it has been increasingly difficult to do studies based on personal interviews because of diminished willingness in the population to take part and changed attitudes to medical science and registration, threatening the use and even the existence of registers, particularly the psychiatric registers, which in some countries had to close down. In Denmark they survived because of their obvious utility for medical statistics and research, although reduced to person identification data and more or less reliable or valid coded diagnoses for in-patient, and from 1995, also out-patient admissions. It became easier to cross-check the registers again in a way that did not reveal person-identifiable data and this opened the possibility for register-based studies. In collaboration with professor Preben Bo Mortensen at the National Centre for Register-based Research at the University of Århus, Denmark, Irving Gottesman in 2005 took up a new register-based Dual Mating study [32] on a population-based cohort of 2.7 million persons. The study was limited to the most reliable register diagnoses of Schizophrenia and Bipolar Affective Disorder in parents and offspring, for the offspring also of schizophrenia-related disorders to cover the schizophrenia spectrum and of Unipolar Affective Disorder. The schizophrenia-related disorder diagnoses included ICD-10 Schizotypal Disorder, Delusional Disorder, Acute and Transient psychotic Disorders, Schizoaffective Disorders, Schizoid and Paranoid Personality Disorders, and their corresponding diagnoses in ICD-8. The risk in the offspring was calculated as cumulative incidence up to age 52, that is, differently from the way morbidity risk was calculated in the earlier literature and only roughly comparable after arithmetical conversion. The results were published in 2010. The risk of

admission with a diagnosis of schizophrenia in 270 offspring of 196 parent couples with both parents admitted with a diagnosis of schizophrenia was 27%, increasing to 39% when schizophrenia-related disorders in offspring were included. For comparison we also calculated corresponding risks in offspring of couples with only one and with no parent ever admitted, with cumulated incidences of 7 and 0.86%, respectively. For Bipolar Disorder the corresponding incidences were 25% in 146 offspring of 83 parent couples with Bipolar Disorder diagnosis, increasing to 36% when Unipolar Disorder diagnosis in offspring was included. With only one and with no parent ever admitted the figures were 4.4 and 0.48%, respectively. Converted to morbidity risk figures they are of about the *same magnitude* as earlier results from literature [21]. The incidences of Schizophrenia and Bipolar Disorder in offspring of couples with one parent with schizophrenia and the other parent with bipolar disorder were 16 and 12%, respectively, suggesting a genetic relationship of some kind between the two disorders.

A diagnosis of Schizophrenia is thus seen to also predispose to schizophrenia-related disorders. It would have been of interest to see if and to which degree schizophrenia-related disorders predisposed to a diagnosis of schizophrenia. Here, however, we left the results unpublished because of inconclusive findings. Even if the incidence of schizophrenia was modestly raised in offspring of couples with only one parent ever admitted with a diagnosis of schizophrenia-related disorders compared to no parents ever admitted, it did not separate out markedly from corresponding figures in offspring with only one parent ever admitted with a diagnosis from almost any other diagnostic group, thus more or less drowning in the "noise" from less reliable diagnoses.

Endophenotypes

The failure to identify schizoid or other spectrum disorders as carriers of the genotype in the non-schizophrenic twins in the Maudsley twin study motivated Gottesman and Shields to introduce the concept of endophenotypes into psychiatry [7], adapted from insect biology in a paper by John and Lewis from 1966 [33], as a distinction between the externally visible exophenotype and the internal endophenotype, not visible to the naked eye without aid. The term was introduced to specify intermediate or intervening variables mediating the chain of events in the complex pathway between the genes and the psychiatric symptoms under epigenetic, environmental and stochastic influences. The identification of endophenotypes conferring vulnerability to psychiatric illness may point to etiological or pathogenetic models important for focused treatment. Along with the growing number of molecular-genetic investigations there has been an increased interest in research on endophenotypes, epigenetic and environmental factors, a research mixture in which Gottesman has been active, visionary and inspiring, coauthoring papers and reviews on the topic with the aim of resolving etiological questions particularly of schizophrenia and the schizophrenia spectrum [34–37].

Recognition

For more than 50 years Irving Gottesman has been a leading figure in psychiatric, especially schizophrenia genetics. He is an Honorary Fellow of the Royal College of Psychiatrists (London) and for his achievements he has received a number of well-deserved awards, including the Stanley Dean Research Award for Contributions to Schizophrenia Research 1988; the International Society for Psychiatric Genetics "Lifetime Achievement Award in Psychiatric genetics" 1997; the Society for Research in Psychopathology "Joseph Zubin Award, Lifetime contributions to psychopathology" 2001; and more recently the American Psychological Foundation Gold Medal for Life Achievement in the Science of Psychology 2007 and the NARSAD Lieber Prize for Outstanding Achievement in Schizophrenia Research 2008. The author of these lines gratefully appreciates the good luck and happy fortune to have had the privilege to have Irving as his mentor and friend for the last more than 30 years.

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