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The Social, Genetic and Developmental Psychiatry Centre: its origins, conception and initial accomplishments

MICHAEL RUTTER* AND PETER MCGUFFIN

SGDP Centre, Institute of Psychiatry, King's College, London

ABSTRACT

Background. The Social, Genetic and Developmental Psychiatry Centre was established by the Medical Research Council, in partnership with the Institute of Psychiatry, King's College London, in 1994.

Method and Results. The paper describes the origins of the Centre; the reasons why a new initiative was needed in the early 1990s; the thinking that led to the proposal for a major interdisciplinary research centre that integrated social, genetic and developmental research perspectives; the approach to international recruitment of world leaders; and the initial research accomplishments with respect to the basic goal of understanding nature-nurture interplay.

Conclusions. The structure and interdisciplinary approach of the Centre have proved a success and the initial accomplishments have begun to meet the objectives of showing how nature-nurture interplay is involved in the development of psychiatric disorders.

THE SOCIAL, GENETIC AND DEVELOPMENTAL PSYCHIATRY CENTRE: ITS ORIGINS, CONCEPTION AND INITIAL ACCOMPLISHMENTS

The Social, Genetic and Developmental Psychiatry (SGDP) Centre is an interdisciplinary centre established in 1994 as a collaborative enterprise between the Medical Research Council (MRC) and the Institute of Psychiatry, King's College, London. The range of disciplines includes psychiatry, psychology, sociology, epidemiology, statistics and genetics. Its intellectual origins lie firmly in the MRC Social Psychiatry Research Unit. The particular way it was conceptualized was also much influenced by the experience of the MRC Child Psychiatry Unit that was established in 1984 under the directorship of Michael Rutter (M.R.).

* Address for correspondence: Michael Rutter, Box P080, SGDP Centre, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK.
(Email: d.ballinger-mills@iop.kcl.ac.uk)

The need for the establishment of the SGDP Centre was driven most immediately by the state of social psychiatry research in the UK in the early 1990s. This paper summarizes the issues that were inherent in each of these themes and concludes by considering the extent to which the SGDP has been successful in the aims expressed at the time it was established.

SOCIAL PSYCHIATRY RESEARCH UNIT (SPRU)

In 1948, Professor (later Sir) Aubrey Lewis had become the first psychiatrist to be made director of an MRC unit – initially termed the Occupational Psychiatry Research Unit (Shepherd, 1980; Shepherd, 1986). During the 1950s the work expanded greatly in its coverage and in 1958, its title was changed to 'Social Psychiatry'.

Lewis's view of what social psychiatry comprised was much broader than the prevailing views of the day. Obviously, it included a focus on the social causes and social consequences of mental disorder but also it was seen as an

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intrinsic aspect of biology. It would not be possible to understand the role of social factors if notice were not taken of their effects on the organism, and of the processes involved in individuals' interpretations of, and responses to, their experiences (Lewis, 1957; Lewis, 1958). Accordingly, the SPRU included physiological studies of schizophrenia (led by Peter Venables), experimental studies of cognitive processing and cognitive deficits (led by Neil O'Connor and Beate Hermelin), epidemiological studies and naturalistic and intervention studies of the effects of residential care on children's development (led by Jack Tizard), studies of social treatments of mental illness and the measurement of psychopathology (led by John Wing), developmental studies (led by M.R.) and sociological studies of the family and of mental hospitals (led by George Brown). The breadth and depth of the work of the SPRU during the 1950s and 1960s is well brought out in the volume edited by Shepherd & Davies (1968).

Unlike many leaders, Lewis appointed people of outstanding intellect who were prepared to challenge the wisdom of the day and also his own views. A high premium was placed on curiosity, a preparedness to notice the unexpected, and a firm commitment to engage in intellectual debate. This made the SPRU an exciting place in which to work.

A further feature of the SPRU was its recruitment, usually at a pre-doctoral level, of scientists who went on to become world leaders. This is most easily indexed by the fact that at least six unit members went on to direct their own research units (Carstairs, Leff, O'Connor, Rutter, Tizard and Wing). In making appointments, Lewis was influenced both by the areas of expertise that he wanted to have in the unit and by the need to attract people of an independent mind who would set their own research agenda.

MEDICAL RESEARCH COUNCIL CHILD PSYCHIATRY UNIT

Shortly after M.R.'s return from the 1979–80 year as Fellow in the Centre for Advanced Studies in Behavioral Studies at Stanford, California, he began to explore the possibility of establishing an MRC unit in child psychiatry. This led, in time, to the establishment of the MRC Child Psychiatry Unit at the Institute of Psychiatry in 1984.

The unifying features of the Child Psychiatry Unit (CPU) were a bringing together of developmental and clinical research perspectives and strategies, an integration of psychosocial and genetic research approaches, a commitment to the rigorous testing of causal hypotheses, and a recognition that to do this would require the application of modern statistical techniques that could deal with the latent constructs that were inherent in the causal hypotheses (Rutter, 1986). Sections of the unit focused on early social development (led by Dale Hay); on the use of longitudinal studies of both general population and high-risk samples to test hypotheses on environmental risk mediation (led by Barbara Maughan and David Quinton); on psychiatric genetics (led by Emily Simonoff); and on statistics and methodology (led by Andrew Pickles). The clinical areas that constituted the main focus were attention deficit disorders with hyperactivity and the disturbances of disruptive behaviour with which they were associated (led by Eric Taylor), depression arising in childhood or adolescence (led by Eric Fombonne) and autism spectrum disorders (led by Anthony Bailey). Throughout, external collaborations were sought and achieved whenever it was apparent that the research goals required either samples or expertise not available within the unit. The extensive collaborations with Lindon Eaves, Judy Silberg, and their colleagues in relation to the Virginia Twin Study of Adolescent Behavioral Development (Eaves *et al*. 1997) was one example; the collaborations with Anthony Monaco and his colleagues, at the Wellcome Trust Centre for Human Genetics, relating to a molecular genetics study of autism constituted another (International Molecular Genetic Study of Autism Consortium, 1998).

PSYCHIATRIC GENETICS RESEARCH UNIT

Over much the same period of time that saw the establishment of social psychiatry, psychiatric genetics became established in the UK under the leadership of Eliot Slater (see Shields & Gottesman, 1971). In 1936, Slater obtained an MRC grant to set up a twin register. In 1948, this led to a system at The Maudsley Hospital by which

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every patient was asked whether they were born one of twins and, if they were, their names went on to a register that provided the basis for much high-quality research in the years that followed. Slater's accomplishments and leadership in psychiatric genetics led to the establishment of the MRC Psychiatric Genetics Research Unit in 1959, with himself as director and Valerie Cowie as deputy director. During the next decade, psychiatric genetics research in the UK was put firmly on the map (Slater & Cowie, 1971) and the unit attracted many visitors from abroad.

One of the most important of these was Irving Gottesman, a visiting fellow from the United States, who established a most effective working partnership with James (Jerry) Shields that continued over the next two decades, giving rise to a seminal monograph on the genetics of schizophrenia (Gottesman & Shields, 1982). Gottesman and Shields emphasized the probabilistic rather than the deterministic role of genes and were the first authors to apply a genetic-environmental multifactorial-threshold model in psychiatry (Gottesman & Shields, 1967). Peter McGuffin, who was recruited to the SGDP Centre in 1998 to succeed M.R. as Director, spent a period as an MRC Training Fellow with Theodore Reich's group at Washington University in St Louis in 1981–82 and came under the tutelage of Gottesman, who was then in the same department. They have maintained close links ever since, publishing numerous papers and two books together (McGuffin *et al*. 1994, 2002).

It might be thought that the Psychiatric Genetics Unit would have shaped the thinking that later led to the setting up of the SGDP Centre. In fact, it did not. This is because Slater's antipathy to social psychiatry (stemming from his uneasy relationship with Lewis and his experience with some social psychiatrists) and his intolerance of the questioning of his views by people outside psychiatric genetics meant that specific environmental factors were generally ignored by him. Also, M.R. was uneasy about Slater's uncritical advocacy of radical physical treatments such as insulin coma therapy and leucotomy for the treatment of psychiatric disorders (see Sargant & Slater, 1954).

Although Slater, with his statistician brother Patrick, had written a seminal paper putting forward the suggestion that the genetic factors in neurosis worked on a polygenic basis and operated through their influence on individuals' responses to stress factors (Slater & Slater, 1944), he never moved on to consider the interplay between genetic vulnerabilities and specific environmental factors, and never collaborated with social scientists. M.R. considered that these various features made it a bad model for the SGDP Centre. Nevertheless, in its use of genetic strategies (see below), the SGDP Centre (once established) did benefit from all that Slater achieved in establishing psychiatric genetics, and in his pioneering recognition of the value of a twin register.

SOCIAL PSYCHIATRY RESEARCH DURING THE 1950s TO 1980s

The period of the 1950s to 1980s was one of intense excitement and creative innovation in the field of social psychiatry in Britain, and especially in the SPRU. It was particularly characterized by five main features. First, it was very broad in coverage. Thus, psychosocial researchers had pioneered the study of extrafamilial environments. This was evident, for example, in the study by George Brown and John Wing of the effects of different types of mental hospital environments on the course of schizophrenia (Brown & Wing, 1962), the studies of residential children's homes by Jack Tizard and his colleagues (Tizard *et al*. 1975), the study of London secondary schools undertaken by M.R. and colleagues (Rutter *et al*. 1979), and the study of community influences as exemplified by the comparison of Inner London and the Isle of Wight undertaken by M.R. and colleagues (Rutter & Quinton, 1977).

Second, in parallel with the appreciation of the importance of extrafamilial influences, there was recognition of the need to be concerned with the ways in which the family environment impinged differentially on the individuals within the family and of the huge individual differences in people's responses to adversity (Rutter, 1972). Brown and Rutter (Brown & Rutter, 1966; Rutter & Brown, 1966) developed the Camberwell Family Interview that provided a series of individual-specific measures including the measure of expressed emotion that subsequently proved to be such a pervasive risk

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variable (Leff & Vaughn, 1985; Sandberg *et al.* 2003). Brown and Harris, as well as Paykel, established good measures of stressful life events and did much to develop both concepts and rigorous ways of measuring the effects of such life events (Brown & Harris, 1978; Brown & Harris, 1989; Harris, 2000) and, in addition, Brown and Harris showed the ways in which prior experiences could increase people's vulnerability to life stressors (Harris *et al.* 1990).

All of this would not have been possible without it also having been appreciated that the rigorous study of psychosocial risk and protected experiences required robust and sensitive discriminating measures of different aspects of the psychosocial environment. That constitutes the third feature that characterized social psychiatry research during this era; the measurement advances were evident in all the examples noted above. The fourth feature was the development of designs that could provide rigorous tests of hypotheses about environmentally mediated risks. These included, of course, the use of genetically sensitive designs such as the variety of twin and adoptees research strategies but they also included a range of natural experiments that made use of longitudinal data combined with naturalistic opportunities created by contrasting environments (Rutter *et al.* 2001*a*). Finally, there were important conceptual advances that recognized the need to get away from viewing risk as an effect that took place at some discrete moment in time and, instead, recognized that risk and protective processes tended to operate over time in ways that could either lead to cumulative effects, or resilience and recovery (Rutter, 1989; Pickles & Rutter, 1991).

THE PERCEPTION OF CRISIS IN THE EARLY 1990s

Given all the achievements in social psychiatry during the 1950s to 1980s, one might wonder why there was a need for the SGDP Centre. However, there clearly was a need. The immediate precipitation was the MRC decision to close the Social and Community Psychiatry Unit in 1993, a mere three years after it had been established as a successor to the SPRU (but with continuing MRC support of its main research programmes outside the Unit context). This had been preceded by the earlier closure of the MRC Unit for Epidemiological Studies in Psychiatry in Edinburgh. Good research in social psychiatry was continuing, particularly in the field of psychiatric services research, but the study of social causes seemed rather to have lost its cutting edge through its reliance on traditional methodologies and its failure to develop new research paradigms. Also, social psychiatry seemed to have considerably narrowed its boundaries and its concepts. There was a failure of many in the field to take on board the possibility of the genetic mediation of postulated environmental risk influences. Also, psychosocial researchers had rather neglected the need to study the effects of experiences on the organism. If there was a carry forward of psychosocial risk effects, it was going to be crucial to understand how, in some circumstances, early experiences could have enduring effects. That meant that psychosocial and biological research had to come together. It was apparent, too, that it would be crucial to study influences in the context of lifespan development as it applies in adult life as well as in childhood (Murray & Lewis, 1987; Brown & Harris, 1989). There was a need to breathe new life into the concepts of social psychiatry and into the range of research designs that it used. If that were to succeed, however, it would be crucial for social psychiatry to be integrated with psychiatric genetics and developmental studies, and this required a new approach.

RECRUITMENT AND ESTABLISHMENT OF THE SGDP CENTRE

The first need was to consider what sort of research structure was going to work best in order to bring this integration about. M.R. discussed possibilities with the MRC and, out of those discussions, there emerged a concept of an interdisciplinary research centre. At that time, the MRC had no such centres but it was agreed that this might, in effect, constitute a pilot study to determine whether the approach was a good one. The centre was to be different from a regular MRC unit, not just in having greater breadth than would ordinarily be the case, but also in the expectation of international quality leadership of several different kinds that would be integrated by the centre director, but not

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directly led in the way that was expected in small- to medium-sized MRC units. The funding structure was also to be different in the sense that the MRC would provide infrastructure support but the research leaders would have to obtain individual programme or project support either from the MRC or elsewhere. This led to M.R. applying, with Professor (later Sir) David Goldberg, the Head of the Institute's Department of Psychiatry, to the MRC to establish the SGDP Centre. Because over the next few years the SGDP Centre proved to be a success, it became the model for further MRC centres. Currently, including the SGDP, there are four in the neurosciences.

There were important strengths at the Institute of Psychiatry to build on in establishing the Centre, but it was obvious from the outset that major new international recruitment was also going to be necessary. This coincided with the time when the MRC, in considering the needs in relation to the broader realms of biomedical science, was realizing that some changes in procedures and a much stronger collaboration with universities were going to be necessary if international recruitment were to succeed. The process of international recruitment started with the appointment of Professors Robert Plomin and Judy Dunn, who were at that time working at Pennsylvania State University (although Judy Dunn had established her early research career working in Robert Hinde's MRC unit at Cambridge in England). Both Plomin and Dunn played a key role in the way the Centre developed.

Following the closure of the Psychiatric Genetics Unit in 1969 at the time that Eliot Slater retired, the research continued under Jerry Shields who, in collaboration with Irving Gottesman, did some of his best work. Following Shields' death in 1978 a section of psychiatric genetics was established within the Department of Psychiatry at the Institute of Psychiatry under the able leadership of Professor Robin Murray. New recruits such as Peter McGuffin expanded approaches (see below), the twin register continued strongly, and molecular genetic research began. However, Britain had lost many of its best statistical geneticists at a time when MRC support for quantitative genetics did not seem to be forthcoming, and there was scarcely any quantitative genetics research in relation to psychological development. The clear need was for a world leader who had a longstanding central interest in nature-nurture interplay, provided a developmental perspective, appreciated the importance of considering dimensions of psychopathology, was committed to spanning quantitative and molecular genetics and, preferably, had experience in the use of animal models in genetic research (see Plomin *et al*. 1977; Plomin, 1994; Plomin & Rutter, 1998). We were most fortunate in being able to recruit Plomin at just the right time. We were similarly fortunate in being able to attract back to the Institute Professor David Fulker, a most innovative statistical geneticist (DeFries & Fulker, 1985) who had been part of the 1980s 'brain drain' to the USA. Unfortunately he died tragically young, at the height of his powers, within two years of his appointment. The Centre was later able to appoint to a joint chair with the Institute's Department of Psychological Medicine Professor Pak Sham, who has played a key role ever since.

It was equally essential to import international leaders in the field of social development who were receptive to genetic ideas and were interested in collaborative research, who studied relationships with peers and siblings and not just parenting, and who understood the study of psychosocial risk in protective factors. This well described Professor Judy Dunn (Dunn & Kendrick, 1982; Dunn & Plomin, 1990). It was also important to attract social researchers with a strong track record in using longitudinal studies that extended from early childhood into adult life, as well as meeting the other criteria. Professors Terrie Moffitt and Avshalom Caspi, as leaders in the Dunedin Longitudinal Study, clearly met those criteria, but also brought other very important strengths. Moffitt, a psychologist with a longstanding interest in genetics (Mednick *et al*. 1987) was exploring the role of cognitive deficits in relation to psychosocial risk (Moffitt, 1993*a*), and was a pioneer in developing effective ways of conceptualizing different varieties of antisocial behaviour (Moffitt, 1993*b*). Caspi had introduced the important concept that psychosocial adversities and stressors often serve to accentuate, rather than change, pre-existing personality attributes (Caspi & Moffitt, 1993), and he was a world leader in the study of long-term personality

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development from early childhood to adult life (Caspi *et al*. 1995).

Although there was good molecular genetic research at the Institute of Psychiatry, it was relatively small-scale and it was essential to recruit experienced molecular geneticists who could provide leadership and integration. Professor Ian Craig from Oxford well fulfilled that role, ably assisted by Philip Asherson and David Ball (both recruited from Cardiff). The final appointment prior to 1998 was that of Francesca Happé, who brought outstanding expertise in the application of cognitive psychology to the study of normal and abnormal development (Happé, 1994).

Peter McGuffin succeeded M.R. as Director in 1998, being selected as a clinical scientist who could build bridges between basic research and clinical practice, who had expertise in the field of adult psychopathology, and who was committed to collaboration between genetic and social researchers for the investigation of nature-nurture interplay (McGuffin *et al*. 1988*a*, *b*). The other appointment at the same time was that of Professor Anne Farmer, who greatly strengthened the field of adult psychopathology through her interest in nosology, as well as nature-nurture interplay (Farmer *et al*. 1992).

The pattern of top-level, often international, recruitment to the SGDP Centre, like the concept of the Centre itself, also set a useful model for the MRC as a whole. It paved the way for the current system of MRC Strategic Appointments in which the university pays the salary but, on the basis of peer-reviewed scrutiny of the person's research track record (rather than on application for a new grant), the MRC provides major research funding for up to four years.

From the outset, the Centre was concerned to develop strong links with researchers in the rest of the Institute of Psychiatry. The overall objectives of the Centre were well reflected in the research into schizophrenia led by Professor Robin Murray. Decades earlier, that research had been almost exclusively biological and focused on adult psychosis. Murray had been a pioneer, however, in recognizing both the importance of the developmental perspective (Murray & Lewis, 1987; Cannon *et al*. 2002) and in collaborating with social researchers in order to investigate why it was that schizophrenia appeared to be so much more common in people of Afro-Caribbean origin (Wessely *et al*. 1991; Castle *et al*. 1998; McKenzie & Murray, 1999; Rutter *et al*. 2001*a*). As such, the work would have fitted very easily into the Centre but, for good reasons, it was decided that it might work better to keep this large and successful research group together outside the Centre and, instead, build collaborative links.

RESEARCH ACCOMPLISHMENTS

In this final section of the paper, the discussion concerns the extent to which the SGDP Centre has succeeded in its basic aim of tackling the interplay highlighted in the title of the Centre.

Environmentally mediated psychosocial risks

Research strategies

One of the most important findings from behaviour genetics research was the fact that genetic influences operated on virtually all aspects of human behaviour and not just on diseases or disorders, or traits such as temperament, that people had tended to view as constitutional (Plomin & Rende, 1991). Much earlier, too, socialization researchers had had to face up to the realization that, just as parents influenced their children, so children also influenced their parents (Bell, 1968). In other words, with all socialization features it was crucial to test for the direction of the causal arrow. Both of these concerns meant that serious questions had to be raised about some of the claims with respect to environmentally mediated risk for psychopathology.

There has been appreciable success in that endeavour, using a range of quite diverse research strategies (Rutter *et al*. 2001*b*). For example, twin-singleton comparisons, using longitudinal data, were used to examine possible environmental influences on the slower language development, on average, of twins as compared with singletons – showing the important effect of mother-child communication (Rutter *et al*. 2003*a*; Thorpe *et al*. 2003). Institutional rearing and foster family rearing were compared to examine possible institutional effects on children's behaviour, using groups taken into the care of the local authority because of a breakdown in parenting, with both groups coming from a seriously high-risk background that was shown to be similar in the two subsamples – showing institutional effects on both

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social relationships and inattention/overactivity (Roy *et al*. 2000, in press). Twin designs have been used to examine the effects of measured risk environments within the context of a model that takes account of genetic influences – showing the effects of family negativity and domestic violence (Pike *et al*. 1996; Koenen *et al*. 2003). Post-infancy adoption was used to measure within-individual change as a function of both the pre-adoption risk environment and the post-adoption protective environment – showing major effects of institutional adoption on both cognition and behaviour (Rutter & the English and Romanian Adoptees Study Team, 1998; Rutter *et al*. 2001*a*).

Long-term longitudinal data extending from childhood to adult life, and including measures of prepsychotic behavioural features, were used to test the hypothesis that cannabis use in late adolescence/early adult life may provoke the onset of schizophrenia in susceptible individuals – demonstrating a cannabis effect (Arseneault *et al*. 2002). Also, the strategy of using comparisons within monozygotic (MZ) pairs (Pike *et al*. 1996) was used to great effect to examine (and demonstrate) the effects of negative expressed emotion on the development of disruptive behaviour (Caspi *et al*. in press). This last approach was particularly powerful because it used different informants for the measurement of the risk factor and the outcome variable; it took account of possible child effects on parents by examining the effects of negative expressed emotion at age five on the child's behaviour two years later at age seven, having taken into account the child's earlier behaviour; and its use of differences within MZ pairs ensured that the effects were not genetically mediated. As a result of research of this kind, it may be concluded that environmentally mediated risks for psychopathology, and for psychological development more generally, are indeed truly operative (Rutter, 2000).

Shaping and selecting of environments

More importantly, the research has cast light on other methodological and substantive issues. To begin with, it is evident that, with the exception of only rather unusual circumstances (such as man-made and natural disasters), individuals play a quite substantial role in the shaping and selecting of environments (Rutter *et al*. 1997). Thus, longitudinal studies have shown the surprising extent to which children's behaviour predicts the risk environments that they experience in early adult life (Champion *et al*. 1995). People both shape and select their environments. With respect to socialization effects, it is necessary to take account of this in relation to both parental behaviour and child behaviour (because parents, of course, pass on genes as well as shape their children's environment). Any study of environmental risk mediation is going to have to take account of social selection influences, because they are often quite strong (Caspi, in press; Borge *et al*. in press).

Equal environments assumption

The initial behaviour genetic findings on the role of gene-environment correlations were used to argue that some effects attributed to environmental risks were actually genetically mediated in part (Plomin, 1994). That continues to be an important message for psychosocial researchers, but it is now clear that there are also implications for genetic research. The twin strategy is crucially reliant on the Equal Environments Assumption (EEA), namely that any differences between MZ and (dizygotic) DZ pairs can be wholly attributed to genes. It is now evident that, at least with some traits (such as antisocial behaviour and emotional disturbance), the EEA is violated (Rutter *et al*. 2001*a*; Carbonneau *et al*. 2002). That is because it has been found that there are environmental effects (from environments showing a G-E correlation) deriving from differences within MZ pairs. The implication is that some of the MZ-DZ difference will be due to environmental, as well as genetic, effects. Equally, there has been a recognition that the genetic effect includes the indirect influences attributable to gene-environment correlations and interactions. Attention is now having to shift onto the study of these indirect effects.

Shared and non-shared environmental effects

Some commentators took the behaviour genetic evidence that non-shared environmental effects generally predominated over shared effects (Plomin & Daniels, 1987) to mean that family-wide influences were of negligible importance. The research is clear-cut in showing that this was a misguided inference. Broad family influences tend to impinge differently on different

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children in the family (Dunn & Plomin, 1990), but family-wide influences (such as negativity or neglect or violence) do have an important risk effect, albeit not affecting all children to the same extent. Also, when psychosocial risks are measured on an individual-specific basis, there may still be important shared environmental effects (Pike *et al*. 1996). The need is to move from the blanket assumption that it is only non-shared environmental effects that are important to a position in which individual-specific risks are measured in the context of an appreciation that it is crucially important to shift from studying the 'anonymous' environment to the study of specific measured environmental risk factors, and to do so with a realization that both shared and non-shared effects are likely to be found and that they will vary in their importance according to both context and outcome. For example, shared effects are probably much more important in the field of antisocial behaviour than they are in the field of depression.

Environments within the normal range

Some behaviour geneticists have claimed that psychosocial factors only have environmentally mediated effects when they concern extreme environments. The research has shown that that is a mistaken assumption. Several of the studies mentioned above have demonstrated effects within the normal range of environmental variation (Rutter, 2000). On the other hand, it is quite likely that psychosocial effects will be quite minor in the case of individuals who are already functioning in the superior range (Duyme *et al*. in press).

Origins of environmental risk

It has become very clear that serious attention needs to be paid to the origins of psychosocial risk factors and to the differentiation of the particular features of the environment that bring risk or protection. For example, Jaffee and her colleagues (Jaffee *et al*. in press) showed that although fathers' involvement in childrearing generally had a positive effect on children's psychological development, it had a negative effect when the father was antisocial. There is a substantial literature on the effects of parental divorce and remarriage where there has tended to be the implicit assumption that these can be conceptualized as time-limited happenings that can be assessed as independent features. The research by Judy Dunn and her colleagues (Dunn *et al*. 1998, 1999, 2000) has vividly shown how mistaken that view is. The formation and break-up of families constitutes a quite complicated process that operates over time. Also, the risk and protective effects need to be conceptualized, measured, and analysed in the knowledge that the effects may derive from the family situation, but they are just as likely to arise from the characteristics of the individuals who are in particular family situations or in the psychosocial circumstances that led up to the family break-up or remarriage.

Effects of life experiences on the organism

Traditional developmental views of the lasting impact of early life experiences have assumed that these are largely dependent on the quality of the environments encountered in later life. Thus, to a considerable extent, apparent continuities are a result of early adversities predisposing to later adversities rather than because early experiences bring about lasting changes in the organism. There is good reason to suppose that these views have substantial validity. On the other hand, the follow-up of children who spent their first few years in very deprived Romanian institutions, and who were subsequently adopted into well-functioning UK families, strongly suggests that some sort of biological programming can occur (Rutter *et al*. 2004). Of all the variables associated with psychological outcomes, the duration of institutional deprivation proved to be much the strongest. Moreover, the effects of duration of deprivation were as strong at 6 years of age, several years after the children had been in the adoptive home, as they had been at age 4 years. The findings at the 11-year follow-up have shown effects of a similar kind that have not attenuated to any marked extent and seem to be unrelated to individual differences in the quality of the adoptive family rearing environment (O'Connor, 2003). Many questions remain on precisely what neural processes are involved but it is obvious that these must constitute a key focus for future research.

Psychopathological progression

Traditionally, psychiatric classifications have dealt with mental disorders as if they constituted discrete independent categories. It has long been

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obvious that the realities were rather different. Not only is co-morbidity very common but also the genetic findings do not map at all exactly onto the diagnostic boundaries as usually conceptualized. One of the key questions concerns differentiation between the possibility that environmental factors influence the ways in which genetic susceptibilities are translated into disorder, and the rather different possibility that the genes themselves have pleiotropic effects that encompass supposedly different psychopathological features. A third possibility is that the presence of one form of mental disorder, through its manifestations, creates a risk for another (Rutter, 1997). Twin studies have begun to cast light on these issues. Thus, it seems that the explanations for the co-morbidity between substance use and depression differ somewhat from those between substance use and antisocial behaviour (Silberg *et al*. 2003). Anxiety and depression probably share the same genetic liability to a very considerable extent (Silberg *et al*. 2003) and the same applies to the associations between general anxiety and specific phobias in childhood (Eley *et al*. 2003). Also, shared genetic liability is an important part of the association between hyperactivity and disorders involving disruptive behaviour (Nadder *et al*. 2002). So far, the research has paid only limited attention to the role of specific environmental factors and clearly that has to be a main item on the future research agenda.

A rather different progression issue concerns the connections between normal development, transient disorder and persistent disorder. Plomin and colleagues (Bishop *et al*. 2003) examined this in relation to language delay at 2 years of age, using assessments at 3 and 4 years to differentiate transient and persistent disorders. Only a modest heritability, with a major environmental effect, was found, but heritability was higher in the case of persisting language difficulties that led to seeking professional help. It is notable that the heritability found was substantially lower than that found in a previously reported portion of this sample (Dale *et al*. 1998), emphasizing the importance of replication. Equally, the heritability was lower than that found in an earlier sample of older twins (Bishop *et al*. 1995), suggesting that genetic influences tend to be greatest with serious persisting delay coming to clinical attention.

A related issue concerns the importance of age of onset as a differentiator, shown with respect to depression. Childhood onset is characterized by a stronger association with psychosocial risk factors, with genetic factors more influential for depressive conditions beginning in adolescence or adult life (Thapar & McGuffin, 1996; Silberg *et al*. 1999; Jaffee *et al*. 2002).

Broader psychopathological phenotypes

Plomin has long argued that genetic contributions to psychiatric disorders may operate through genetically influenced dimensions that operate across the full normal distribution and not just in relation to qualitatively distinct disease categories (Plomin & Rende, 1991). The postulate essentially involves two rather different components. First, there is the argument that continuously distributed dimensions constitute a crucial part of risk-protective processes. There is a good deal of evidence that this is the case, across the field of internal medicine and not just in psychiatry, even though there are few direct examples using identified genes (Plomin & Rutter, 1998). However, questions remain on the extent to which personality traits are distinct from subclinical levels of disorder (Farmer *et al*. 2002). Second, there is the suggestion that the susceptibility genes involved constitute commonly occurring allelic variations that do not have any necessary direct causative effect on mental disorder, rather than rare mutations that usually lead fairly directly to some handicapping condition. Research findings are beginning to accumulate to support the validity of Plomin's views on both these features (Rutter, in press). Thus, it has been found to apply in the case of dyslexia (Cardon *et al*. 1990). It also applies to the role of the monoamine oxidase-A (MAO-A) gene in relation to antisocial behaviour (Caspi *et al*. 2002) and the serotonin transporter gene (Caspi *et al*. 2003) in relation to depression (see below).

Most psychiatrists are likely to be receptive to these arguments as put forward in relation to common disorders such as depression and antisocial behaviour. On the other hand, the severe disorders such as schizophrenia or autism have generally been viewed as qualitatively distinct from normality. In some respects, of course, they are distinct but there is growing evidence

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that the genetic liability to both extends well beyond the traditional severely handicapping concepts of the disorders. In the case of schizophrenia, this has involved the presence of so-called schizotypal personality features (Jones *et al*. 2000) and in autism, subtle, but quite marked, deficits in social and communicative functioning, generally termed either the broader phenotype, or lesser variant, of autism (Le Couteur *et al*. 1996; Murphy *et al*. 2000). It seems desirable now that molecular genetic research focuses on these broader features as well as on the traditional diagnoses.

Cognitive deficits in psychopathology

Although there is strong evidence that autism spectrum disorders (ASD) involve cognitive deficits associated with neural malfunction that is strongly influenced by genetic factors (Bailey *et al*. 1996), there is little knowledge so far on just how these features 'fit together', or on the neural processes involved. Happé and her colleagues have tackled the matter in three ways. First, functional imaging in conjunction with specific cognitive tasks has been used to determine whether individuals with ASD used the same brain areas to understand mentalizing tasks that involved 'theory of mind' skills, as did normal controls. The results showed that they did not, the main difference lying in the apparently weaker connectivity between the relevant brain areas (Castelli *et al*. 2002). Second, they tested the hypothesis that the broader autism phenotype was indexed by weak central coherence (referring to the processing of details rather than the meaning of the whole), finding that the fathers of individuals with ASD did indeed show this pattern (Briskman *et al*. 2001; Happé *et al*. 2001). Third, they compared patterns of cognitive deficit in individuals with ASD and individuals with an attention-deficit/hyperactivity disorder, with findings showing that both showed executive planning impairments but only those with ASD showed weak central coherence. Clegg *et al*. (in press) showed that 'theory of mind' deficits of the kind associated with ASD were present in adults who had had a severe developmental disorder of language, and that problems in social relationships persisted well into adult life despite major gains in language skills. There is no question but that cognitive deficits are strongly implicated in autism and in developmental language disorders; this may also apply to milder deficits in first-degree relatives of individuals with autism. Nevertheless, many puzzles remain and findings on the neural underpinning are only just beginning to be established. It is also apparent that social cognitive differences may play a role in early disruptive behaviour (Hughes *et al*. 1998).

Sex differences in psychopathology

Despite the fact that being male or being female is obviously genetically determined, much of the literature on sex differences and mental disorder has focused on supposed lifestyle differences for explanations. Unfortunately, most of the research has been highly speculative in nature and has not dealt adequately with the conceptual and methodological issues involved. Moffitt *et al*. (2001) sought to provide a model of how sex differences might be investigated by focusing on antisocial behaviour in the context of the Dunedin Longitudinal Study. The findings were striking in showing that the size of the sex difference (and in some cases, even its presence) varied considerably by the type of antisocial behaviour. Contrary to many previously expressed views, the risk factors for antisocial behaviour were generally similar in males and females. What was different was that the risk factor of neurodevelopmental impairment was much more frequently found in males and this particularly applied to early-onset lifespan-persistent antisocial behaviour. It remains to be determined why the rate of such impairment is so much higher in males.

The findings on antisocial behaviour prompted more detailed consideration of both the pattern of sex differences in psychopathology and the multi-stage causal processes that might be operative (Rutter *et al*. 2003*b*). It was apparent that male preponderance largely applied to early-onset disorders that tended to involve neurodevelopmental impairment, and that female preponderance largely applied to adolescent-onset emotional disorders. The implication is that there may be a common factor that operates across disorders within each of these two groups but which differs between the two groups. One further consideration that has emerged from the study of sex differences is that it will be necessary to account for both the consistency of sex differences

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and variations in the size of their effect. For example, studies from all over the world have been consistent in showing that boys are much more likely than girls to show difficulties in reading (Rutter *et al*. 2004). On the other hand there is marked variation among countries in the size of the sex difference. Similar considerations apply with respect to antisocial behaviour (Rutter *et al*. 1998*b*). That is, it is a consistent finding that most crimes are much more frequently committed by males than by females but the size of the sex difference has halved in the last half-century. Clearly, there is a need for the research to explain both features, and it seems clear that the research strategies are going to need to bring together genetic, environmental and developmental perspectives.

Nature-nurture interplay

The most basic issue in relation to the aims of the Centre is the elucidation of the ways in which the interplay between nature and nurture are involved in the causal processes for psychopathology. Findings from the Virginia Twin Study of Adolescent Behavioral Development (VTSABD) showed that both G-E correlations and interactions were involved in the susceptibility to depressive disorders in girls and in the rise in the rate of such disorders during adolescence (Silberg *et al*. 1999; Silberg *et al*. 2001*a*, *b*). The findings also suggested that the genetically influenced vulnerability to postpubertal depression mainly operated through the prior manifestation of pre-pubertal anxiety (Silberg *et al*. 2001*b*). Statistical modelling, undertaken by colleagues in Virginia, showed that genetic influences on the vulnerability to depression operated through these three main routes – i.e. via main effects on anxiety, gene-environment correlations, and gene-environment interactions (Eaves *et al*. 2003). Life events had little impact in the absence of genetic susceptibility, but did play an important role in causation when combined with genetic susceptibility. Much the same pattern was evident in relation to the effects of child maltreatment on the development of disruptive behaviour (Jaffee *et al*. in press). The importance of gene-environment correlations and interactions, and the need to separate the two, has led to the development of improved statistical models for use in twin studies (Purcell, 2002; Purcell & Sham, 2002).

Gene-environment interaction

Inevitably, there are uncertainties involved in the study of gene-environment interplay when the actual susceptibility genes have not been identified. The situation becomes quite transformed once such genes are identified (Plomin & Rutter, 1998). Although there were many pointers from research in other branches of medicine that gene-environment interactions were likely to be important (Rutter & Silberg, 2002), it is only quite recently that this has been shown directly in relation to mental disorders. The first demonstration came from the Dunedin Longitudinal Study. Caspi *et al*. (2002) demonstrated an interaction between a functional polymorphism in the promoter of the MAO-A gene and child maltreatment in relation to the development of antisocial behaviour. Interestingly, there was no main genetic effect; there was a significant main environmental effect, but the biggest effect came from the gene-environment interaction. The finding has recently been replicated by colleagues in Virginia (Foley *et al*. in press). This constitutes the first confirmed interaction between a measured genotype and a specific environment in the field of psychopathology.

More recently, Caspi *et al*. (2003) have shown a comparable effect with respect to the interaction between a 'short' version of the serotonin transporter gene and a high level of life stressors. As with the MAO-A gene, the risk for depression derived not from the gene on its own and not from life stressors on their own, but from a combination of the two acting together. The importance of this finding derives from several different features. First, Caspi *et al*. were able to show that it was most unlikely that this interaction actually reflected gene–gene interaction, rather than gene-environment interaction. That is because they showed that the interaction did not apply to life events that arose after the onset of depression. If the life events were simply a reflection of genetic vulnerability, the effect should be evident at all times, irrespective of the timing of the life events. If, on the other hand, life events truly represented an environmentally mediated risk, the effect should be found only with respect to life stressors that preceded the onset of depression, and that is exactly what was found.

Second, the particular gene that was implicated is one that controls the neurotransmitters

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that are affected by antidepressants. Accordingly, the finding potentially opens the way to a better understanding of the biology of depression, although the details of the finding raise questions about ways in which antidepressants are thought to work. Third, like the quantitative genetic findings, the results point to the importance of indirect routes of genetic effect, operating via nurture, with respect to multifactorial mental disorders (Rutter, in press). This runs counter to the traditional notion that susceptibility genes are likely to act directly as influences on the liability to psychiatric conditions. Nevertheless, the same findings also indicate that the genetic effects are not environment-specific. Thus, the serotonin-transporter gene seems to be concerned with the effects of both physical maltreatment and stressful life events on depression. Equally the MAO-A gene is concerned with the effects of maltreatment on antisocial behaviour and not on depression. Once more, the results force something of a rethink on how genes operate.

Fourth, the findings have implications for research strategies in psychiatric molecular genetics. It has often been supposed that the way forward lies in the genotyping of huge numbers of individuals in order to detect genes of small effect. The implication has been that this can be done with a disregard for environmental risk factors. These findings raise queries about this strategy – at least in relation to antisocial behaviour and depression. The interactions were found in samples of moderate size (about 1000), but the leverage was obtained by having a known well measured environmental risk factor, as well as a candidate gene, as a starting point. It seems that geneticists are going to have to pay more attention to environmental risk factors than they have in the past, and to measuring them well.

CONCLUSIONS

In the past, genetic research, psychosocial research, and developmental studies have tended to remain rather separate with respect to both the concepts employed and the empirical research undertaken. The SGDP Centre was set up with the assumption that that needed to change and that progress was going to be greatly facilitated by the three coming much closer together. Research undertaken within the Centre has taken some important steps in showing that this is indeed the case. Findings from other research groups are giving rise to similar conclusions (see Rutter, 2002*a*, *b*). It no longer makes much sense for genetics, social psychiatry, and developmental psychopathology to be seen as separate endeavours because progress in each of these is so heavily reliant on progress in the other two, and on the three coming together in collaborative studies.

The days of quantitative behavioural genetics as a means of measuring the heritability of individual psychological traits without any concern for the effects of specific environments are numbered. On the other hand, it is very clear that genetic influences are widely pervasive in many different, and important, connections. The effects are often indirect, operating mainly via nurture, and now the focus will need to be placed more directly on nature-nurture interplay. Social psychiatry is being revitalized through its conjunction with genetic and developmental research strategies. Social causation is an important reality but individual differences in response to adversity are enormous and it is clear that genetic effects play a crucial role in those individual differences. Developmental studies remain strong, particularly as a result of the combination of long-term longitudinal studies with genetic information, and the beginnings of research to assess the effects of experiences on the organism. No longer is development seen as something restricted to childhood and child psychiatry; it is proving as important in the fields of schizophrenia and adult depression as in the disorders of early life. Cognitive processing has come to be seen as a crucial part of the workings of the mind in relation to psychopathology, and functional imaging is providing the means to connect thought processes with their neural underpinnings.

The first decade of the SGDP's existence has been associated with both substantive empirical and conceptual advances. However, much remains to be done and the research endeavour in the future will need to incorporate other areas of science. In particular, it will be crucial to seek to trace the pathways between genes and behaviour at all levels of analysis, from cells to social systems. In addition to the use of large-scale molecular epidemiological studies, achieving

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this goal will require the use of animal models (a programme led by Leo Schalkwyk, recruited in 2000) and the study of gene expression and the molecular biology of cells (in which new lecturer Ursula D'Souza will play a key role). Ultimately, the aim is that the Centre's unique contribution will be the provision of an understanding of how genes work at the behavioural level in relation to the developmental interplay between genes and environment – a field that has been termed 'behavioural genomics' (Plomin *et al*. 2001, 2003; McGuffin *et al*. 2002).

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