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**The contribution of the Rüdin school to psychiatric genetics: the light and the darkness.**

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In this special issue Kendler and Klee<sup>1</sup> present for the first time English translations of five papers from the Rüdin school in Munich published in German between 1916 and 1933, together with commentaries on each paper. These papers are of historical importance because they were among the first to systematically explore the inheritance of dementia praecox (schizophrenia) using state of the art clinical and statistical approaches. The first<sup>2</sup> was a study of risk in siblings. This was followed by pioneering studies of risk in offspring<sup>3</sup> and nieces and nephews<sup>4</sup>, by the first systematic twin study of schizophrenia<sup>5</sup> and one of the first studies to explore clinical and aetiological heterogeneity in schizophrenia using genetic data<sup>6</sup>. In many ways these papers are an important part of the foundations of modern psychiatric genetics and are valuable historical documents that remain relevant as the field grapples with some of the same issues faced by these pioneers. Kendler and Klee<sup>1</sup> bring out many of these points in their scholarly commentaries.

From today's perspective, it is striking that these were all single-author papers written by male professors of psychiatry. Nowadays most psychiatric genetics papers are authored by large teams and are as likely to be led by those with backgrounds in statistical genetics, computational biology, epidemiology and psychology, as by psychiatrists. There is a lack of gender balance in psychiatric genetics, as in science generally, and while our field has an increasing number of female scientists and some in top leadership positions who are role models for the future, this remains an area of concern. There is an even more stark lack of diversity in other characteristics particularly ethnicity, and again this is a problem shared with science more generally. It is encouraging that the International Society of Psychiatric Genetics (ISPG) emphasises diversity and inclusion as part of its core values, and one of its four goals is to foster an inclusive, diverse and global research community<sup>7</sup>. However, it is clear that this is a journey that is only just beginning.

These papers were pioneering in their rigour and sophistication relative to previous research. Kendler and Klee place them clearly in the context of the history of psychiatric genetics and illustrate their influence on subsequent family and twin studies and on the many ensuing attempts to use genetics to inform nosology. The papers also raise many issues that remain relevant today. They emphasised the importance of systematic ascertainment, good experimental design, rigorous phenotype definition and follow-up. They also stressed the importance of applying modern statistical approaches and working with knowledgeable statisticians. Nowadays statistical geneticists are an integral part of psychiatric genetics and, as noted above, frequently lead major studies. It seems uncontroversial to argue that many of the field's successes in the last 15 years would not have taken place without their close involvement. However, the challenges of assembling large and powerful samples for genomic studies have led to less attention being paid to ascertainment and clinical phenotyping<sup>8</sup>. If left unchecked, this is likely to have important consequences not least on our ability to understand how genetics influences the extensive symptomatic heterogeneity seen in those with a diagnosis of schizophrenia as well as the variability in course and outcome<sup>8</sup>. Modern psychiatric genetics has access to a rapidly increasing number of sophisticated methods. But ultimately, as Rüdin and his followers were aware, the explanatory power of genetics is limited by experimental design, particularly ascertainment, and by the quality of the phenotype data with which genetic variation can be compared.

It is particularly interesting to see how these authors were preoccupied with the question of whether schizophrenia is an appropriate "unit-character" suitable for genetic research based on Mendelian methods. These studies, using systematic ascertainment and careful

phenotyping of relatives as well as probands, were the first to systematically explore the range of outcomes associated with genetic risk of schizophrenia. Their findings that schizophrenia, as defined by Kraepelin's concept of dementia praecox, is genetically related to other psychotic disorders and what we now call the schizophrenia spectrum personality disorders certainly raised questions about the boundaries of the "biological unit" that could be related to underlying genetic risk. In recent years, genomic studies have revealed more extensive pleiotropy both among psychiatric conditions and with non-psychiatric traits and disorders<sup>9</sup>, and confirmed the complex, polygenic nature of psychiatric phenotypes<sup>10</sup>. It therefore seems unlikely that we should expect to find discrete biological units analogous to the characteristics of Mendel's peas. However, the pragmatic question remains: Is schizophrenia the most suitable phenotype for genetics, and indeed research more widely, as we seek to understand underlying mechanisms and develop new predictive algorithms? This remains a contentious and widely debated area, though many of those who propose retaining the diagnosis of schizophrenia as a suitable construct for research acknowledge its shortcomings but argue that it should not be replaced until there are robustly validated alternatives (see<sup>11</sup> and associated articles in a special issue of *Schizophrenia Research*). Whatever your position in this debate, if we are to move forward, given the polygenicity and pleiotropy revealed by genomic studies, we are going to need to develop and evaluate novel ways of defining and characterizing psychiatric syndromes and symptoms and relating these to underlying genetic and neurobiological variation<sup>8</sup>.

As we read these papers and digest their historical importance, we can't help being aware of the dark shadow cast by their provenance. It's clear from Kendler and Klee's<sup>1</sup> translations and commentaries that this work was largely motivated by the belief that eugenics offered an effective and ethical approach to reducing the burden of mental disorders in the population. Belief in the potential effectiveness and acceptability of eugenics was widely held at that time and attempts to practice eugenics, though directive genetic counselling and sterilisation, were not confined to Germany<sup>12</sup>. However, it was in Nazi Germany that this was implemented in increasingly extreme and ultimately murderous ways. This was partly justified by the scientific findings of the Rüdin school, though, as Kendler and Klee are careful to document, the four authors varied widely in their support and enthusiasm for Nazi racial policies. Kendler and Klee<sup>1</sup> have taken the view that the historical importance of these papers is such they deserve to be read in translation and their scientific implications discussed, but that this should be considered alongside descriptions of the authors support for, and involvement in, the implementation of Nazi eugenic and racial policies. I think they are correct to take this position. The deep connection between Nazi policies and these papers raises uncomfortable questions about the potential for misuse of genetic findings, particularly in psychiatry, which we cannot ignore.

Among the many lessons to be learned, this history reminds us of our responsibilities as scientists to present our findings and their implications cautiously. These responsibilities do not stop when we place our findings into the public domain. Psychiatric geneticists have a social responsibility, whether individually or collectively through professional organisations, to ensure that their research is used ethically, and there is a need for them to work with other stakeholders, including patients and the wider public, in crafting policies to maximise benefits and minimise potential negative consequences<sup>13</sup>. In this regard, it is encouraging that the ISPG has made robust statements on the use of polygenic risk scores to screen embryos for adult mental health conditions and the use genetic data to fuel racist ideologies<sup>14</sup>. Increasingly it is becoming clear that our social responsibilities as scientists start when research is being planned. In response to concerns raised by various advocacy groups, many

funding agencies are now mandating patient and public involvement in the planning stage of research and increased involvement of relevant stakeholders in the planning and prioritisation of research. Recently a large genomic study of autism (Spectrum 10K) was halted, pending wider and more intensive community consultation, following fears about the sharing of genetic data and an alleged failure to properly explain the benefits of the research being raised by a group led by autistic people<sup>15</sup>. One of the concerns raised was that the research could lead to prenatal screening and pointed to the “well-known history of eugenics around disability”.

In conclusion, these papers are early landmarks in the quest to understand the genetics of schizophrenia and remind us of many scientific issues that remain relevant today. Psychiatric genetics has the potential to improve the lives of those with psychiatric conditions, though better diagnoses and treatments. However, while it might have a bright future, it has a dark past. These translations and their historical context also remind us of the potential for misuse, of our social responsibilities as scientists, and why wider society is right to hold us to high ethical and social standards.

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