The SAGE Handbook of Mental Health and Illness

Edited by
David Pilgrim, Anne Rogers
and Bernice Pescosolido

The SAGE
Handbook *of*

Mental health *and* Illness

The field of mental health is now an ideological and terminological battle ground. The diagnostic categories, and the terms used to refer to the people affected, are all strongly and validly contested. This important book helps policy makers, practitioners and researchers to pick their way across this minefield relatively unscathed, to appreciate in fine grain detail the social context within which mental illnesses unfurl, and how this context shapes (often in profoundly socially excluding ways) the lives of people with mental health problems. As a corrective to biological reductionism, this wise book actively expands our understanding of how social forces permeate all aspects of mental illness.
Professor Graham Thornicroft, Institute of Psychiatry, UK

Pilgrim, Rogers and Pescosolido's volume is a wide-ranging and cross-national examination of many core issues in the sociology of mental health. It presents a variety of perspectives on fundamental substantive and policy issues in mental health and illness. Its scope and range make it ideal for scholars and students in a variety of disciplines concerned with social aspects of psychological distress and disorder.
Professor Allan Horwitz, Rutgers University, USA

This book provides the reader with an updated, in-depth yet comprehensive, overview of key issues in our understanding of mental ill health and mental health. The text illustrates well changes in the way we conceptualise mental ill health and health over the last twenty years, referring us to past and present reasons for these changes, such as a greater emphasis on mental wellbeing, mental health promotion, recovery, and social inclusion. A number of countries, professions and disciplines are represented in the book by both well known authors in this field, and some newcomers to it. Together they have succeeded in offering the reader an impressive range of ideas, knowledge and evidence that challenge some of the cherished notions we have as a culture about mental ill health and mental health.
Professor Shula Ramon, Anglia Ruskin University, UK

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Preface

We are grateful to all the contributors of this Handbook and hope that its readers find the chapters useful, informative and stimulating. Although not an exhaustive list of topics are covered (our field of interest is very broad and virtually unending), enough are available in the following pages to mirror much of the way in which mental health and mental disorder are currently explored in the Anglophone academy by and for social science. The book could be considered in its entirety as a fair sample of the work being done in the field indicated by its title or it could be used as a reference book by students of mental health and mental disorder with a particular interest.

Our choice of topics has been broadly divided into one section on mental health in its social context and another in which clinical and mental health policy matters are addressed more pointedly. This division is somewhat arbitrary and the allocation of a chapter in this or the other part of the book might be open to fair challenge. However, the partition is offered as a way of signalling the distinction between the general and the particular even if the two need to, or can, always be considered fruitfully in relation to one another. The two parts are merely the first of a few signposts for the reader picking up the book for the first time, which could have seemed a large picture to comprehend, if we had merely listed one chapter after another.

Each of the two parts will contain their own introduction to note the key points of each chapter and at times to offer our own commentary on points of contact or contrast between the contributions. As editors, we have made no demands on any of the contributors to write in this or that way about the topic they address. Our role has merely been one of feedback and trimming rather than academic guidance, as they are all experienced specialists in their field. In other words, when commissioning the chapters at the outset, our concern was to have a series of topics represented in the book and we turned to those we trusted to write well about the one allocated to them. We hope that the reader is rewarded by our policy of trust in the writers. Finally, we have taken the editors' privilege of supplying our own contributions at points in the book (with some help from friendly colleagues) and so that policy of trust also extends to ourselves.

David Pilgrim
Anne Rogers
Bernice Pescosolido

SECTION I

Mental Health and Mental Disorder in Social Context

Editors' Introduction

The first chapter is written by a medical geneticist, Angus Clarke. As will be clearer in later chapters (see Thomas and Bentall in Section 2) bio-reductionism remains a recurring point of contention and grievance for social scientists studying mental health. It is useful then to begin with this topic but written by a professional biologist with a critical eye about, and commitment to, 'the social'. Clarke explains in some detail how geneticists think about behaviour, dismissing at the outset strong claims from either side of the 'nature – nurture' debate. He provides a useful and informed discussion for readers with no background in genetics about how that broad field considers mental disorders. Not only does this field entail empirical complexity, it also implies some pre-empirical questions about conceptual coherence in relation to distinctions between the normal and the abnormal.

In line with these more fundamental pre-empirical questions, if the empirical link between genetics and behaviour in its social context is complicated it is not a simple matter either to 'measure' mental disorder as the next chapter indicates. Jerome Wakefield and Mark Schmitz address this vexed question, in particular relation to community samples, which contain people who have had no professional contact and do not (necessarily) view themselves as being mentally disordered. The problems of both reliability and construct validity for psychiatric epidemiology also remain for social scientists, especially those reliant on nosological systems, such as DSM (from the American Psychiatric Association) or ICD (from the World Health Organization). Funding agencies like the NIMH in turn demand their use (whatever doubts might be harboured by individual researchers). The detailed methodological challenges addressed in this chapter are particularly pertinent to consider in the light of the DSM now going into a fifth edition, due to

appear in May 2013 (http://www.dsm5.org/pages/default.aspx). This further revision is being constructed at a time when hard and fast distinctions between particular disorders and between many disorders and normality are often still not easy to make.

In the next chapter, Benedikt Rogge offers a contribution from Germany (a special thanks to him, from us, for rising to the challenge, so admirably, of writing in a second language). He addresses the recent pre-occupation within social science and social policy about wellbeing and positive psychology and begins where the last chapter left off: mental health is a fuzzy concept. After the problems of defining mental health and mental disorder are addressed, Rogge then summarizes the shift towards 'positive psychology' and places it within a wider sociological context of debate about 'the self'. This draws our attention to the disciplinary separation (as well as potential common interest) between psychiatry, psychology and sociology. Positive psychology and the sociology of the self may now be complementary exercises to place alongside the clinical focus on defects, pathology and distress found in psychiatry and clinical psychology.

This prospect is also picked up in the next chapter by Gillian Bendelow, who begins as a sociologist with a focus on emotional health as a discourse to be considered separately from the concerns of clinical professionals. In particular she wants to start a discussion about mental health and the emotions with a reconsideration of the traditional psycho-somatic split, the legacy of Cartesian dualism. Her attention to medicalization and the limits of a focus on biomedical antecedents links to later chapters (particularly from Olafsdottir in this section and Thomas and Bentall in the next). However, Bendelow also cautions against the risks of new emphases on holism, which create the spectre of 'healthism' and invite new forms of surveillance and social control.

The next chapter returns us to social epidemiology, with a particular focus on ethnicity and race from a British viewpoint. James Nazroo and Karen Iley emphasize the role of social and economic inequalities in the production of both ethnic/racial differences in risk of severe mental illness. Those inequalities also construct the experience of ethnic/racial minorities, when their members experience mental health problems and have services contact. However, this chapter appears in this part of the book rather than the next because the process of service contact mirrors wider social processes about race and inequality. This and other chapters (see Chew-Graham, Hermann and Secker in the next section of the book) are a window into the established class gradient in mental health, which we simply take for granted now as social scientists (see our preface). The authors go on to examine methodological criticisms of studies in the field to date and round off their chapter with a consideration of the experience that ethnic/racial minorities have of their problems, which connect the experience of service contact with the shared wider racialised context which both patients and services are embedded in.

If race is one important dimension to the experience of mental health problems, so too is gender. This topic is discussed by Jane Ussher with a focus on the

experience of depression. She looks at the extensive empirical evidence on gender differences in the diagnosed incidence of depression and prevalence but then goes on to explore competing explanations. The latter include hormonal, as well as psychological and sociological accounts, especially in relation to material and role inequalities. She also introduces other variables, which are important but contested; domestic violence and lesbian relationships (discussed as well later, in the chapter by Pilgrim and Rogers). Gender inequality is thus posited as an important source of mediation between social stressors and personal distress. Ussher also summarizes some evidence on cultural differences, which is extended in the next contribution, also written from Australia.

Renata Kokanovic discusses depression, but this time in relation to the cross-cultural challenges of formulating the meaning of experienced and expressed distress. Her examination of depression raises some important conceptual points suggested in earlier chapters; Ussher's just noted, but also those from Bendelow, Rogge and most fundamentally from Wakefield and Schmitz. Can we readily distinguish depression from normality and is misery experienced and expressed in the same way in all cultural contexts? Given that the World Health Organization has been concerned about a 'pandemic' of depression, the other question implied is 'a pandemic of what?' Kokanovic's exploration allows us to reflect on these questions and like Ussher raises some challenges for social scientists about the tensions between realist and constructivist accounts of common distress.

Questions of stress and experienced distress are then considered more extensively by Susan Roxburgh, who focuses on the stress process model. This consists of three primary elements: stressors, intervening explanatory variables and stress outcomes. Each of these elements is considered in turn by the author. The intervening variables include resources, such as social support, which are picked up for more consideration at the end of the book in the chapters by Secker and Pescosolido. Finally Roxburgh looks at the outcomes of stress, especially depression (sadness, demoralization and alienation) and anxiety (feelings of tension, restlessness and irritability). These are the main, often mixed, manifestations of 'common mental disorders' treated in primary care (see Chew-Graham in Section 2).

In the subsequent chapter by Scott Schieman, the stress process model is also used as a framework for understanding the relationship between faith and mental health. Despite a common assumption about secularization, belief in God as a causal agent remains important for many people (even if they have no agreed named religion or attend religious rituals regularly). For this reason, Schieman argues that it is important for students of mental health in society to look carefully at the interaction of faith, stressors and personal resources. This reminds us of the importance of 'intervening explanatory variables' in Roxburgh's earlier account. It is also an opportunity to rehearse competing arguments about whether religion is pathogenic or helpful in the lives of ordinary people.

In the next chapter, Brea Perry joins one of us (Pescosolido) to consider the emergence of stigma about mental disorder, especially in relation to that identified in early life. On the one hand, prevalence rates of recorded mental disorder

are at their highest in the very young (and the very old), on the other we know little about public attitudes towards childhood problems. This chapter provides an empirical account from the USA of how the general public comprehends health conditions in childhood (ADHD, depression and asthma). This makes a start at producing an evidence base about ordinary understandings of childhood problems that might be the basis for public education and other policies.

Stigma is addressed in a more general way by Graham Scambler in the next chapter, which starts with Goffman and Wittgenstein as early authoritative discussants about the separation of normal from non-normal conduct in society. Stigma has to be considered in the same sociological breath as norms: it cannot be understood as a free-standing topic. Scambler places specific consideration about mental illness within a wider context of the sociology of stigma and in relation to labelling theory, biographical disruption and narratives of personal tragedy. He extends this to challenges from disability theory, moving on to a discussion about the possibility of stigma reduction programmes. Once more, this discussion brings in some ontological and epistemological aspects of social science, in relation to the tension between materialist and constructivist accounts.

If stigma is one outcome of norm transgression, then the re-framing of the latter, from sin and crime to illness, is the starting point of Sigrun Olafsdottir's exploration of medicalization, with attention being paid to the interests of the medical profession, the drug companies and managed healthcare. As she notes, this confluence of interests is at its most obvious in the USA and hence the stronger interest in the medicalization thesis there than in other parts of the world. The author provides a critique of this US-bias in theorizing medicalization and introduces a comparative approach as a corrective. This does not undermine the basic model of medicalization but it does imply a needed sensitivity to cross-national/cultural differences.

In the final chapter in this section of the book, two of us (Pilgrim and Rogers) start with a criticism of the taken-for-granted cultural assumption about mental disorder as the source of danger. We argue that a more valid account should understand it as a two way street. Danger is also a common source of mental disorder – in the home, on the streets, in the workplace and most dramatically in war zones. (The chapter by Roxburgh on stress is pertinent here, as is the part of Ussher's chapter that has already considered domestic violence.) The notion of danger is discussed in relation to both violence and risk and this permits us to note the tension, which exists in debates about mental health policy in relation to social control (serving the state and third party interests) and beneficent paternalism (the use of legal powers to ensure treatment of mental disorder). This policy emphasis starts to explore topics to appear in Section 2, especially in the chapters from Scull and Rose and Campbell.

1

The Limits to Psychiatric and Behavioural Genetics

Angus Clarke

INTRODUCTION

My starting assumption is that genes are 'involved in' behaviour; consequently, genetic variation contributes to variation in behaviour. To deny that would be not merely unreasonable but incoherent, although there is still some appetite for the old nature – nurture pseudo-controversy. The too-crude dismissal of the importance of genetic factors can still appeal to those who enjoy attacking the straw-man genetic determinist, who is thought to argue for the 'primacy' of genetics over the environment (Sonuga-Barke, 2010). If there is any sense in talk of the 'primacy of genetics', it is that an individual's set of genes is given and fixed from conception and is from then on available for interaction with the (changing) environment. What does not make sense is to think of either an individual's genes or their environment as being the principal determinant of future behaviours in isolation from their environment or their genes (respectively).

A full repertoire of genes is required for all behaviour (whether the latter is designated as normal or abnormal). All but a few of the smallest chromosomal deletions, that result in some genes being present in one copy per cell instead of the usual two, are associated with cognitive impairment and therefore with difficulties for the individual in organizing their behaviour. Even chromosomal duplications – resulting in three copies of the relevant genes – usually affect cognition and behaviour as well as other aspects of growth and development.

Such chromosomal anomalies become interesting – and challenge our understanding – when we find that a particular deletion or duplication is associated not merely with a diffuse cognitive impairment but with some more specific and unusual behaviours. The idea that a disruption to the set of chromosomes leads to a 'spanner in the works' and thereby a disruption to thought and communication can be accommodated within a very primitive model of 'genes acting within the brain'; but how would a specific chromosomal anomaly lead to a specific behavioural anomaly?

The types of evidence we can draw upon to assess the effects of genetic variation on psychiatric disease and behaviour more generally include observations of people with disturbances of cognitive development and behaviour (including mental illness), where there is a good reason to accept a chromosomal or genetic basis for the disturbance. We might also observe the familial clustering of diagnosed mental illness or cognitive impairment, sometimes presented in terms of 'heritability'. In addition, we might have an apparent association of genetic variants from across the genome with diagnosed mental illness or a variation in behavioural traits.

In this chapter, I examine the types of evidence and argument that have been used to relate genetic factors to behaviour, primarily that deemed to be abnormal. We consider what types of conclusion such evidence is able, in principle, to support in the light of a realistic model of gene-environment interaction.

EVOLUTION AND ETHOLOGY

One context in which genes are related to behaviour is in discussions of our evolutionary past. It is clear that the behavioural patterns enabled by our genes have been compatible with our survival as a species. This has always entailed both cooperation and competition with our fellow humans; it is with whom one cooperates, with whom one competes that is important. Observations of primate behaviour can give insight into our remote past because our ancestors resembled contemporary primates (Cheney and Seyfarth, 2007). However, while such accounts may tell us something about the evolutionary success of different behavioural strategies, they do not allow us to draw inferences about how specific genes are related to particular behaviours. The genetic constitution of a species will impose constraints on the repertoire of behaviours available to an individual of that species but this gives us no access to understanding the way in which the genetic variation between individuals leads them to behave differently.

Armchair evolutionary reflection leads us to consider how the behaviour of an individual will let him or her contribute maximally to the next generation of the species. Such an approach focuses on competition within a species and forces us to acknowledge the importance of *sexual* selection, as well as the narrower type of natural selection for mere survival. While we must combat parasites and infectious diseases in order to survive, and be able to endure occasional injury

and famine, such qualities will not be transmitted to the next generation if we leave no offspring, that is, if we cannot attract a mate and ensure that our children survive to maturity. A crude Darwinian approach starts from the position of 'selfishness' to identify the behavioural traits that will prove to be essential for individuals both to survive and to reproduce effectively. However, can we account through such reasoning for the range of human behaviours found in modern societies?

With such a question, as in science generally, one must search for the 'counter-examples' that could disprove a hypothesis. One obvious question has related to altruism. How can one make sense of apparently altruistic behaviour, such as issuing a warning cry about a predator or assisting members of the species in rearing their offspring, within a Darwinian framework? Risk-taking or burden-sharing by one individual on behalf of others can be accounted for through the conventional operation of natural selection, if those helped in this apparently 'altruistic' fashion are relatives. In such circumstances, the 'altruist' is promoting the survival of relatives and thereby the transmission of his/her own genes when they are passed on by a relative. Such considerations apply in particular to some of the social insects, as with sterile worker bees labouring to ensure the success of the hive, but also to birds and mammals with cooperative rearing of the young. More complex patterns of indirect reciprocity in human societies may have developed from such practices (Nowak and Sigmund, 2005) and looking for cooperation between non-kin does not provide clear counter-examples (Clutton-Brock, 2009).

Evolutionary psychology constitutes an attempt to account for a range of human behaviours and attributes – normal and abnormal – by postulating similarly 'natural' processes, explicable in terms of natural selection. Its weakness is that the processes it describes must have happened in the distant evolutionary past if they are to account for human behaviours, personality traits and psychopathology evident today. This field of enquiry is all too vulnerable to the criticism that it is essentially a series of Kiplingesque speculations in the tradition of the *Just So Stories*. The descriptions of human gender roles and personality types may ring true, or may at least be amusing, but the causal accounts are largely speculative, neither adding firm knowledge nor yielding useful (testable) hypotheses.

However, despite this criticism, there are of course good reasons for expecting different patterns of social behaviour in male and female humans, as in many other animals, not only primates. One especially important factor in recent human evolution may have been the appearance of spoken language, which may have led to the rapid development of 'wit' – in both senses – through female choice of mate and the processes of sexual selection. However, one can only speculate about the details and the naturalistic fallacy – arguing from 'is' to 'ought' – is all too common in this domain. From the possibility that our hunter-gatherer forebears may (at certain times, in certain places) have had a particular pattern of social organization, we can draw no conclusions about how we *should* organize our collective lives today.

Claims about 'intelligence' are related to the speculations of evolutionary psychology. Thus, the idea that the human X chromosome is especially involved in 'intelligence' receives a limited degree of support from some evidence. There does appear to be an excess of X chromosome genes among those in which mutation causes serious cognitive impairment (Turner, 1996), although that does not allow one to conclude that variation in genes on the X chromosome accounts for more than that chromosome's rightful share of the genetic contribution to variation in intelligence (however, this is measured). Such reasoning is entirely invalid. Furthermore, these claims ignore the greater chance of a gene on the X chromosome coming to attention through mutation and the greater chance of the mode of inheritance being apparent.

In summary, an evolutionary (Darwinian) approach to the study of animal (and human) behaviour is necessary – 'nothing in biology makes sense except in the light of evolution' – *but* such an approach is limited in what it can establish as fact about the past or as desirable about the present. There are altogether too many examples of popular science writing that seek for solutions to today's social and political problems through the application of crude ideas about our collective past.

'IT'S A KNOCK-OUT': STRUCTURE AND FUNCTION IN THE BRAIN

Other approaches in addition to genetics have been taken in the search for understanding of the central nervous system (CNS). These approaches all have in common a commitment to the reductionist project. This is not intended as a criticism because a reductionist approach has to be the starting point for any scientific study of the central nervous system. Only in this way can one recognize the limits of reductionist explanation – by coming up against them. Assigning functional roles to specific regions of the brain through the analysis of the effects of damage from tumour, infarction, haemorrhage or experimental lesions is a long-established approach that was essential in the early stages of neuroscience and remains so today. The central difficulty of this approach has been to understand the rules of inference from the observations made, which are remarkably similar between the different contexts of neuroscience and genetics. In neuroscience, what can one conclude about the function of part X of the brain if behaviour Y occurs when a lesion is produced there? In genetics, what can one conclude from the emergence of behaviour Q when gene P is inactivated or altered (mutated) in some other way?

In relation to neuroanatomy, there has been a progressive development of our ability to make such inferences as the working model of the brain has increased in sophistication through the accumulation of our knowledge of previous observations and experimental interventions. The *normal* function of one of the basal ganglia, for example, might not be most helpfully understood as the suppression of involuntary contra-lateral writhing movements, although that might be the most prominent feature of a lesion there, whether pathological or experimental.

There has been a similar process of sophistication in our understanding of the function of genes. The naming of genes is now more formalized but used to be based upon the phenotype that arose when a mutation occurred in the gene. The 'white-eye' gene of *Drosophila* usually produces eye pigment, which is not produced when the gene is mutated so that the eyes are then white. In one sense, this leads to a paradoxical naming of a normal gene or the corresponding protein by its opposite (as with the dystrophin protein, a lack of which results in Duchenne muscular dystrophy) or the naming of a gene by a disease-related feature irrelevant to the function of the normal gene (as with the archetypal example of the polyglutamine repeat disease, Huntington's disease and the huntingtin protein, whose normal function is related to the disease after which it has been named by coincidence only).

More recently, the role of particular neural circuits and pathways has been defined in animal models in increasing detail using these approaches of inferring function from the effects of the ablation of brain structures. Two recent illustrations, drawn almost at random from many, include the switching on or off of fear in mice (Herry et al., 2008) and the pursuit of rewards in rats (Burke et al., 2008).

Another productive, reductionist approach to structure-function relationships in the brain is that of imaging, including functional imaging, which is able to identify neural circuits active during specific tasks and sensory processing. As David Hume indicated long ago, the temporal association of two events does not establish causation. Such experiments may therefore not be able to distinguish the causal driver of a neural process from those associated circuits involved in its modulation, if indeed there is usually something corresponding to a 'causal driver' so that the distinction has a meaning (Logothetis, 2008).

With this approach, it may even be difficult to distinguish actual neural activity from anticipated but aborted activity, as blood flow in the cortex can be directed in anticipation of an imminent task that then fails to be carried through to performance (Sirotin and Das, 2009). Whether the findings of such studies are regarded as explanations or, more properly, as increasingly detailed descriptions of the phenomena to be explained, will depend upon the investigator's point of view.

This rather abstract argument is relevant to the topic of this chapter when considering the question of a behavioural phenotype and what shape an explanation of such a phenotype might take, if an explanation can be discerned at all. Let us look at the parallels in a closely related field. The recognition of an unusual pattern of physical features is the core activity in dysmorphology – the clinical study and delineation of patients with congenitally abnormal physical features, often also accompanied by abnormalities of the CNS and of cognitive development.

The early development of this discipline centred on the recognition of recurrent patterns of malformation or unusual physical features and whether these were usually sporadic events in a family or had a tendency to recur. Once cytogenetics had developed to the point of diagnostic applications, some conditions but not others were found to be associated with chromosomal anomalies, initially with

an abnormal chromosome number (as in Down syndrome or Turner syndrome) and then with more subtle anomalies, such as chromosomal deletions or duplications. The extent to which trisomy 21 is not only associated with but can be said to 'explain' Down syndrome is an interesting question at many levels, with obvious parallels in the neurosciences. While trisomy 21 may explain why one child rather than another is affected by Down syndrome, it only permits a detailed mechanistic explanation of some of the physical and behavioural features of the condition. Even where it can account for the incidence of dementia at an early age in those with Down syndrome, *it is unable to account for why an individual has a specific lapse of memory on one occasion but not another*.

The interplay between clinical and laboratory genetics has been enormously productive in developing a taxonomy of dysmorphology. The recognition of an association between cases of a clinical disorder and particular cytogenetic or molecular genetic findings leads to the recognition of a subgroup of the clinical disorder where this association is not apparent. Such atypical cases will often have a different cause and may, in time, be recognized as an altogether different entity in their own right. One could mention the emergence of Noonan syndrome from Turner syndrome as an example, or the recognition of CDKL5-related disease from among the 'early onset of seizures' variant of Rett syndrome. To what extent can we expect similar progress in our understanding of the genetic basis of the disorders affecting behaviour?

SYNDROMES AND BEHAVIOUR

Many of the dysmorphic syndromes affecting embryogenesis and then physical and cognitive growth and development are associated with abnormal patterns of behaviour. These abnormal behaviours are most often the result of substantial cognitive impairments that restrict the assimilation of sensory input, its cognitive processing and then the behavioural responses. Some of these syndromes show very characteristic patterns of behaviour, such as the 'cocktail party' chatter of a child with Williams syndrome, the social awkwardness of some males with fragile X syndrome or the social interest but slow responses of someone with Rett syndrome. Such behaviours can sometimes be recognized as a part of the overall 'gestalt' of the condition or they may be more apparent when behaviour is studied with objective systems of description and measurement. In relation to the physical features of some dysmorphic syndromes, it is becoming possible to sketch out a plausible sequence of events from the underlying genetic cause of the condition through the consequences of that in the embryo and foetus to the physical features of the affected child or adult, as with the structural proteins disrupted in Williams syndrome (including a deletion of the elastin gene) or Marfan syndrome (a fibrillin gene mutation).

Are we then beginning to be able to give a coherent account of the pathway from the genetic alteration underlying a syndrome to the specific behavioural

features found in that condition? The short answer – all we have space for here – is 'No!' Such explanatory pathways for these and other dysmorphic syndromes have not yet been constructed in a plausible fashion, except to state the obvious, that an abnormality in a gene required for normal brain development and function will have cognitive and behavioural consequences.

We must indeed be very cautious in attributing behaviours common in those with a specific condition directly to the primary genetic basis of the condition, rather than to some indirect habits of social interaction that develop because of the physical appearance of the young child, the pattern of their cognitive abilities or particular difficulties they have with the senses or with organizing motor activities. However, the observation of an association between a genetic anomaly, its particular physical features and a particular pattern of behaviour is not fundamentally in doubt, even if the mechanisms through which the genetic change leads to the pattern of behaviour often remain obscure.

SINGLE GENE EFFECTS

Are we any further forward with understanding the effects of single genes on behaviour in the absence of developmental problems and severe cognitive impairment? As with development of the brain, so with conditions which lead to its degeneration: single gene disorders that lead to the loss of neurons and neuronal connectivity lead to the loss of capacity and so to dementia – as in Huntington disease and the familial forms of early-onset Alzheimer disease. But what about the effects of single genes on more specific items or patterns of behaviour, other than simply causing severe cognitive impairment?

There are distinct single-gene (Mendelian) disorders and chromosomal deletion syndromes associated with patterns of behaviour more usually seen in the absence of a clear genetic anomaly. The behavioural pattern of autism, for example, is often found in children with tuberous sclerosis (TS) (caused by mutation in the TSC1 or TSC2 genes) and sometimes in children with constitutional PTEN gene mutations (Butler et al., 2005). The diagnosis of 'schizophrenia' occurs at a high frequency (more than 25 per cent) in adults with the 22q11 deletion typical of people affected by the DiGeorge and Shprintzen (velo-cardio-facial) syndromes. Children with TS usually develop benign intra-cerebral tumours (tubers) and those with mutations in PTEN – another tumour suppressor gene affecting growth in early life – often show macrocephaly and so the effect in both cases may be mediated by abnormal growth of the brain.

Other Mendelian loci in which mutation is associated with autism are those encoding the neuroligin proteins NLGN3 and NLGN4 (Jamain et al., 2003). These cell adhesion molecules are positioned on the postsynaptic side of synapses and are believed to interact specifically with neurexin 1 on the presynaptic side; it is of great interest – although perhaps tantalizing – that deletions and other disruptions of the neurexin 1 gene NRXN1 are implicated as contributing

to 'schizophrenia' (Kirov et al., 2009). Such single gene effects, however, have been found in few cases of psychiatric disease and in no cases of behavioural variation 'within the normal range'. Given the high frequency of psychiatric disease, with 'schizophrenia' having a life-time incidence of ~1 per cent, and given the long history of investment in research into these conditions, what can we say about the contribution of genetic factors to these important disorders? Recent studies of genetic variation across the genome suggest an overlap between the factors contributing to 'autism' and to 'schizophrenia', raising the possibility that these conditions may not be distinct diagnostic entities.

PSYCHIATRIC DISORDERS AND MULTI-FACTORIAL INHERITANCE

Genetic research into psychotic disorders, such as 'schizophrenia' (SZ) and 'bipolar disease' (BPD) has long been justified by its proponents indicating studies of heritability, especially twin studies comparing identical twins with fraternal twins or siblings. These studies often show a high value of heritability (up to 80 per cent in many studies). As molecular genetic studies became feasible in the 1980s, researchers set out to identify familial cases of SZ and BPD in order to conduct linkage analyses and map the important loci.

Although there were a few positive results, it became clear that single genes of major effect segregating in families (i.e. Mendelian loci) are not contributing substantially to the incidence of these disorders. As molecular methods developed along with the statistical and bioinformatic methods required to interpret their findings, it became possible to search for loci of lower penetrance – less likely to cause disease – until with current methods it has become clear that even powerful genome-wide association studies (GWAS), with (cumulatively) many thousands of cases and controls, have been unable to identify genetic variation accounting for more than a small fraction of the supposed genetic contribution to the risk of these diseases.

However, it is important to note that a few loci, implicated through segregation of disease in those rare families where a gene of major effect does seem probable, have now also been implicated in these more recent GWAS studies as perhaps contributing weaker disease predispositions in a much greater number of cases (O'Donovan et al., 2009). Of particular interest is the finding that two of the loci at which variation is associated with SZ are also associated with the risk of BPD. This raises the possibility that the genetic predisposition to both disorders is at least partly shared, so that they may not be two distinct conditions but instead somewhat different manifestations of a single category of major psychosis. And these factors also overlap with those implicated in autism.

The research community now needs to learn from these findings what they can tell us about the mechanisms underlying these disorders: what cellular mechanisms and/or neural pathways become dysfunctional in the presence of the predisposing variants, and how does this increase the risk that an individual will

become psychotic? Understanding these functional mechanisms – the basic neurophysiology – may give insight into new therapeutic possibilities for these common and immensely distressing and burdensome conditions. (For other accounts of psychosis see Bentall and Thomas, this handbook.)

LIMITATIONS OF THE COMPLEX DISEASE MODEL OF THE PSYCHOSES

Although the overview of current research into the genetic basis of SZ and BPD outlined above is fair, there are some complexities that need to be considered if we are to place the recent research findings in context. We need to question the evidence on which SZ has been considered so highly heritable and we need to think about what the term 'heritability' includes.

At this point, I should make explicit my 'ideological' position as both a paid-up realist (Bhaskar, 1975) and social constructionist (Berger and Luckmann, 1966). The world and our observations of it are real; the ideas we have about the world, however, are constructed and communicated in language and through processes of social interaction and negotiation. Diagnostic categories are social constructions that may correspond in more or less helpful and appropriate ways to observable reality; the construction of diagnoses in psychiatry has been and inevitably remains a more complex and contested area than in trauma surgery but the suffering associated with 'psychiatric disease' is real – incontestably – whatever labels we choose to employ.

First, it has become clear that some cases of diagnosed SZ are associated with the de novo occurrence (in the proband) of a small chromosomal deletion or, less often, a duplication. These are known collectively as copy number variants (CNVs) and are detected on DNA microarrrays (gene chips), which can compare the relative dosage of gene sequences from across the genome. The same technology is proving very useful in identifying the genetic basis of previously unexplained cases of dysmorphic syndromes and other disorders of physical and/or cognitive development.

What does this mean? Well, comparisons of identical and fraternal twins have been the mainstay of heritability studies in SZ, and if a condition has been caused by a new genetic change of major effect (such as a CNV) then it is likely to affect both of a pair of identical twins but only one of a pair of fraternal twins. A CNV arising as a new mutational event will therefore lead to a high estimate of heritability for the disorder simply because it is a new mutation of high penetrance affecting identical but not fraternal twins. This will lend unwarranted support to the ideas of the 'complex disease' origin of SZ, because the causal model underlying the estimate of heritability will have been misconceived. CNVs known to be associated with SZ are being recognized in 2–3 per cent of cases, and de novo CNVs in as many as 10 per cent of cases of SZ (Xu et al., 2008) although that figure is higher than other published figures (reviewed in O'Donovan et al., 2009).

What remains uncertain is whether the de novo CNVs found in SZ represent a small subgroup of SZ. In contrast, they could be the tip of the iceberg, with many other cases arising as de novo events undetected by microarray technology because they are much smaller, perhaps point mutations or other intragenic mutations within loci included in the CNV sites. It may take a few years for uncertainty to be clarified, especially if de novo events contribute to some classes of disease and not to others. If the CNVs constitute only the tip of an iceberg of new or recent mutations occurring in the last few generations, then this could account for both the high estimates of heritability and the lack of success of GWAS studies in accounting for more than a small fraction of the heritability. The new generation sequencing technologies will help to resolve the issue in the long term, as much greater volumes of sequence data become available from patients with different patterns of disease. In the short to medium term, however, such data will doubtless generate more information than can be interpreted with confidence, as more sequence variants of uncertain significance will be encountered.

The second complexity we need to address is the nature of the 'heritability' estimated in twin studies and other experimental designs. This is the proportion of the variance in a quantitative trait that can be attributed to variation in the relevant genetic factors as a fraction of the total phenotypic variance. So the term applies only to quantitative traits and not to categorical traits, and it includes all the relevant genetic factors and not only the straightforward (independent) components of these factors. If all the relevant genetic factors interacted by modifying the risk of disease in a simple, multiplicative fashion, as would be the case for combining independent risk factors, then there would be less reason to query the interpretation of heritability estimates (although the point made in the paragraphs above would still remain valid). From what we know of other (lower) organisms, however, it seems most unlikely that GxG and GxE effects can be ignored. The problem is that, for many reasons, humans are poor organisms for estimating interactions between (i.e. among) genes and between genes and the environment.

Specific gene-gene (GxG) interactions are difficult to identify unless one has access to information about the phenotypes associated with each genotype from among the range of those possible. Because of the vast range of genetic variation within the human species, the nonrandom pattern of mating among humans, the long time-course from birth to maturity and the quantity of phenotypic information required, it is doubtful if enough data could ever be captured to permit such analyses. Indeed, there may not be enough people alive for the range of relevant genotypes to be represented. And this puts to one side the question of analysis and of interactions with the environment.

Our environments, of course, are also highly complex and variable; we live for decades and early experience may well shape our later mental health; we do not often marry or mate 'at random' and our family sizes are small and becoming smaller. The possibility of gathering enough information about the mental health outcomes of a large enough set of individuals of known genotype to assess the

risks of disease for a range of specific genotypes at numerous interacting loci and in the face of a range of different early and adult environments is therefore small unless one makes vastly simplifying assumptions as to what factors can be ignored. If the GWAS studies had shown (or come to show) that specified genetic factors do account for a large proportion of the (estimated) heritability, then that would have supported the simplifying assumptions underlying that work.

However, none of this has happened (yet). Given this complexity and uncertainty the methodological assumptions about psychosis and heritability in psychiatric genetics in the first part of the twentieth century were clearly flawed and driven by eugenic pre-suppositions. Indeed many of assumptions embedded in the legacy of that period in biological psychiatry remain highly speculative (Kingdon and Young, 2007). Put simply, the eugenic assumption of degeneracy pre-figured the desire to find confirmatory empirical evidence and weak methodologies of inquiry were deployed to find the latter (Marshall, 1990; Pilgrim, 2008).

GENE INTERACTIONS IN QUANTITATIVE TRAITS

In model organisms, where experimental designs are possible and mating can be controlled, such as with the fruitfly *Drosophila melanogaster* in particular, data can be collected that give us good insight into gene-gene (GxG) and gene-environment (GxE) interactions influencing a wide range of traits including important behaviours. Especially helpful has been a long series of studies by Trudy Mackay and her colleagues, often using recombinant inbred strains of flies kept in a small number of distinct environments and studied with the help of breeding programmes. Of course, none of these facilities exist in human populations but the difficulty of demonstrating or measuring in humans the effects that have been identified in fruit flies does not mean that they are absent from our species.

Trudy Mackay's work in *Drosophila* on both life-span (longevity) (Leips and Mackay, 2000; Vieira et al., 2000) and sensory bristle number (Dilda and Mackay, 2002) shows that there are strong interactions between genes, between genes and sex and between genes and the environment, especially temperature (as I have outlined in more detail elsewhere – Clarke, 2004). This work has been integrated with microarray studies of gene expression to identify genes likely to be important influences on lifespan (Geiger-Thornsberry and Mackay, 2004; Lai et al., 2007). The methods required for the quantitative genetic analysis of behavioural traits have been established some years ago (Anholt and Mackay, 2004) and have begun to yield important insights (Ayroles et al,. 2009), although it is interesting that research focused on mutagenic screens to identify single gene loci influencing such traits is still yielding the most important findings (Vosshall, 2007).

Such work demonstrates that the genetic architecture of complex traits involves many loci interacting in a truly complex fashion and suggests that the studies that

could feasibly be conducted in humans will fail to identify many such effects, at least into the medium term. In addition, it seems that there are single genes of great importance for specific behaviours – and in which mutation will disrupt one or more such behaviours – but that many loci influence patterns of behaviour in a complex web of GxG and GxE interactions, even if they cannot all be identified in our own species. For this to be true, there must be a high level of genetic polymorphism that is of functional importance and that is maintained not merely by mutation and drift (the random consequences of breeding patterns) and not the effects of selection.

Is that likely? The answer has to be 'yes' in *Drosophila* and there is no reason why it would not also be true for our own species. Phenomena such as frequency-dependent selection, density-dependent selection, sexually antagonistic selection and other types of disruptive selection are well known (Rice et al., 1992; Sokolowski et al., 1997) so that there is no need to expect heterozygote advantage and drift as the only mechanisms to account for high levels of polymorphism. The evidence in favour of recent natural selection in humans is limited but this relates principally to shifts in allele frequency leaving evidence in the pattern of linkage disequilibrium; such findings tell us nothing about the maintenance of polymorphism as discussed here.

GENE-ENVIRONMENT INTERACTIONS IN MENTAL DISORDERS

Thoughtful reviews of the genetics of complex disorders in humans have indicated such difficulties as those identified above in looking at such traits and disorders in humans (Kendler and Greenspan, 2006; Lewis and Brunner, 2004; Weiss, 2008). It would clearly be immensely difficult to obtain data about GxG interactions across a range of standardized environments in our species, without assuming that other genes are not involved in the trait under investigation. Despite this, some information has been collected about the overall effect of specific single alleles in at least two different environments (i.e. the GxE interactions) for several psychiatric disorders.

Highly dramatic and largely unsupportable claims have been made about the contribution of genetic variation at the MAO locus to violent behaviour but more modest claims about the interaction of a functional polymorphism at this locus with a personal history of physical abuse as a child do have some supporting data, indicating that those subject to abuse in childhood and who have lower levels of MAOA activity are more likely to display antisocial behaviour as adults (Caspi et al., 2002).

Another example of GxE interactions evident in humans is of the association between a genetic variant in another enzyme influencing levels of amine neurotransmitters and antisocial behaviour. Among those given a label of ADHD, the frequency of antisocial behaviour differed with the alleles of a polymorphism at the COMT locus (Caspi et al., 2008) and similar findings have been made

elsewhere (Fowler et al., 2009; Maestu et al., 2008). The interpretation of such findings, however, is not straightforward and needs great care to avoid erroneous over-generalizations (Thapar et al., 2007a). In particular, the intrauterine environment may modify the effects of genotype and postnatal environment as influences on subsequent psychopathology (Langley et al., 2007) and there are methods that could begin to disentangle such effects (Thapar et al., 2007b).

Turning to autism, the findings of an association with CNVs (deletions and duplications) as discussed above is of great interest, especially because of the implication of specific genomic regions containing plausibly 'relevant' gene loci (Glessner et al., 2009; Wang et al., 2009). While autism is clearly not a single disorder, and can be strongly associated with mutations at some specific genes (e.g. Butler et al., 2005), most cases are not associated with a clear Mendelian disease. Therefore, the extent to which the CNVs identified in these two 2009 studies have arisen de novo (or have been transmitted from an affected parent) is also of great interest because of the distorting (inflating) effects of such events on measures of heritability, as discussed above.

The degree to which common variants in the population modify the phenotype of autism while individually rare but cumulatively common major mutations (such as CNVs or the presence of rare Mendelian diseases) trigger the development of such problems remains to be determined; at least it is clear that these issues are now being addressed by the molecular researchers, who are not content to adopt a 'traditionally' deterministic stance (Happe et al., 2006; Stephan, 2008; Weiss et al., 2009).

In the area of 'depression', too, evidence is emerging that people of certain genetic constitutions are more liable than others to respond to stressful life events by becoming sad and distressed (Caspi et al., 2003; Risch et al., 2009). Such findings bring psychiatric genetics much closer to the lay perspective on causation of such illness as being in part triggered by circumstance, in part the result of personality.

In the case of SZ, some of the predisposing genetic factors appear to be the same as in autism and BPD (Lichtenstein et al., 2009 and references cited above). If these findings are upheld by further evidence, then these diagnostic categories will clearly require reassessment. The finding of post mortem epigenetic differences within specific regions of the brain between patients affected by SZ and controls lends some credibility to the idea that early life experience may contribute to disease through such a mechanism (Mill et al., 2008). While some familial mutations are known that can act as strong triggers of SZ (Blackwood et al., 2001), it is perhaps intrinsically unlikely that such inherited variants of major effect would be common as the fertility of those with disease is likely to have been impaired both by reduced survival (especially in the past, before effective treatments) and impaired social skills.

The frequent finding of novel CNVs affecting genes in neurodevelopmental pathways in cases of SZ (Walsh et al., 2008) suggests that many cases of such disorders arise de novo and that other such new mutation events undetectable by

array CGH will account for further cases. The most plausible conclusion at present seems to be that major (and often new) events trigger disease and that common functional variants will modify the nature and course of disease and perhaps thereby influence the particular diagnosis made according to today's taxonomy; polymorphisms at the loci of major effect (e.g. Stefansson et al., 2003) may also act as such modifiers when the trigger is a major event elsewhere in the genome (Carroll and Owen, 2009).

GENETICS OF NORMAL TRAITS AND INTELLIGENCE

There is a long tradition of studies of 'intelligence', as measured by the Intelligence Quotient and its heritability. These have usually used twin and adoption studies and have indicated a high heritability (often of 0.6 – 0.8). These findings have then often been misused by those with a prior political commitment to support some particular social policy such as – typically – the uselessness of investing in the early education of those belonging to lower social classes or specific ethnic groups.

Such misapplications of research findings make the elementary error of treating heritability as if it were a fixed biological constant instead of being a variable that depends upon *the particular social environment* operating at the time. Moreover, this error is compounded when we consider that the environments to which different research groups were exposed were systematically different, as is the case in societies with wide socioeconomic differentials (Fischer et al., 1996; Lewontin, 1991). There is no need for us to recite these analyses here (Gould, 1981). Instead, let us simply recall that the prospect of misapplication of research findings in this area – looking at IQ differences between social and ethnic groups – is so great and the chance of 'useful' results contributing to the educational success of future generations so slim that the case for undertaking or supporting such research hardly exists (Clarke, 1997a; Harper, 1997). Some did believe in good faith that elucidating the genetic basis of variation in IQ within the normal range would help to understand the causes of severe cognitive impairment but these studies have failed to deliver that promise and were never likely to do so as the methodologies involved were intrinsically flawed.

It is clear that many measures of the heritability of IQ in contemporary society have been systematically inflated by the techniques employed (Devlin et al., 1997) and that IQ as measured is heavily dependent on socio-economic status (Turkheimer et al., 2003). Furthermore, the idea that there are 'genes for intelligence' seems implausible. *Rather, there will be specific patterns of alleles at multiple loci that interact with each other and the environment to modify a number of cognitive abilities.*

The suggestion that one particular allele at a locus will be consistently associated with superior 'wit' is most implausible. In that case, one would expect there to be strong selection – both conventional natural selection and, especially, sexual

selection – in favour of that allele and it would then not remain polymorphic. Rather, it is much more likely that variation at loci important for cognition and communication is maintained by the advantages brought by each allele in different GxG and GxE circumstances – as discussed above for *Drosophila* longevity, for example. The whole sorry saga of the genetics of IQ appears to be a tale of misunderstandings by researchers who have either been politically motivated or who have simply placed too much value on a narrow, scholastic intellect that happens to have brought them a degree of academic success.

APPLICABILITY OF GENE-WIDE ASSOCIATION STUDIES (GWAS) TO CLINICAL RISK ASSESSMENT

The research into the association between common genetic variation and the risk of the common, complex diseases has been struggling to explain its lack of success in accounting for more than a small fraction of the heritability of disorders, from cancer and diabetes to 'schizophrenia' (Maniolo et al., 2009). The reader who has reached this point will be familiar with much of the explanation. We have seen inflated estimates of heritability, as well as the difficulty in assessing GxG and GxE interactions in our species. However, there are some additional factors to consider: epigenetic variation acquired in early life as a 'predictive adaptive response' (Moore and Williams, 2009); the often underestimated contribution of rare variants to common diseases (Bodmer and Bonilla, 2008); and the impossibility of pangenome panels of SNPs (Conrad et al., 2009; Estivill and Armengol, 2007) to capture CNVs that have relocated to other sites around the genome (Schrider et al., 2010).

Even in the case of disorders, where the nosology is relatively straightforward – and certainly much less contested than in psychiatric disease – the use of genetic association studies using the SNP-based GWAS approach is of little, if any, clinical utility. It is poor at assigning healthy individuals to clinically useful risk categories and so is generally of little, or no, value. If it could be justified as at least accurate, there would remain many reasons as to why it may not be helpful, such as the sometimes paradoxical (medically unhelpful) behavioural and psychological responses to high or low risk information (Clarke, 1995, 1997b). However, its power to account for the heritable fraction of disease risk is so limited, not even that inadequate justification is available to those who offer such 'services' on the open market (Edelman and Eng, 2009; Janssens et al., 2008). Such irresponsibility must surely be motivated by desire for a quick return on investment rather than any professional sense of good healthcare (Clarke, 1995, 1997b). The scientific value of the underlying research is not in doubt – it is only the *application* of the research findings to assign healthy individuals to risk categories that is unwarranted (Jakobsdottir et al., 2009).

The suggestion that such tests should be made available to assess the risk that an individual might suffer from psychiatric disease is still less justified for at

least two important reasons (Braff and Freedman, 2008; Couzin, 2008). First, those likely to seek such testing will probably have a close family history of psychiatric disease. Accordingly, the SNP-based GWAS results will be irrelevant if the disease in the person's family is at least in part caused by an important de novo genetic event or at least one that has occurred within the last few generations. Second, such results could add to the stress known to precipitate at least some types of psychiatric morbidity.

CONCLUSION

Genetic variation contributes substantially to the occurrence of psychiatric disease and research into this is not only worthwhile but has recently begun to yield important results. However, from what we know of the genetic factors involved, the claims made about the genetic contribution to psychiatric disease in the past – especially some of the assessments of 'heritability' – appear to have been inflated and to have minimized the contribution to disease of the combined effects of many rare genetic variants and of Gene × Environment and Gene × Gene interactions. It is likely that our understanding of mental illness and its classification may well require a radical revision, when and if our understanding of the genetic factors involved has been consolidated; this reassessment may also prove to be very helpful in developing new therapeutic approaches.

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2

The Challenge of Measurement of Mental Disorder in Community Surveys

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INTRODUCTION

Community studies in psychiatric epidemiology attempt to determine the number of people suffering from mental disorder in general and from each specific type of mental disorder, and to identify the characteristics and risk factors correlated with each disorder and possible etiological factors in the disorder's occurrence. The information derived from such community studies influences mental health policy, guides prevention and screening efforts, impacts the planning for efficient distribution of mental health care, and forms the primary justification for decisions regarding the level of funding of mental health services and research. To accomplish the aims of such community studies, researchers must develop measures that can assess psychiatric symptoms among individuals who often neither consider themselves to be mentally ill nor seek mental health treatment and so have never been professionally diagnosed. Since the beginning of psychiatric epidemiology, formulating reliable and valid indicators of disorder to use in such surveys has represented a major challenge to the ingenuity of researchers.

Well-trained clinicians, with the help of an adequately detailed history and diagnostic interview, can generally identify a case of mental disorder when they see one. However, identifying people with a mental disorder in the general

population, most of whom have never seen a clinician, is a very different matter. It is generally too expensive to use mental health professionals to survey large samples, so lay interviewers with a fixed set of questions are almost always used in such studies. Consequently, epidemiological surveys lack many of the safeguards and corrective mechanisms available in a clinical evaluation by a trained mental health professional who can flexibly explore the nature and sources of a patient's distress. Thus, even though they attempt to replicate clinical diagnoses in the community population, such studies can be more prone to diagnostic error.

In order to try to capture the judgment of a clinician, the main strategy that has been used in recent years in constructing epidemiologic instruments to measure mental disorder is simply to take the diagnostic criteria sets that clinicians use to diagnose patients, presented in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (2000), and to translate those criteria into questions in a research instrument. This chapter will explore the special problems that have arisen in epidemiologists' attempts to transfer diagnostic criteria from the domain of clinical evaluation to the much different epidemiological arena where disorder is measured in the general population by survey.

WHY CLINICAL SAMPLES ARE INADEQUATE MEASURES OF COMMUNITY PREVALENCE

Early attempts at obtaining prevalence estimates of mental disorder in the community used clinical samples and simply surveyed how many individuals had received treatment in hospitals, private practices, and other service venues. There are several fundamental problems with estimating community prevalence in this way. Not all disordered individuals have access to mental health services, and many either do not recognize that they have a disorder or prefer not to seek help even if they do. Moreover, it is common for individuals to consult professionals and even to receive treatment for normal conditions of intense grief or concern about life events. One can get a sense of how much of a difference clinical sampling versus direct community sampling of a population can make to prevalence estimates from Srole et al.'s (1978) classic study of mental disorders in midtown Manhattan. Srole's group studied both a clinical sample and a community sample within the same area. Based on the clinical sample, the prevalence of mental disorder was estimated to be 12.9 percent – in an area saturated with mental health services and professionals. Yet, based on the community survey, the prevalence according to a conservative criterion was estimated to be 23.4 percent and by a looser criterion 81.5 percent (Manis et al., 1964).

In addition to providing misleading estimates of prevalence, clinical samples may also provide more subtly biased answers to other questions that epidemiological studies are designed to answer, such as questions about the demographic breakdown of mental disorders. A good example of the sorts of problems to which clinical sampling is prone can be found in the seemingly contradictory

socioeconomic-level prevalence data in two classic clinical-prevalence studies, Hollingshead and Redlich's (1958) study of New Haven and Srole et al.'s (1978) study of midtown Manhattan. Hollingshead and Redlich's clinical data, based on a census of New Haven mental treatment centers, including public and private hospitals and outpatient offices and facilities, indicated dramatically higher disorder prevalence rates in lower socioeconomic (SES) classes, whereas Srole et al.'s clinical data indicated higher rates of disorder in the upper classes. Hollingshead and Redlich's finding that the lower the class, the greater the proportion of psychiatric patients, was claimed by them to support the etiological hypothesis that social stress is a primary cause of mental illness. Hollingshead and Redlich found the following clinical prevalence rates per 100,000 population in various socioeconomic classes: I–II (highest), 556; III, 538; IV, 642; and V (lowest), 1,659.

These findings are in stark contrast to the results of the Midtown Manhattan study of clinical venues, which found the following total patient rate per 100,000 in three SES classes: Upper, 1,703; Middle, 1,178; Lower, 1,060. Aside from the fact that the rate is overall much higher, there is the striking fact that the direction of the relationship between SES and treatment rate is reversed; it seems that in New Haven, the poor get ill more frequently, whereas in Manhattan, the rich get ill more frequently. Do these data reflect an actual difference in the relationship between SES and mental disorder in the two locations?

Almost certainly they do not, because Srole et al. also did a community study and their population statistics (as opposed to their clinical prevalence rates) indicated that lower socioeconomic classes do have higher rates of disorder. How, then, did it come out that Srole et al.'s clinical prevalence rates indicated the opposite of both Hollingshead and Redlich's results and their own community study?

The answer seems to have more to do with treatment availability than with a correlation between SES and disorder. When the Midtown SES data are broken down by treatment site, they look as follows: Public Hospitals: 98 (upper); 383 (middle); 646 (lower), Private Hospitals: 104; 39; 18, Clinics: 61; 160; 218, Office Therapists: 1,440; 596; 178. These dramatic differences in direction of relationship between SES and patient population in different settings exist also in the New Haven data, as a reanalysis by Srole et al. revealed. In fact, the direction of the relationship between SES and patient population is the same for each category in both studies; in both cases, more poor people use public hospitals and more middle or upper SES people use office therapists. The difference in the overall prevalence rates is due to the fact that the mix of available services is different in the two locations. New Haven's services are more oriented toward public hospitals, which are used disproportionately by the poor, whereas Manhattan's services (at least at the time of Srole et al.'s study) contain a much greater proportion of private outpatient therapists, who are used by the better off. It appears that different services are used by different SES segments of the population, and the mix of services offered in a given locale may substantially affect the rates at which individuals from given SES categories use the services.

Even in community studies that directly interview samples of community members rather than patients, the service-based bias can still arise in an indirect and more subtle form. This can happen if the criteria used in identifying the community members who are disordered contain features that refer to service use as a way of trying to distinguish disorder from normal distress. This approach has been used in some recent psychiatric epidemiologic surveys as well as some prominent reanalyses of those data sets (Narrow et al., 2002). This approach can reintroduce the same biases based on service access or inclination to seek help that afflicted clinical surveys.

GENERAL SYMPTOM CHECKLISTS AND THE PROBLEM OF FALSE POSITIVES

Before the new wave of instruments used in most recent epidemiological studies (which we will shortly consider), most studies used instruments consisting of general symptom checklists, and simply defined some threshhold of number of symptoms as the point above which an individual is considered disordered. These instruments yielded an overall, unidimensional score of disordered status rather than specific diagnoses, although specific diagnoses could sometimes be derived from suggested subscales. For example, the Langner (1962) scale, used in the landmark "Midtown Manhattan Study," contained 22 questions.

LANGNER SCALE QUESTIONS

1 I feel weak all over much of the time.
2 I have had periods of days, weeks, or months when I couldn't take care of things because I couldn't "get going."
3 In general, would you say that most of the time you are in high (very good) spirits, good spirits, low spirits, or very low spirits?
4 Every so often I suddenly feel hot all over.
5 Have you ever been bothered by your heart beating hard? Would you say: often, sometimes, or never?
6 Would you say your appetite is poor, fair, good, or too good?
7 I have periods of such great restlessness that I cannot sit long in a chair (cannot sit still very long).
8 Are you the worrying type (a worrier)?
9 Have you ever been bothered by shortness of breath when you were *not* exercising or working hard? Would you say: often, sometimes, or never?
10 Are you ever bothered by nervousness (irritable, fidgety, tense)? Would you say: often, sometimes, or never?
11 Have you ever had any fainting spells (lost consciousness)? Would you say: never, a few times, or more than a few times?

12 Do you ever have any trouble in getting to sleep or staying asleep? Would you say: often, sometimes, or never?
13 I am bothered by acid (sour) stomach several times a week.
14 My memory seems to be all right (good).
15 Have you ever been bothered by "cold sweats"? Would you say: often, sometimes, or never?
16 Do your hands ever tremble enough to bother you? Would you say: often, sometimes, or never?
17 There seems to be a fullness (clogging) in my head or nose much of the time.
18 I have personal worries that get me down physically (make me physically ill).
19 Do you feel somewhat apart even among friends (apart, isolated, alone)?
20 Nothing ever turns out for me the way I want it to (turns out, happens, comes about, that is, my wishes aren't fulfilled).
21 Are you ever troubled with headaches or pains in the head? Would you say: often, sometimes, or never?
22 You sometimes can't help wondering if anything is worthwhile anymore.

In general, a score of four or more positive answers to questions on the Langner scale was considered to indicate disorder. Looking at the scale's questions, one immediately sees two weak points. First, one might easily answer four or more questions positively for reasons other than that one has a mental disorder. Many of the listed symptoms could be normal reactions to misfortunes in life, or even symptoms of physical disorder. It has been commonly observed that many of the listed symptoms in this and comparable instruments – from feeling alone or that one's wishes are not fulfilled to feelings of worry, nervousness, or low spirits – could easily indicate a normal response of *demoralization* to negative life events. If one is reacting normally to a difficult environment, one is not disordered, but the Langer scale and other symptom scales might classify one as disordered. A second important weak point is that general scales like Langner's scale do not distinguish among different disorders.

It turns out that the number of false positives with the Langner scale is considerable (Dohrenwend and Dohrenwend, 1982). Based on statistics provided by Langner (1962), one can calculate that, in a community sample diagnosed by mental health professionals (and using these professionals' diagnoses – which themselves may contain false positives – as the "gold standard" criterion against which Langner's scale is tested), the scale substantially over-reported the rate of mental disorder. The rate of disorder goes from a "true" rate of 23 percent (as measured by the professionals' diagnoses) to a measured rate of 31 percent. The challenge of the false positives problem is also brought out by the fact that, in Srole et al.'s (1978) study, fully 82 percent of the surveyed community population reported some psychiatric symptomatology. The 82 percent estimate of the prevalence of psychiatric symptoms has often been cited in critiques as a *reductio ad absurdam* of the validity of psychiatric epidemiological estimates based

on symptom checklists. What it really shows, though, is that to have a useful epidemiological instrument, one must pay extremely careful attention to the false-positives problem and distinguish true disorders from normal distress. General symptom checklists of the Langner-scale type did not adequately make such distinctions.

TRANSITION TO THE USE OF DSM CRITERIA AS THE BASIS FOR MEASUREMENT OF MENTAL DISORDER IN EPIDEMIOLOGIC SURVEYS

The major approach taken in psychiatric epidemiology since the 1970s and the development of *DSM-III* (American Psychiatric Association, 1980, 1987) has been the use of operationalized symptom-based measures of specific mental disorders derived from *DSM* diagnostic criteria. Such measures base diagnosis on what essentially comes to a symptom checklist, in which a certain number of symptoms is necessary and sufficient for diagnosis of a specific disorder. These measures are "decontextualized" in the sense that they look only at symptoms and do not consider the subject's circumstances or what those circumstances might mean to the particular subject. Such criteria have the advantage that they provide standardized outcomes that do not vary from interviewer to interviewer. Because they do not require (or even permit) probes about the personal meaning of responses, interviewers do not need clinical training. This considerably lowers the cost of administering surveys, an especially important consideration in epidemiological research where large samples are necessary to adequately study a variety of disorders many of which occur rather rarely in the population.

As we saw, earlier studies also used de-contextualized symptoms, but in a generalized scale that confused distress with disorder. In more recently devised instruments, the problems of general symptom checklists are dealt with in several ways. First, separate sets of symptoms are presented for each disorder, so that disorders can be discriminated from each other. Second, a disorder may be indicated by a large number of possible symptoms, with diagnosis being triggered only when the individual has a certain number out of a list of typical symptoms. Third, exclusion clauses are used to eliminate the possibility that symptoms are caused by problems other than the target disorder, such as physical disease; for example, the criteria for depressive disorder might include an exclusion clause that attempts to reflect the *DSM* requirement that: "The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism)" (American Psychiatric Association, 2000: 356). Some of these features are illustrated in examples presented later. As we shall see, even using all these strategies, false positives remain a challenging problem because of the as yet unresolved problem of distinguishing intense normal distress from mental disorder.

Because *DSM* diagnoses are based on symptoms, epidemiologists could develop standardized interview structures simply by translating *DSM* criteria

into questions for surveys of the general population, using a symptom checklist approach similar to that of earlier studies but with more complex algorithms for making a diagnosis. Lay interviewers could ask these questions in standardized, preprogrammed formats, and the answers could then be analyzed by computer to categorize respondents as disordered or not. Epidemiologists relied on the *DSM* as the authoritative guide to diagnostic criteria, but also adopted the *DSM* approach as practical and cost-effective. There was little in the way of independent examination of whether the *DSM* criteria are valid when translated from the clinical setting to the very different context of the community survey (Dohrenwend and Dohrenwend, 1982).

The categorical system of the *DSM-III* and subsequent editions of the *DSM* was thus the basis and indeed part of the inspiration of all large American community studies of psychiatric disorders that have been implemented since the late 1970s. Simultaneously with the development of the *DSM-III*, the National Institute of Mental Health decided to launch the Epidemiologic Catchment Area Study (ECA), the first study that would measure the prevalence of particular types of mental disorder in the community (Robins and Regier, 1991). "Catchment areas" was the term used to specify areas covered by community mental health services in the legislation that led to the community mental health system, and the ECA studied a sample of five such areas – Los Angeles, CA, New Haven, CT, Durham, NC, Baltimore, MD and St. Louis, MO. Based on the *DSM-III*, ECA researchers constructed the Diagnostic Interview Schedule (DIS) to be used by the study, which in turn formed the basic approach of the Composite International Diagnostic Interview (CIDI) that was used in subsequent studies in the United States (on which we focus here) and internationally (Kessler et al., 1994, 2005a). These instruments measure specific diagnostic conditions in community populations that were supposed to be comparable to the major clinical entities found in the *DSM*.

Because the *DSM-III* required that conditions satisfy an extended criteria set before being classified as a specific disorder, psychiatric epidemiologists expected *DSM* diagnoses to provide not only category-specific diagnoses but also more realistic estimates of the amount of mental disorder in the community. The core assumption was that a structured diagnostic interview would allow researchers "to obtain psychiatric diagnoses comparable to those a psychiatrist would obtain" (Robins et al., 1985: 952). It was hoped that the results would provide good estimates of how much untreated mental disorder existed. These estimates, in turn, would provide policy makers with knowledge of how much unmet need existed for psychiatric services.

The rigid standardization of structured interviews had the advantage of improving the consistency of symptom assessment across interviewers and research sites and the consequent reliability of diagnostic decisions (Wittchen, 1994). However, the standardized questions and scoring procedures in community studies preclude the possibility of using discretion and thus treat all symptoms, regardless of their context, as signs of pathology. For example, the sorts of experiences

that produce normal sadness responses – breakups of romantic relationships and marriages, job losses, severe physical illness, disappointed career goals, and the like – are rampant in community populations and produce feelings and "symptoms" of blueness, fatigue, lack of appetite and so on that are much like those in depressive disorder (Horwitz and Wakefield, 2007; Wakefield et al., 2007), yet these experiences of normal sadness might end up being counted as symptoms of disorder using the symptom checklist approach (see next).

RELIABILITY AND RECALL PROBLEMS IN MEASUREMENT OF DISORDER IN RECENT PSYCHIATRIC EPIDEMIOLOGY

Three large-scale, heavily funded projects have been the primary sources of information about the occurrence of mental disorders in the US population: the Epidemiologic Catchment Area study (ECA: Robins and Regier, 1991), the National Comorbidity Survey (NCS: Kessler et al., 1994), and the National Comorbidity Survey Replication (NCS-R: Kessler et al., 2005a). Each of these projects used structured interviews, administered by lay interviewers. In the ECA, the measurement tool for assessing mental disorders was the Diagnostic Interview Schedule (DIS), which was based on *DSM-III* diagnostic criteria. In the NCS, the measurement tool was the University of Michigan version of the Composite International Diagnostic Interview (UM-CIDI), which was based on *DSM-III-R* diagnostic criteria. The NCS-R served as a replication and extension of the NCS, and used the World Mental Health Initiative revision of the CIDI (WMH-CIDI), which was mainly an update of the CIDI to *DSM-IV* criteria.

The changes from the ECA to the NCS not only incorporated the changes in diagnostic criteria from *DSM-III* to *DSM-III-R*, but also involved several key modifications in the implementation of the lay interviews, in order to improve the recall process of the respondents (Kessler et al., 1998). A main reason for these modifications was that serious problems emerged in the test–retest reliability of the ECA instrument. These problems were revealed when the data from the one-year ECA follow-up were compared to the data for the same sample from the original ECA data collection and yielded some serious discrepancies in symptom reports. It turned out that many respondents to the second wave provided reports about what symptoms they had ever had that were inconsistent with the reports they provided on the first ECA wave (Simon and VonKorff, 1995). For example, a respondent might report in the second wave never having experienced a symptom that he or she had reported in the first wave as having been experienced; or an individual might report never having experienced a symptom in the first wave and then in the second wave report having had the symptom prior to the time of the first wave.

Based on the assumption that the ECA inconsistencies were due in part to a memory retrieval problem, the NCS made several changes to address such issues. For example, important stem questions for each diagnosis were placed at the

beginning of the entire interview so that fatigue would not be a factor; the interviewer emphasized to the respondent the importance of carefully examining her/his memory; and the questions were asked at a slower pace to stress active recall during the interview. The NCS did produce generally higher levels of symptom reports, but because there was no one-year follow-up of the NCS sample, it remains unknown whether the methods it used actually increased reliability and validity of recall or merely increased reports of symptoms of questionable relation to disorder.

Thus, the question of reliability remains a serious and unresolved concern for psychiatric epidemiology. The degree of potential urgency of this concern has not become generally appreciated because, perhaps unsurprisingly, very little published research resulted from the second wave of the ECA (Kessler et al., 1998). However, other studies in which respondents were interviewed multiple times suggest the problem of reliability of symptom reports is a serious one that extends beyond the ECA (Wells and Horwood, 2004).

Of particular importance for understanding the test–retest reliability problems in the ECA is that instruments like the DIS and CIDI may be based on faulty assumptions about human memory, especially when using questions beginning with the phrase "Have you ever…" (Rogler et al., 1992). The key issue is that these structured interviews entail problems associated with episodic memory, which requires the respondent to accurately recall whether and when an episode happened (Barsky, 2002; Belli, 1998; Rogler et al., 1992). Of the three main problems in episodic memory, encoding, storage, and retrieval, the last may be the most malleable to variations in interview methodologies (Rogler et al., 1992). This is the target of the main changes in memory aid processes implemented in the NCS: place the main stem questions at the beginning of the questionnaire, emphasize the importance of the respondent to carefully examine her/his memory, and provide a slower pace of the questions to stress active recall during the interview (Kessler et al., 1998).

Many studies have examined the test–retest reliability of epidemiologic instruments in the past 20 years, including extensive studies of the DIS and the CIDI. Unfortunately many of these studies use clinical samples and very short time intervals between the interviews, some as short as one day (Andrews and Peters, 1998; Hasin et al., 2006; Ross et al., 1995; Rubio-Stipec et al., 1999; Wacker et al., 1990; Wittchen, 1994; Wittchen et al., 1998). It has been noted that although reliability can be quite good in samples having high disorder prevalence, such as clinically based samples, the reliability in community samples can be considerably worse (Wells et al., 1988).

Results from prospective studies further indicate the problems in retrospective studies such as the ECA and NCS/NCS-R, by finding dramatically higher lifetime prevalence estimates when disorders are assessed longitudinally (Mattison et al., 2007; Moffitt et al., 2007; Wells and Horwood, 2004). For example, in considering respondents aged 32 and younger, the NCS-R found lifetime prevalence estimates of 25 percent for Major Depressive Disorder and 6 percent for Generalized Anxiety Disorder (Kessler et al., 2005a), whereas results from the

Dunedin Study, using repeated assessments in which the assessment instrument was administered several times over a period of years, showed estimates of 44 percent and 15 percent for those two disorders by age 32 (Moffitt et al., 2007).

Note that the higher Dunedin prevalence rates are achieved by diagnosing a lifetime disorder for all respondents who qualify for an episode of the disorder in any one or more of the assessments. One finding that suggests that this approach may have some validity is that similar values for one-year prevalence estimates are obtained from the Dunedin Study and from the NCS-R. However, this cumulative approach does not recognize that false positive diagnoses may greatly inflate the resulting lifetime prevalence estimates.

DSM AND THE PROBLEM OF FALSE POSITIVES

Although the goal of diagnosis in *DSM* and epidemiological instruments is primarily the same, namely, obtaining valid diagnoses using operationalized criteria for specific mental disorders, the distinct features of clinical and epidemiological contexts can result in potentially serious problems of false positive diagnoses in epidemiological instruments. For a variety of reasons, persons who in a clinical setting might readily be identified as nondisordered are more likely to be wrongly identified as disordered in an epidemiological study using the same *DSM* criteria.

For one thing, clinical interviewing and treatment extend over time and allow the clinician the luxury of correcting a mistaken initial diagnosis based on later findings. As new information emerges, the clinician might even conclude that there were extenuating circumstances and that the individual does not genuinely suffer from a disorder after all.

The clinician can even "disagree" with the official *DSM* criteria when the context of symptoms warrants such an exception. For these and other reasons, the cost of an initial false positive diagnosis in a clinical setting is not as great as the cost of a false negative, where an individual may not get treatment that is needed. And, even if there is a false positive, some purpose may be served because treatment may still be useful with subclinical conditions. In contrast, epidemiological diagnoses are almost always based on one contact and there are no feedback loops or corrective mechanisms by which diagnostic evaluations can be reconsidered in light of emerging information. Nor is there second-guessing the criteria; epidemiological surveys rely exclusively on the diagnostic criteria in the epidemiological instrument in an algorithmic all-or-none fashion. Thus, false positives remain false positives. And, false positives defeat the essential point of an epidemiological study, which is to count disorders.

Moreover, clinical populations are highly self-selected and contain individuals who have been willing to undergo considerable inconvenience to obtain help with their problems. The psychological and institutional obstacles that help-seekers must overcome mean that members of the clinical population are likely

to be suffering from very high levels of distress, disability, or other harm, which may be indicative of a genuine disorder. This tends to make the issue of conceptual specificity superfluous. Diagnosis becomes a matter of choosing the category of disorder that best applies to the patient. This is a very different kind of problem than the one that faces epidemiologists. Epidemiological surveys encompass many people who report problems similar to those of clinical populations but who have never sought out a mental health professional. In such cases, the seriousness of the condition, and thus its disorder status, may be questionable. These divergent features of clinical and epidemiological contexts should make one wary about uncritically transposing clinically derived criteria into the epidemiological domain.

But the problem also lies with the *DSM* criteria themselves. It turns out (Wakefield, 1993, 1996) that many *DSM* criteria are inconsistent even with *DSM*'s own definition of disorder and consequently are prone to give rise to false positives. In particular, two of *DSM*'s definitional requirements for disorder are frequently violated by its own criteria. The first is that the condition must be due to a psychological or biological dysfunction; many of the criteria describe human harms (e.g., intense anxiety, excessive use of alcohol) that need not originate in dysfunctions. The second requirement that is often violated is the stipulation that the harm cannot be the result of social conflict or the attempt by society to control disapproved behavior; many of the criteria involve "symptoms" that are clearly manifestations of social conflict (e.g., arrest for use of illegal drugs, disapproval of one's alcohol use by one's family) and are not harms directly caused by dysfunctions. Here are just a few examples of how *DSM*'s rules for diagnosis diverge from the concept of disorder and encompass nondisordered problems of living (we thank the American Psychological Association for permission to use here some material previously published in Wakefield [1996]).

Major depressive disorder

Diagnosis of major depressive disorder is based on having several out of a set of symptoms typical of an extreme sadness response, for example, sadness, emptiness, lack of enjoyment in one's usual activities, loss of appetite, lack of concentration, trouble sleeping, and so on. The criteria correctly contain an exclusion for uncomplicated bereavement (i.e., one is not diagnosed as disordered if the symptoms are due to a normal-range response to having recently lost a loved one, with up to two months of symptoms allowed as normal), but they contain no exclusions for equally normal reactions to other losses, such as a terminal medical diagnosis in oneself or a loved one, separation from one's spouse, or losing one's job. If in grappling with such a loss, one's reaction includes just two weeks of depressed mood, diminished pleasure in usual activities, insomnia, fatigue, and diminished ability to concentrate on work tasks, then one satisfies *DSM* criteria for major depressive disorder, even though such a reaction need not imply pathology any more than it does in bereavement.