Nature, nurture and mental disorder: old concepts in the new millennium

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Background Evidence from twin and adoption studies has highlighted the importance of gene–environment interaction in the aetiology of mental disorders, and advances in molecular genetics have raised hopes of more rapid progress in this field of investigation.

Aims To review epidemiological knowledge concerning genetic and environmental risk factors for a cross-section of psychiatric conditions, and evidence of interaction between the two types.

Method Searches of the literature in genetic and psychiatric epidemiology, including contributions to this supplement.

Results Overall, firm knowledge on both genetic and environmental causal factors is still fragmentary, although progress has varied among diagnostic categories. Environmental aspects have been dealt with only perfunctorily in most genetic epidemiological research.

Conclusions Better definition and classification of environmental hazards, and closer inter-disciplinary cooperation, will be necessary in future. Specific gene–environment interaction effects seem likely to prove most important in neuropsychiatric syndromes, and a less specific genetic influence on susceptibility to environmental stress among the common mental disorders.

Declaration of interest None.

Epidemiology is essentially a collective science, in which progress has always depended largely upon that made in other fields of medical science (Frost, 1941), and the struggle of today's epidemiologists to keep pace with advances in molecular genetics forms part of a long-standing tradition. Yet there is still uncertainty as to whether 'molecular epidemiology' should be regarded as a radical new departure, or in more modest terms simply as a helpful travelling companion (McMichael, 1994). These doubts are amplified in psychiatric epidemiology, where the customary enthusiasm for new causal models is tempered by awareness of the chequered history of psychiatric genetics, as well as of the complex nature of most forms of emotional disorder.

EARLY PSYCHIATRIC THEORIES AND THE EUGENIC MOVEMENT

The notion that mental illness arises from a combination or interaction of causes, both predisposing and provoking, can be traced far back in the psychiatric literature (Cooper, 1986). It was given expression by Esquirol in his *Des maladies mentales* and elaborated by Wilhelm Griesinger, who distinguished between traumatic events, prevailing external conditions and certain internal states (including hereditary predisposition), which could combine to give rise to insanity. This simple causal model, anticipating the classic epidemiological triad of specific agent, environment and host susceptibility, was adopted by many authorities, including the founding father of psychoanalysis, whose own conception of disease was (he declared) "a purely practical one and a question of summation, that predisposition and the eventualities of life must combine before the threshold of this summation is overstepped" (Freud, 1909).

In European orthopsychiatry, however, interest became centred more and more on the 'endogenous' aspects of mental illness, and in particular – following the introduction of twin research as a way to study the relative powers of nature and nurture (Galton, 1876) – on the strength of hereditary influences. Both early twin studies in psychiatry (Luxenburger, 1928; Rosanoff *et al*, 1934) and the prototypic German and Scandinavian field studies of the inter-war years (Strömgren, 1950) were fuelled by a wish to demonstrate empirically the importance of heredity in mental disorders, and in Nazi Germany the research findings were misused by Ernst Rüdin and his followers to justify a de-based doctrine of 'racial hygiene' (Weber, 1997). The eugenic movement, of which Galton was an early protagonist, had long promulgated the notion that mental illness, feeble-mindedness, criminality, alcoholism and sexual promiscuity were all expressions of national or racial degeneracy, whose remedy lay in a policy of selective birth control extending to sterilisation of those unfit to bear children. Ideas of this nature commanded widespread political support in the early 20th century, inspired new legislation in a number of countries, and under the Hitler regime were used to justify mass extermination of the mentally ill and handicapped (Meyer-Lindenberg, 1991).

In our own day workers in human genetics have been at pains to dissociate themselves on scientific as well as moral grounds from eugenic theory, while those in the field of psychiatric genetics have striven to free their discipline from the stigma imposed upon it. Nevertheless, in global terms eugenic notions remain a major socio-political issue. In Sweden, compulsory sterilisation persisted until 1976 (Armstrong, 1997). In the People's Republic of China, a new eugenics law was proclaimed in 1994, with the aim of preventing 'new births of inferior quality', particularly in underdeveloped and economically poor areas (*Lancet*, 1995). In the USA and elsewhere, the growing prospects of genetic screening for job selection (Gostin, 1991) and medical insurance (Wilkie, 1998) have led some observers to conclude that the eugenic movement has not disappeared but merely been privatised. Against this background, the importance of maintaining high ethical standards in genetic research will continue to be essential for scientific advance.

GENETIC EPIDEMIOLOGY TODAY

Although the advent of molecular biology has greatly increased the potential scope of genetic research, its impact on public health epidemiology is still hard to assess. The main achievements of medical genetics to date have been concerned with relatively rare Mendelian disorders, whereas genetic epidemiology now deals increasingly with common chronic conditions in which an inherited predisposition may interact with environmental exposures in complex ways (Kendler, 1995). Hence any tendency to neglect environmental research in favour of a reductionist 'molecular epidemiology' is bound to be retrogressive (McMichael, 1994). Moreover, the new genetic-marker strategies, like the older family, twin and adoption study designs, are not central to epidemiological method, but rather overlap with it to greatly varying extents. Linkage studies in particular are usually restricted to – or at least over-sample from – families multiply affected by the target disorder, with no defined population base (Risch, 1997). This approach can be regarded as clinical epidemiology in the broad sense, but cannot make use of population denominators.

Allelic frequency counts have been conducted in large-scale population studies, most notably for rare single-gene conditions such as Tay–Sachs disease and Gaucher's disease (McCabe & McCabe, 1997), but also in studying 'susceptibility' genes. Evaluation of the research findings becomes more difficult in allelic association studies of complex polygenetic disorders, causing some workers to prefer family-based studies to population surveys because of their greater feasibility and accuracy of case–control comparison (Smeraldi & Macciardi, 1995). The epidemiological paradigm, in short, is an ideal to which genetic-marker research aspires but often cannot attain.

Despite important applications to infectious disease (e.g. detecting human variants that modify susceptibility to human immunodeficiency virus infection, or subtyping drug-resistant strains of tuberculosis), molecular genetic research has been largely concentrated on predisposing factors of noninfectious disease. Here the hereditary component of the nature–nurture model has come to be equated for practical purposes with the human genome: "a linear arrangement of approximately three billion deoxyribonucleotides partitioned into 22 autosomes and two sex chromosomes" (Ellsworth et al, 1997). The aim of the Human Genome Project, as its name implies, is to identify the 60 000 to 80 000 genes which encode for polypeptides and ultimately to establish all the estimated 3.2 billion base-pair sequences. Currently (late 1999) some 428 million of these sequences had been completed, while the programme Online Mendelian Inheritance in Man (OMIM) has identified over 10 000 genes related to known human characteristics, including many disease phenotypes. Screening tests are already available for single-gene disorders such as cystic fibrosis (Brock, 1996) and Duchenne and other muscular dystrophies (Davies, 1997), while predisposing genetic factors have been identified in diseases less evidently familial, such as breast and ovarian cancers (Miki et al, 1994).

Impressive as these achievements are, it is already clear that mapping the human genome is only the first step towards understanding its functions and must be followed by what Anthony (2001, this supplement) refers to as "an emerging 'Human Proteome Initiative'", namely systematic studies of gene functions in order to establish a database of protein expression and effects. This is an objective now becoming technologically feasible, although fraught with difficulties (Cantor & Little, 1998). Meanwhile, the assumption that individual risk exposure due to any specific gene product is simply the product of zygosity and years of life has to be regarded with great caution.

The impact of genetic technology on public health practice has been assessed by Khoury (1997) in terms of improved knowledge of host susceptibility and its implications for personal prevention. Epidemiology's contribution, in his opinion, will consist in replacing straightforward case–control comparison of groups with and without specified environmental exposures by more complex designs in which genotypic variants will be ascertained and evidence of interaction with environmental risk factors routinely tested for. A fundamental implication for disease control is that, where such quests succeed, public health measures can be focused on 'phenotypic prevention'; that is to say, on avoiding the health consequences of a genetic anomaly, rather than on 'genotypic prevention' aimed at stopping its transmission to the next generation.

The concept of gene–environment interaction has thus come to occupy a central position in the epidemiological search for causes. While it is a truism that any disease is in the broadest sense 100% genetic and at the same time 100% environmental, this general model acquires clinical and public health utility only once there is empirical evidence that susceptibility to certain environmental noxae is mediated by specific gene products or their lack. Concrete examples include the effect of dietary phenylalanine on mental development in children with phenylalanine hydroxylase deficiency; dietary iron overload causing multiple organ failure in persons with the hereditary haemochromatosis gene; and the combined effect of maternal cigarette-smoking and transforming growth factor alpha polymorphisms in producing congenital oral defects (Khoury, 1997; Yang & Khoury, 1997). In each of these examples the conclusion for public health policy is that preventive action should be focused on reducing the specific environmental exposure for those at high risk.

Technological progress, including use of the polymerase chain reaction and automated methods of analysis, have resulted in the mapping of a dense web of polymorphic genetic markers. As the number of identified susceptibility genes, and the databases on their associations with specific diseases, grow more rapidly, new problems are being created by the sheer volume of scientific data. Even for single-gene diseases, many allelic variants have been found. For complex, polygenetic conditions the quantity of information generated as the human genome is sequenced seems likely to be astronomical (Khoury, 1997). To proceed from linkage to identifying and cloning the genes involved will be an enormous task.

In addition to these methodological problems, there is growing concern over the socio-political implications of the Human Genome Project and related research. Advocates of gene mapping tend to present genes as the principal determinants of health and sickness, and genomics as the key to medicine's future. In the words of one leading authority (John Sulston, then director of the Sanger Centre, reported in the *Observer*, London, 3 October 1999):

> "Think of the human genome as the Book of Life. We are about to read the first chapter, as important an accomplishment as discovering the Earth goes round the sun or that we are descended from apes."

While such claims can be dismissed as public relations 'hype', many critics believe that they are symptomatic of a dangerously hubristic attitude of mind. If DNA is seen as the 'book of life', human diseases may come to be regarded simply as typographical errors. In the words of Lippman (1992):

"This new cartography, by adopting the blueprint as a metaphor for genes, leads to restricted conceptions of health and illness, reinforces inequities in the distribution of health and, by privatizing and individualizing responsibility for health, creates and legitimizes a new area for social control."

The issue is one calling for wider debate, and it seems vital that public concerns about the ethical, legal and social implications of genetic technology, including the commercial pressures in favour of predictive testing, should be met by greater openness in government as well as an improved quality of scientific reporting in the media.

DEVELOPMENTS IN PSYCHIATRIC GENETICS

The same doubts and anxieties, both scientific and ethical, are shared today by many psychiatrists. The heady optimism of the early 1990s, when advances in genomics were welcomed as heralding a revolution in psychiatric research and practice, has given way in more recent reviews to a distinctly cautious tone. Rutter & Plomin (1997) qualify their own generally up-beat assessment as "more of a promissory note than an account of accomplishments with proven clinical applications". Despite some dramatic successes of molecular genetics, declare Merikangas & Swendsen (1997), application to psychiatric disorders has proved disappointing as a result of critical differences which exist between these conditions and the diseases to which genetic marker techniques have been successfully applied. According to Vieland et al (1995), the molecular basis of genetic effects on complex, non-Mendelian disorders has proved elusive and gene mapping in that context is an uphill struggle. Peltonen & Lönnqvist (1995) note that candidate gene strategies have so far been unsuccessful, probably because of incorrect selection of the genes in question, and that we still lack the basic biological knowledge about most mental disorders which is a prerequisite for success in such endeavours.

Concerns about the ethical and social implications of the new biology have also been strongly voiced by some psychiatrists. In the words of Thomas et al (1996):

"Biological psychiatry plays a dual role, seeking out the causes of mental illness with the aspiration of cure and at the same time absolving society of any responsibility for mental illness . . . we have unwittingly devalued the importance of societal factors. . . . Unemployment, poor housing, homelessness, poverty, racial discrimination, are assumed to be irrelevant. We are [thus] excused from asking awkward questions of ourselves and our political leaders."

Thus, despite all scientific and technological advances of the intervening years, the wry comment by Penrose (1971), that genetics and psychiatry make strange bedfellows, has not yet entirely lost its pertinence. It should be noted, however, that all the cited comments refer to 'psychiatric disorders' as a collective entity, whereas in fact the prospects for genetic research may vary greatly from one diagnostic category to another. While it is not possible here to examine this question for the whole spectrum of psychiatric disorders, the four broad categories reviewed in this supplement by Whalley (Alzheimer's disease), Tsuang et al (schizophrenia), Heath et al (alcohol dependence) and Goldberg (the common, prevalent forms of depression and anxiety) taken together give some indication of the extent of this diversity.

Alzheimer's disease

Leaving aside Huntington's disease, whose Mendelian pattern of transmission has been known for decades, a particularly favourable candidate for molecular genetic research is Alzheimer's disease (AD), since its neuropathological and neurochemical characteristics are now quite well defined. A number of studies published in the 1980s indicated a cumulative risk for dementia in first-degree relatives approaching 50% in the highest age group, suggesting that the genetic factor could be a single autosomal dominant gene with age-dependent penetrance (Folstein & Powell, 1984). Subsequent research has failed to support this hypothesis, pointing instead to causal heterogeneity.

Although twin studies in old age are hedged about with difficulties, several reports from twin cohort projects in the USA and Scandinavian countries have confirmed that there is an important genetic component in AD (Breitner et al, 1995; Raiha et al, 1996; Bergem et al, 1997; Gatz et al, 1997). In these studies concordance rates were consistently found to be higher in monozygotic (MZ) than in dizygotic (DZ) twins, but rates among MZ twins varied widely (for probandwise concordance, in particular, from 21% to 83%). Hence, although the disparities are largely understandable in terms of differences in research designs and methods, no firm conclusions can be drawn about the strength of genetic effects. For vascular and mixed dementias, the evidence in favour of any genetic influence is less clear.

Studies of multiply affected families with early-onset AD have so far identified three gene mutations of causal significance: the amyloid precursor protein (APP) gene on chromosome 21 and the so-called presenilin (PS) genes 1 and 2 on chromosomes 14 and 1 respectively (Lendon et al, 1997). The total number of documented cases is small, and these mutations together are thought to account for only a small fraction of prevalence in the general population. Thus Cruts et al (1998), investigating a population-based series of 101 unrelated cases of familial and sporadic early-onset AD, detected none with APP mutations and only seven (6.9%) with PS1 or PS2 missense mutations.

In addition, susceptibility to AD is known to be influenced by the apolipoprotein E (APOE) locus on chromosome 19, persons who are homozygotic for the $\epsilon 4$ allele carrying a greatly increased risk. In a re-analysis of pooled autopsy studies (Nalbantoglu et al, 1994), the odds ratio associating the $\epsilon 4$ allele with presence of AD changes was estimated at 6.2 and the population-attributable risk owing to this factor at 53%. Autopsy series are, however, unrepresentative, and the strength of association found in area surveys of unselected elderly populations in Finland (Kuusisto et al, 1994) and Australia (Henderson et al, 1996) is less impressive. In the latter study, estimated prevalence of dementia (all causes) by age 90 years was only around 50% for APOE $\epsilon 4$ homozygotes, indicating that this allele is not a sufficient cause of AD.

Risk of AD is thus probably determined in part by environmental exposures, but their nature remains unknown, with the exception of earlier brain trauma. In a re-analysis of seven case–control studies (Van Duijn et al, 1994), both a history of head injury and late maternal age at birth were associated with an increase in risk, whether a family history of dementia was present or not. No evidence was found for an interaction of other risk factors with

the genotype as indicated by family history, the findings being consistent with a model in which these determinants act independently of one another. Indeed, the only evidence of gene–environment interaction to emerge from this meta-analytic study was a negative association between cigarette-smoking and incidence of AD among those with a family history of dementia. A community-based case–control study in New York (Mayeux et al, 1993) yielded more positive evidence of interaction, but here the relative excess of previous brain trauma among dementia sufferers, compared with matched controls, was entirely due to head injuries incurred after the age of 70 years and less than 5 years before the diagnosis of clinical dementia, so that this may have been a prodromal rather than a causal phenomenon.

More recently, interest in the long-term sequelae of brain trauma has been stimulated by a report of amyloid beta-protein deposition, similar to that characterising AD, in the brains of nearly one-third of younger patients who had survived for varying periods after severe head injury (Roberts et al, 1994). A significantly raised frequency of the APOE ϵ4 allele was found in cases with beta-protein deposition when compared with other cases, suggesting an interaction between a predisposing genetic risk factor and the effects of brain trauma (Nicoll et al, 1996). Whether these findings model the pathogenesis of Alzheimer's disease remains to be seen.

Schizophrenia

Although the overwhelming majority of all relatives of patients with schizophrenia are not themselves suffering from schizophrenia, evidence from family, twin and adoption studies has consistently pointed to an important hereditary influence. Kendler (1988) concluded, from family studies using blind diagnoses, control groups, personal interviews and operational diagnostic criteria, that the risk in close relatives is 5–15 times that in the general population. Similarly, Gottesman (1991), on the basis of pooled data from some 40 family studies, found an average risk ratio of 9.3 among first-degree relatives. Adoption studies have provided further supporting evidence, although small case numbers and the use of 'schizophrenia spectrum' diagnoses have made for difficulty in interpreting the findings (Susser & Susser, 1987).

Estimates of the strength of genetic effect vary greatly between studies. On one hand it has been argued that apparently non-genetic variation may be due simply to "stochastic events affecting gene expression or structure" (McGuffin et al, 1994). On the other hand, register-based twin studies from the Nordic countries have indicated generally moderate MZ/DZ likelihood ratios that leave a large part of the attributable risk unexplained. Kringlen (1995), for example, computed mean pairwise concordance rates of 25.6% and 7.5% and mean probandwise concordance rates of 39.0% and 14.0% for MZ and DZ twins, respectively. The extent to which the high proportion of 'normal' MZ co-twins can be explained in terms of reduced penetrance hinges on unresolved methodological problems, but on balance the evidence in favour of some environmental influence seems compelling.

Given the evidence for a genetic role in schizophrenia, it is unsurprising that much research has focused on identifying specific markers. The successes of linkage studies of neuropsychiatric disorders have not yet been matched in schizophrenia or affective psychosis, for which no disease-related gene mutation has been firmly identified. Nevertheless, linkage studies have identified several chromosomal regions with a possible linkage to schizophrenia. Hopes were high in the late 1980s, when two groups (Bassett et al, 1988; Sherrington et al, 1988) reported familial cases with linkage to a gene on chromosome 5. Unfortunately, attempts at replication failed and the findings came to be regarded as false positives. This has become a familiar pattern, linkage studies suggesting a number of possible gene loci which cannot be subsequently replicated, while the newer approach of scanning the human genome for DNA markers has so far produced only equivocal findings. Tsuang et al (2001, this supplement) observe, however, that within the past few years evidence for linkage has been strengthened by replication of positive findings at loci on chromosomes 6p and 8p, while others have been reported on 10p, 13q, 15q and 22q.

Because of the lack of established genetic markers, attempts to detect and quantify gene–environment interaction have to rely on family, twin or adoption study designs into which some measures of specific environmental exposures can be incorporated. The hypotheses relating to obstetric complications and to maternal influenza during the second trimester of pregnancy (see Tsuang et al, Kunugi et al and Munk-Jørgensen & Ewald, 2001, this supplement) are obvious candidates, raising a question as to whether the effects of genetic predisposition to schizophrenia might be mediated through an increased vulnerability to prenatal or perinatal exposures.

Tsuang et al (2001, this supplement) propose a neurodevelopmental model, according to which prenatal maldevelopment affecting key neural networks forms a substrate for schizophrenia. As yet clear evidence is lacking, and the work of Murray's group suggests that obstetric complications are more often implicated in cases with no positive family history (Dassa et al, 1996). To make matters more complicated, women diagnosed with biological mothers suffering from schizophrenia have been shown in record-linkage studies to be at increased risk for complications of childbirth and reproductive pathology more generally (Jablensky et al, 1999), so that genetic and environmental influences may indeed be closely interlinked.

That early-life exposures also play an important role is suggested by findings of the Finnish Adoptive Family Study of Schizophrenia (Wahlberg et al, 1997), in which adoptees with biological mothers suffering from schizophrenia have been compared with other adoptees, and the adoptive parents of both groups investigated for evidence of psychopathology and 'communication deviance'. Although the index-group children as a whole do not appear to be at increased risk, those among them whose adoptive parents have high communication-deviance scores are particularly vulnerable as shown by evidence of thought disorder: a conclusion consistent with a genetically determined vulnerability to psychosocial influences in childhood. These results are intriguing, but the study's heavy reliance on Rorschach Test scores in assessing both the children and their adoptive parents gives rise to difficulties of interpretation.

Chronic alcoholism and alcohol dependence

It is a commonplace that alcoholism differs fundamentally from both AD and schizophrenia in having a known environmental factor – i.e. alcohol consumption – built into the diagnostic concept. Both alcohol consumption and the prevalence of alcoholism show strong cohort effects, socially determined changes in national drinking patterns since the Second World War being

associated with an increased probability of dependence among alcohol users (Grant, 1997). Moreover, the frequencies of such alcohol-related problems as road traffic accidents, violent behaviour and liver cirrhosis are known to be reducible by changes in alcohol taxation and licensing laws (Toomey & Wagenaar, 1999). These facts underline the importance of societal forces, rather than biological variation, in determining the extent of the public health problem and pointing the way to preventive action.

Nevertheless, evidence has steadily accumulated of a familial aggregation in alcohol abuse and dependence, which seems to be in part genetically determined. Merikangas & Swendsen (1997), reviewing control studies published up to that time, computed an average prevalence ratio of 7.0 for first-degree relatives, and noted an excess of cases among male MZ co-twins compared with DZ co-twins (ratio 1.6 : 1). In adoption studies of both genders, the biological relatives of affected persons manifested an average prevalence ratio of 2.4 compared with their adoptive relatives.

Research based on the Virginia Twin Register is of particular interest because of the large size of the samples and their representative nature (Kendler *et al*, 1994; Prescott & Kendler, 1999). Here also, pairwise concordance was found to be higher among MZ than among DZ twins, both for women (47% *v.* 32%) and for men (55% *v.* 31%). The computations were, however, based on extremely high 'lifetime' prevalence estimates for alcohol misuse (in the case of men, 34% for MZ and 38% for DZ twins), which must place a question mark against the method of case identification.

The search for specific genetic markers by means of linkage analysis and allelic association studies has so far yielded mainly inconclusive results, with pointers to susceptibility loci on chromosomes 1, 2, 7 and 16 but no firm evidence. Most association studies have concentrated either on dopamine and serotonin receptors or, more specifically, on the aldehyde dehydrogenase (ALDH) and alcohol dehydrogenase (ADH) genes (Goldman, 1995). Heath *et al* (2001, this supplement) point out that alcoholism research benefits from the advantage of having already identified polymorphisms of these two genes which in populations of Asian ancestry are associated with differences in alcohol dependence risk. Possession of a single *ALDH2*2* allele causes raised blood acetaldehyde concentrations and a characteristic flushing response after ingestion of alcohol, and is associated with a decreased risk of alcohol dependence. Individuals who are *ALDH2*2/*2* homozygotes have such an adverse reaction to even moderate doses of alcohol that this genotype has not been found in large series of people with alcoholism in Japan. Since, for better or worse, the allele in question is rarely found among persons of European ancestry, this does not help to explain variations in risk within such populations.

What stands out clearly from the above is that any genetic influence on alcoholism can only be partial and must in some way combine or interact with environmental exposures. Evidently there is potential scope for studies in which both genetic and environmental indicators are measured and entered into multivariate analyses. Current prospects for such research might seem most favourable with respect to early predisposing factors, since a set of childhood environmental variables is known to be highly predictive of alcohol misuse in adult life (McCord & McCord, 1960; Vaillant & Milofsky, 1982). In practice, demonstration by means of family studies is problematic, both because the risk factors in question (e.g. parental marital conflict, low family cohesion and poor attachment to parents) are difficult to measure reliably and because they themselves may be attributed to inherited characteristics. Hence adoption study designs are required which can separate the effects of family behaviour patterns from those of biological inheritance.

In a US cross-sectional study of 300 adoptees aged 18–40 years (Cutrona *et al*, 1994), no direct effects for either genetic or environmental factors were found to predict the development of alcohol abuse or dependence. Among female adoptees, though, evidence of adoptive parental conflict and psychopathology based on the Family Environment Scale did appear to interact with a biological family history of alcohol problems to increase the risk of alcoholism significantly. Although this finding suggests a relatively specific form of gene–environment interaction, at least among women, it must be viewed with caution. The interaction factor was significant only at the 5% level and, as in the Virginia Twin Register studies cited above, the frequency of reported alcohol misuse cases was so high as to suggest either strong selectivity in recruitment or else the use of a very low threshold in identifying cases.

Common forms of depression and anxiety

Epidemiological and genetic research into the affective disorders is still handicapped by problems of classification. Whereas bipolar (manic–depressive) psychosis shows evidence of hereditary influence at least as strong as that in schizophrenia, evidence bearing on both non-psychotic, unipolar forms of depression and the anxiety disorders (generalised anxiety state, phobic and panic disorders) is on the whole less compelling. Merikangas & Swendsen (1997), while confirming strong familial aggregation of both unipolar depressive and anxiety disorders, computed relatively modest differences in probandwise concordance between MZ and DZ twins: 1.5 : 1 for depression, 2.4 : 1 for panic disorder and 1.6 : 1 for social phobia. Andrews *et al* (1990) in an Australian study found no evidence of genetic effects on mild depression and anxiety, and Tambs & Moum (1993) in a large-scale questionnaire survey in Norway also reported only a weak degree of heritability.

From a genetic standpoint, any gain in studying these conditions as separate entities is questionable. Kendler *et al* (1987) in a study of nearly 4000 Australian twin pairs found no evidence for genes predisposing to depression which did not also predispose to anxiety. More recently the same group, collaborating with Swedish researchers, arrived at the same broad result from a massive control study based on the Psychiatric Twin and National Twin Registries in Sweden (Roy *et al*, 1995). Their conclusion that generalised anxiety disorder and major depressive disorder share common genetic determinants but have partly differing environmental causes is consistent with the model for 'common mental disorders' proposed by Goldberg & Huxley (1992). One should note that these extensive surveys share a weakness of method in their reliance on mailed questionnaires or telephone interviews to establish the diagnosis.

Because the common affective disorders seem to fit dimensional models as readily as categorical ones, some investigators prefer to regard both depression and anxiety as continuously distributed population variables, with individual differences governed by the concerted action of a number of

genes, each having only a small contributory effect. Both linkage and association methods have been extended to the study of such variables, whose microbiological correlates are sought for at 'quantitative trait loci'. Technological advances have made it possible to scan the whole human genome for loci associated with defined traits, by means of high-capacity automated techniques allowing thousands of DNA samples to be analysed simultaneously.

The quantitative trait locus (QTL) approach has definite advantages in studying more or less permanent characteristics, the analysis of continuous variables yielding greater statistical power than that conferred by diagnostic categories and allowing interaction terms to be quantified. The search for genes associated with the general intelligence factor '*g*' exemplifies this approach in cognitive psychology (see Plomin & Craig, 2001, this supplement). Its applications to remittent morbid conditions presents greater difficulty, and in the case of depressive and anxiety states this tends to be sidestepped by substituting a latent trait such as 'neuroticism' (Henderson & Blackwood, 1999). The strategy has its drawbacks, in that trait–state correlations are only partial, and the psychological trait measures in question are generally crude. Neuroticism scores, for example, are usually based on yes/no responses to questions such as 'Does your mind often wander while you are trying to concentrate?', 'Are you inclined to be moody?' and 'Are you sometimes bubbling over with energy and sometimes very sluggish?' (Eysenck, 1958). Drawing conclusions about the genetic basis of affective disorders from material of this nature must be a perilous undertaking.

The importance of distinguishing affective states from underlying traits is neatly illustrated by a study based on the Virginia Twin Registry (Kendler *et al*, 1995), in which information on occurrence of stressful life events and the onset of major depressive episodes over 1 year was collected for a population-based sample of over 1000 female twin-pairs. Occurrence of any of four types of severe event (death of a close relative, assault, divorce or marriage break-up, and serious marital conflict) was associated with a more than 10-fold increase in depression onsets within the same month. Genetic predisposition, as gauged by twin concordance, also played a part, suggesting a strong gene–environment interaction. Thus the 1-month probability of a depression onset was calculated for those

with unaffected co-twins as 0.5% and 6.2%, respectively, and for those with affected co-twins as 1.1% and 14.6%, respectively, depending on the absence or presence within that month of a severe life event. The best-fitting model of interaction suggested a genetic control of sensitivity to the psychological impact of life events. Making allowances for the limitations of data gathered retrospectively by telephone interview, these findings represent an advance in our understanding of the causal mechanisms involved. As a next step, a careful differentiation of 'independent' and 'dependent' types of life events, along the lines pioneered years ago by the Bedford College group (Brown & Harris, 1978) could be applied to meet the frequently raised objection that exposure to stressful life events is itself largely under genetic control (Plomin, 1994).

In summary, this brief review of four diagnostic groups, drawn from across the broad spectrum of psychiatric morbidity, indicates how sketchy in most areas is our knowledge of both genetic and environmental causal factors, and how divergent are the lines of research that must be pursued in gathering evidence on the different categories.

DEFINING THE 'ENVIROME': ENVIRONMENTAL RISK FACTORS OF MENTAL DISORDER

Behavioural scientists who are reluctant to accord a major independent role to environmental factors have adopted a number of different standpoints. Of these, perhaps the most extreme is to claim that the deviation of a complex psychiatric disorder such as schizophrenia from clear-cut Mendelian transmission can be explained purely in terms of 'incomplete penetrance' and 'variable expressivity' of the genes (McGuffin *et al*, 1994). Even without positive evidence for environmental influences, the rates of concordance reported from modern twin and adoption studies make these arguments implausible.

An alternative response has been to recognise environmental effects, but to treat them in effect as background noise rather than as signals. No attempt need then be made to explore their nature, beyond partitioning variance in twin and family studies between 'shared' and 'non-shared' or unique environment: a procedure

that can be useful only if it serves as a starting point for direct microenvironmental research.

Third, probands and family members may be questioned about their social behaviour and attitudes on general topics and the resulting scores entered into multivariate analyses as 'sociocultural correlates' of the biological variables. Since, however, on the basis of twin studies it has been claimed that the behaviours and attitudes in question are themselves inherited (e.g. Martin *et al*, 1986), such analyses are in danger of yielding tautological results.

A fourth position, commonly adopted by behavioural psychologists, is to accept the importance of environmental exposures but to recognise only those that are cognitively mediated, as in the case of life events perceived to be threatening or to signify loss (e.g. Felsner *et al*, 1983), and hence to neglect chemical, biological – and indeed also social – risk factors of which individuals may be unaware.

The fifth standpoint emphasises that while environmental hazards can be important, individual probabilities of exposure to them are largely genetically determined, first because both genes and early surroundings are normally provided by the family of origin (passive correlation), and second because a person's genetic endowment governs both the selection of a personal environment and the person's relationship with it (active and evocative correlation) (Rutter & Plomin, 1997; see also Neiderhiser, 2001, this supplement).

Finally, it is argued that we know as yet too little about the mode of action of environmental risk factors for gene–environment studies to make real progress until much basic research has been undertaken. Thus Plomin (1994) in the course of an informative review commented that, just as genetic effects must be explained ultimately at a molecular level, so environmental effects need to be explained in terms of molecular regulatory processes, and added:

> "For the environment, there is nothing comparable to the laws of heredity worked out by Mendel, to DNA, or to the triplet code. . . . Although much remains to be learned about genetics, understanding of genetic processes seems to be light years ahead of our understanding of environmental processes."

This assessment pays no regard to the achievements of public health medicine over the past two centuries, which have been based primarily on environmental epidemiology rather than detailed analysis of

pathogenetic mechanisms. None the less, one must agree that research in this field is hampered by lack of a sound theoretical foundation. "The environment", declared Einstein, "is everything which isn't me" (cited by McDowall, 1987), thus laying claim to it as a personal construct. A biologist might, however, argue that to each of Einstein's own genes the environment consisted of the rest of his DNA complement, and a behavioural geneticist that the great man's selection of Princeton as a habitat, in preference to Berlin, provides a fine example of active gene–environment correlation. Evidently we stand in need of a clear pragmatic concept for defining the human environment and classifying the hazards it presents to health in general and mental health in particular.

Anthony, who together with his colleagues coined the term 'psychiatric enviromics' (Anthony et al, 1995) defines it in this supplement as "a deliberately complementary search for specific environments or environmental processes and conditions that promote mental health and reduce the occurrence of psychiatric disturbances" – i.e. a positive concept – but concedes that for practical purposes the best starting point

is likely to be the negative concept of preventing mental illness, and proposes a catalogue of environmental exposures and conditions damaging to mental health, based on the manual by Ernest Gruenberg (1980). In addition, however, a number of more recent guidelines could also contribute to the development of an up-to-date inventory (World Health Organization, 1988a,b, 1991; Shaffer et al, 1989; Royal College of Psychiatrists, 1993).

Table 1, which draws on these various publications, is restricted to forms of risk for which relatively specific measures, largely targeted on individual prophylaxis, are at least potentially available, and is certainly not intended to be comprehensive. One may surmise that in purely quantitative terms, macrosocial influences such as mass unemployment, poverty, inner-city decay, ethnic conflicts and enforced migration are more powerful determinants of psychiatric morbidity as a whole. Against these forces, however, preventive action needs to be targeted on whole populations or population subgroups, rather than on individuals, so that specific gene–environment interactions are likely to prove less significant.

Clearly, the traditional dichotomy into predisposing and provoking causes of mental disorder – although not invalid – must now be regarded as an oversimplification. Systematic attempts to order and classify such a complex, disparate set of influences will call for some kind of multiaxial framework. How might this be constructed? Adapting the simple typology put forward by McDowall (1987), environmental health hazards can be classified as:

(a) natural physico-chemical;

(b) man-made physico-chemical;

(c) biological/organic (hitherto mainly natural, but in future presumably also man-made);

(d) macrosocial;

(e) micro- or psychosocial.

An additional category of occupational factors can also be distinguished, but in practice is an amalgam formed from the other five.

A second possible axis of classification relates to the tempo with which risk exposures in a population undergo change. In Table 2, physico-chemical, biological and social hazards are arranged, with illustrative examples, according to whether the change

Table 1 Preventive actions aimed at reducing mental health damage caused by environmental exposures or their consequences

Prenatal and neonatal interventions

Immunisation against maternal rubella and influenza

Voluntary screening for HIV and syphilis infection

Dietary supplementation during pregnancy, including folate supplements

Antenatal monitoring and care to prevent teratogenic toxicity, foetal alcohol syndrome and neonatal narcotic dependency

Measures in infancy and childhood

Immunisation against measles, pertussis and herpes simplex encephalitis

Eradication campaigns against meningococcal meningitis and congenital syphilis

Iodine supplementation in deficiency-endemic areas (orally and in salt)

Detection and dietary treatment of phenylketonuria and other metabolic errors

Detection of non-accidental injury, physical and sexual abuse

Monitoring of prolonged medication (e.g. anti-epileptic drugs)

Reduction of neurotoxic exposures (e.g. lead pollution from petrol additives)

Measures in adolescence and early adult life

Prevention of brain trauma through road traffic accidents (highway speed limits, drink-driving controls, seat belts, crash helmets)

Programmes targeting risk-taking behaviour (use of alcohol and 'designer' drugs, AIDS infection, etc.)

Crisis helplines; youth and student advisory/counselling services

School-leaver and welfare-to-work rehabilitation programmes

Occupational health and safety programmes (e.g. reducing exposure to organic solvents, organophosphates, heavy metal compounds)

Measures in middle and later adult life

Reduction of risk for cerebrovascular disease, hypertension and stroke by control of diet, alcohol consumption, etc.

Detection of conditions with neuropsychiatric complications (e.g. vitamin B_{12} deficiency and megaloblastic anaemia, hypothyroidism, Borrelia infection)

Avoidance of iatrogenic neuropsychiatric syndromes (e.g. confusional states, oral dyskinesia) by tailored dosage and monitoring of medication

Medico-social support in high-risk situations (e.g. recent bereavement, discharge from hospital, admission to long-term care)

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.

Table 2 Macroenvironmental factors of psychiatric disorder: a simple typology with examples

Time dimension	Biological and chemical noxae	Physical hazards	Political and social mass phenomena
Community disasters and sudden increases in the level of hazard	Acute toxic epidemics: 　ergot psychosis in Pont St Esprit Sequelae of toxic disasters: 　methyl isocyanate in Bhopal	Natural disasters: 　earthquakes, floods, volcanic 　eruptions Man-made disasters: 　Cocoanut Grove fire 　Buffalo Creek dam burst 　Aberfan school (coal-mining waste)	Cults and sects: 　Jonestown mass suicide 　Race riots and massacres 'Mass hysteria' outbreaks: 　koro epidemics in south-east Asia
Rapid environmental change	Virus disease epidemics: 　1918 influenza pandemic 　(postencephalitic syndromes) 　HIV pandemic Industrial poisons: 　mercurial waste in Minamata 　carbon disulphide in rubber 　industry 　toxic oil syndrome in Spain 　exposure to organic pesticides	Military service in wartime: 　psychiatric casualties; drug 　dependency in Vietnam Low-level flying and aircraft noise: 　neuroses; learning problems Coal-gas in domestic fuel supplies: 　changes in suicide risk	Political persecution: 　aftermath of concentration camps 　effects of deportation and 　displacement 　urban terrorism (child behaviour 　problems, etc.) Growth of long-term unemployment in depressed industrial areas (suicide and parasuicide)
Slow change or static situation	Alcohol consumption levels Lead exposure from water pipes and atmospheric pollution (learning disability; subclinical intoxication) Marketing and prescribing of pharmaceuticals (parasuicide; drug dependency)	Standard of prenatal and obstetric care (spectrum of reproductive casualty) Traffic accident rates (brain damage in young adult age-groups)	Influence of schools (differences in delinquency, child guidance rates) Hospital admission and segregation of young children Housing developments: 　lack of 'defensible space' Long-stay care (institutionalism and social breakdown syndrome)

Source: Cooper (1990).

in rates is sudden and massive, as in a communal disaster; relatively rapid, as in an infectious epidemic; or slow-moving to static, as for natural neurotoxic exposures. At population level, sudden changes will tend to operate as provoking factors, and slow changes or steady states as predisposing factors, although it is not difficult to think of exceptions.

An obvious inference from Tables 1 and 2 is that identifying concomitant risk factors in the environment, for example by means of cross-sectional case–control studies, will not suffice to delineate the 'psychiatric envirome': past exposures must also be identified, extending back to those that affect intrauterine development or indeed the previous generation. A number of contributions to this supplement provide supporting evidence:

(a) the review by Sharpley et al (2001, this supplement) of functional psychosis rates among first- and second-generation African–Caribbean immigrants in Britain highlights long-term consequences of migration and social disadvantage;

(b) Fan & Eaton (2001, this supplement) demonstrate the combined influence of birth abnormalities and socio-economic status in childhood on risk for adult emotional disorder;

(c) the report by Ritsher et al (2001, this supplement) of their longitudinal study of depression in families over three generations points to inter-generational low social status rather than social selection as a causal factor;

(d) Lawrence Whalley's (2001, this supplement) investigation of early-onset dementia rates in Scotland reveals case-clustering in areas that were characterised by social deprivation two generations earlier; here, high mortality and morbidity, low educational achievement, unemployment, hardship and poverty seem to be intertwined in a nexus from which causal and selective influences are almost impossible to disentangle.

Each of these projects affords a tantalising glimpse of the ways in which intergenerational processes and early developmental faults can accumulate in a population to form a matrix for psychiatric morbidity.

GENE–ENVIRONMENT CORRELATION AND INTERACTION

Although gene–environment relationships are now highly topical in epidemiology, few substantive findings have so far been reported with regard to mental disorders. This is readily understandable when one considers that such research is in its infancy and is still handicapped by an absence of well-established candidate genes for most conditions, together with the lack of any firm conceptual framework for environmental exposures.

Attempts to date at characterising gene–environment correlation (G r E) and interaction ($G \times E$) have been of limited heuristic value. Some confusion still exists between the statistical concept of interaction as departure from a multiplicative model, and the epidemiological concept of it as co-participation in the same causal mechanism of disease development, with departure from an additive model (Yang & Khoury, 1997). The six patterns of interaction which these authors distinguish on theoretical grounds have yet to be demonstrated for psychiatric disorders, as also in great measure has the differentiation of passive, active and evocative correlation, mentioned above.

So far most of the available evidence has come from family and twin studies in which family history and MZ/DZ concordance are employed as indicators of genetic inheritance. Such studies will continue to be of critical importance, especially when representative population samples can be drawn and DNA testing carried out. Their potential scope is already indicated by a series of findings on the risk for affective disorders, which call for further investigation:

(a) a common, partly genetic susceptibility may combine with different types of environmental exposure to result in either depressive or anxiety states (Kendler *et al*, 1987);

(b) shared genetic inheritance and early upbringing can have disparate predisposing effects within nuclear families, because of differential parenting behaviours (Reiss *et al*, 1995);

(c) genetically influenced susceptibility, as gauged by twin concordance, can interact with stressful events in adult life to provoke the onset of new major depressive episodes (Kendler *et al*, 1995).

Adoption research designs have inevitably focused on biological family history (G) and psychosocial risk factors in the adoptive families (E). The latter, including family conflict, poor cohesion and deviant communication, appear not to be diagnosis-specific, but largely shared in common by categories including schizophrenia (Wahlberg *et al*, 1997), conduct disorder (Cadoret *et al*, 1995) and alcoholism (Cutrona *et al*, 1994). Adoption studies have been influential in demonstrating interaction effects, but their findings cannot be directly extrapolated to the wider population, and their usefulness may in future become more limited as the frequency of adoption at a very early age declines.

Gene marker studies, whether based on direct analysis of DNA or on gene expression products, have so far provided only fragmentary evidence, chiefly because of the lack of candidate genes with established pathogenic relationships to the target conditions. Supportive findings include increased risk of an Alzheimer 'cascade' following head injury, in persons carrying the *APOE* ϵ4 allele (Nicoll *et al*, 1996); an influence of D_2 dopamine receptor alleles on the consequences of family stress for children's cognitive functioning (Berman & Noble, 1997); and the putative effect of a serotonin transporter gene polymorphism on risk for affective symptoms, which, however, has not been confirmed by a systematic study (Jorm *et al*, 1998). Clearly, such tentative findings do not amount to more than straws in the wind, and it is too early yet to judge how important advances in molecular genetics will prove to be for this field of enquiry.

CONCLUSION

Overall, firm knowledge concerning either genetic or environmental causes of mental disorder is still at a premium, although progress has varied a good deal among the main diagnostic categories. That the environmental aspects have as a rule been dealt with only perfunctorily by behavioural geneticists can be explained in part by the lack of a firm conceptual framework to order the principal types of 'candidate' hazard – physico-chemical, biological, macrosocial and psychosocial – and the nature of exposures to these which may serve to increase host susceptibility or provoke illness onset. Such candidate hazards should be plausible on biological or psychological grounds, and are likely to differ between diagnostic groups.

Once environmental risks have been more firmly defined and exposures to them made quantifiable, the foundation for truly scientific gene–environment interaction studies will have been laid, and we may then expect to see real progress. The kind of multi-disciplinary initiative proposed by Anthony (2001, this supplement) could be of great help, though the Human Genome Project seems an unlikely analogy in terms of scale and size of research funding – not to mention prospects for patenting and commercial exploitation. How far 'psychiatric enviromics' will prove to be a distinct area of research within environmental epidemiology remains to be seen.

Future developments in this whole field cannot yet be predicted with any confidence. What few pointers there are suggest that genetically controlled interaction will be identified with features of the physico-chemical and biological environments, and will prove critical in some neuropsychiatric syndromes with clearly demonstrable central nervous substrates. For most other psychiatric disorders, evidence of such 'lock and key' effects may emerge in due course, but it seems at least equally probable that genetic factors will be shown to operate in less specific ways: by influencing the developmental consequences of early adversity, increasing sensitivity to stressful events in adult life, or modifying the clinical features of illness.

How radically mental-illness epidemiology should be adapted to meet the challenge of genomic science is open to debate. Henderson & Blackwood (1999) in a recent editorial affirmed that psychiatric epidemiology is currently becalmed, and that failure to resolve the difficulties of incorporating molecular genetics into its agenda could leave much of the discipline stranded in the 20th century. The danger should not be dismissed, but other scenarios can also be envisaged. Application of the new technology to mental health problems may prove disappointing and disillusion follow, as so often in psychiatry. Interest may move on to gene expression and proteomics, as Anthony suggests (2001, this supplement). The impending global population and ecological crises may in the decades ahead bring about a major shift in medical research priorities and a renewed awareness of the need for public health measures based on systems-level change, rather than personal prevention. On the whole, McMichael's (1994) assessment of 'molecular epidemiology' as a helpful travelling companion is probably the right one.

Should reductionist designs in causal research now be replaced by some kind of integrative synthesis? Steven Rose (1997, and 2001, this supplement) has argued forcefully that it is time to abandon the outworn nature–nurture dichotomy, and that in psychiatry attention should be focused instead on the life trajectories of people with mental illnesses. His standpoint, which in essence is close to the psychobiological

teaching of Adolf Meyer, is one with a strong appeal for many clinicians and therapists, and carries implications for population research that may pose one of the great future challenges for psychiatric epidemiology. Yet the underlying urge to isolate and quantify different aetiological components will not disappear, partly because analytical reductionism is central to modern scientific method, but also because in psychiatric thinking the concepts involved are so closely bound up with fundamental issues concerning the deterministic or dynamic nature of mental illnesses.

REFERENCES

Andrews, G., Neilson, M., Hunt, C., et al (1990) Diagnosis, personality and the long-term outcome of depression. *British Journal of Psychiatry*, **157**, 13–18.

Anthony, J. C. (2001) The promise of psychiatric enviromics. *British Journal of Psychiatry*, **178** (suppl. 40), s8–s11.

__ , Eaton, W. W. & Henderson, A. S. (1995) Looking to the future in psychiatric epidemiology. *Epidemiologic Reviews*, **17**, 240–242.

Armstrong, C. (1997) Thousands of women sterilized in Sweden without consent. *British Medical Journal*, **318**, 563.

Bassett, A. S., McGillivray, B. C., Jones, B. D., et al (1988) Partial trisomy of chromosome 5 co-segregating with schizophrenia. *Lancet*, **i**, 799–801.

Bergem, A. L., Engedal, K. & Kringlen, E. (1997) The role of heredity in late-onset Alzheimer disease and vascular dementia. A twin study. *Archives of General Psychiatry*, **54**, 264–270.

Berman, S. & Noble, E. P. (1997) The D2 receptor (DRD2) gene and family stress: interactive effects on cognitive functions in children. *Behavioral Genetics*, **27**, 33–43.

Breitner, J. C. S., Welsh, K. A., Gau, B. A., et al (1995) Alzheimer's disease in the National Academy of Sciences – National Research Council Registry of ageing twin veterans. III. Detection of cases, longitudinal results, and observations on twin concordance. *Archives of Neurology*, **52**, 763–771.

Brock, D. J. (1996) Prenatal screening for cystic fibrosis: 5 years' experience reviewed. *Lancet*, **347**, 148–150.

Brown, G. W. & Harris, T. O. (1978) *Social Origins of Depression: A Study of Psychiatric Disorder in Women*. London: Tavistock.

Cadoret, R. J., Yates, W. R., Troughton, E., et al (1995) Genetic–environmental interaction in the genesis of aggressivity and conduct disorders. *Archives of General Psychiatry*, **52**, 916–924.

Cantor, C. R. & Little, D. P. (1998) Massive attack on high-throughput biology. *Nature Genetics*, **20**, 5–6.

Cooper, B. (1986) Mental disorder as reaction: the history of a psychiatric concept. In *Life Events and Psychiatric Disorders: Controversial Issues* (ed. H. Katschnig), pp. 1–32. Cambridge: Cambridge University Press.

__ (1990) Epidemiology and prevention in the mental health field. *Social Psychiatry and Psychiatric Epidemiology*, **25**, 9–15.

Cruts, M., van Duijn, C. M., Backhovens, H., et al (1998) Estimation of the genetic contribution of presenilin-1 and -2 mutations in a population-based study of presenile Alzheimer disease. *Molecular Genetics*, **7**, 43–51.

Cutrona, C. E., Cadoret, R. E., Suhr, J. A., et al (1994) Interpersonal variables in the prediction of alcoholism among adoptees: evidence for gene–environment interaction. *Comprehensive Psychiatry*, **35**, 171–179.

Dassa, D., Sham, P. C., van Os, J., et al (1996) Relationship of birth season to clinical features, family history, and obstetric complications in schizophrenia. *Psychiatry Research*, **64**, 11–17.

Davies, K. E. (1997) Challenges in Duchenne muscular dystrophy. *Neuromuscular Disorders*, **7**, 482–486.

Ellsworth, D. L., Hallman, D. M. & Boerwinkle, E. (1997) Impact of the Human Genome Project on epidemiologic research. *Epidemiologic Reviews*, **19**, 3–13.

Eysenck, H. J. (1958) A short questionnaire for the measurement of two dimensions of personality. *Journal of Applied Psychology*, **43**, 14–17.

Fan, A. P. & Eaton, W. W. (2001) Longitudinal study assessing the joint effects of socio-economic status and birth risks on adult emotional and nervous conditions. *British Journal of Psychiatry*, **178** (suppl. 40), s78–s83.

Felsner, R. D., Jason, L., Moritsugu, J. N., et al (1983) *Preventive Psychology: Theory, Research and Practice*. New York: Pergamon.

Folstein, M. F. & Powell, D. (1984) Is Alzheimer's disease inherited? A methodological review. *Integrative Psychiatry*, **Sep–Oct**, 163–170.

Freud, S. (1909) Analysis of a phobia in a five-year-old boy. In *Standard Edition of the Complete Psychological Works of Sigmund Freud*, vol. 10, published 1955 (ed. and transl. J. Strachey), pp. 5–147 (quotation pp. 145–146). London: Hogarth Press.

Frost, W. H. (1941) Epidemiology. In *Papers of Wade Hampton Frost, MD* (ed. K. E. Maxey), pp. 493–542. New York: Commonwealth Fund.

Galton, F. (1876) The history of twins as a criterion of the relative powers of nature and nurture. *Royal Anthropological Institute of Great Britain and Ireland Journal*, **6**, 391–406.

Gatz, M., Pedersen, N. L., Berg, S., et al (1997) Heritability for Alzheimer's disease: the study of dementia in Swedish twins. *Journals of Gerontology, Series A: Biological and Medical Sciences*, **52**, M117–M125.

Goldberg, D. (2001) Vulnerability factors for common mental illnesses. *British Journal of Psychiatry*, **178** (suppl. 40), s69–s71.

__ & Huxley, P. (1992) *Common Mental Disorders. A Biosocial Model*. London: Tavistock/Routledge.

Goldman, D. (1995) Candidate genes in alcoholism. *Clinical Neuroscience*, **3**, 174–181.

Gostin, L. (1991) Genetic discrimination: the use of genetically based diagnostic and prognostic tests by employers and insurers. *American Journal of Law and Medicine*, **17**, 109–144.

Gottesman, I. I. (1991) *Schizophrenia Genesis: The Origin of Madness*. New York: Freeman.

Grant, B. F. (1997) Prevalence and correlates of alcohol use and DSM–IV alcohol dependence in the United States: results of the National Longitudinal Alcohol Epidemiologic Survey. *Journal of Studies on Alcohol*, **58**, 464–473.

Gruenberg, E. M. (1980) Mental disorders. In *Maxcey–Rosenau – Public Health and Preventive Medicine*, 11th edn (ed. J. M. Last), pp. 1303–1358. New York: Appleton–Century.

Heath, A. C., Whitfield, J. B., Madden, P. A. F., et al (2001) Towards a molecular epidemiology of alcohol dependence: analysing the interplay of genetic and environmental risk factors. *British Journal of Psychiatry*, **178** (suppl. 40), s33–s40.

Henderson, A. S. & Blackwood, D. H. R. (1999) Molecular genetics in psychiatric epidemiology: the promise and challenge (editorial). *Psychological Medicine*, **29**, 1265–1271.

__ , Easteal, S., Jorm, A. F., et al (1996) Apolipoprotein E epsilon 4, dementia and cognitive decline in a population sample. *Lancet*, **246**, 1387–1390.

Jablensky, A., Zubrick, S., Morgan, V., et al (1999) Obstetric complications and offspring outcomes in women with schizophrenia and affective psychoses: a population study. *Schizophrenia Research*, **36** (special issue), 44.

Jorm, A. F., Henderson, A. S., Jacomb, P. A., et al (1998) An association study of a functional polymorphism of the serotonin transporter gene with personality and psychiatric symptoms. *Molecular Psychiatry*, **3**, 449–451.

Kendler, K. S. (1988) Familial aggregation of schizophrenia and schizophrenia spectrum disorders. *Archives of General Psychiatry*, **45**, 323–327.

__ (1995) Genetic epidemiology in psychiatry. Taking both genes and environment seriously. *Archives of General Psychiatry*, **52**, 895–899.

__ , Heath, A. C., Martin, N. G., et al (1987) Symptoms of anxiety and depression: same genes, different environments? *Archives of General Psychiatry*, **44**, 451–457.

__ , Neale, M. C., Heath, A. C., et al (1994) A twin-family study of alcoholism in women. *American Journal of Psychiatry*, **151**, 707–715.

__ , Kessler, R. C., Walters, E. E., et al (1995) Stressful life events, genetic liability, and onset of an episode of major depression in women. *American Journal of Psychiatry*, **152**, 833–842.

Khoury, M. J. (1997) Genetic epidemiology and the future of disease prevention and public health. *Epidemiologic Reviews*, **19**, 175–180.

Kringlen, E. (1995) Twin studies in mental disorder. *Baillière's Clinical Psychiatry*, **1**, 47–62.

Kunugi, H., Nanko, S. & Murray, R. M. (2001) Obstetric complications and schizophrenia: prenatal underdevelopment and subsequent neurodevelopmental impairment. *British Journal of Psychiatry*, **178** (suppl. 40), s25–s29.

Kuusisto, J., Koivisto, K., Kervinen, K., et al (1994) Association of apolipoprotein E phenotypes with late-onset Alzheimer's disease: population based study. *British Medical Journal*, **309**, 636–638.

Lai, T. J., Guo, Y. L., Guo, N. W., et al (2001) Effect of prenatal exposure to polychlorinated biphenyls on cognitive development in children: a longitudinal study in Taiwan. *British Journal of Psychiatry*, **178** (suppl. 40), s49–s52.

Lancet (1995) Western eyes on China's eugenics law. *Lancet*, **346**, 131.

Lendon, C. L., Ashall, F. & Goate, A. M. (1997) Exploring the etiology of Alzheimer disease using molecular genetics. *Journal of the American Medical Association*, **277**, 825–831.

Lippman, A. (1992) Led (astray) by genetic maps: the cartography of the human genome and health care. *Social Science and Medicine*, **35**, 1469–1476.

Luxenburger, H. (1928) Vorläufiger Bericht über psychiatrische Serienuntersuchungen an Zwillingen (Preliminary report on psychiatric studies of twins series). *Zeitschrift für gesamte Neurologie und Psychiatrie*, **116**, 297–326.

McCabe, L. L. & McCabe, R. B. (1997) Population studies of allele frequencies in single gene disorders: methodological and policy considerations. *Epidemiologic Reviews*, **19**, 52–60.

McCord, W. & McCord, J. (1960) *Origins of Alcoholism*. Stanford, CA: Stanford University Press.

McDowall, M. E. (1987) *The Identification of Man-Made Environmental Hazards to Health. A Manual of Epidemiology*. London: Macmillan.

McGuffin, P., Asherson, P., Owen, M., et al (1994) The strength of the genetic effect. Is there room for an environmental influence in the aetiology of schizophrenia? *British Journal of Psychiatry*, **164**, 593–599.

McMichael, A. J. (1994) Invited commentary – 'molecular epidemiology': new pathway or traveling companion? *American Journal of Epidemiology*, **140**, 1–11.

Martin, N. G., Eaves, L. J., Heath, A. C., et al (1986) Transmission of social attitudes. *Proceedings of the National Academy of Sciences of the USA*, **83**, 4364–4368.

Mayeux, R., Ottman, R., Tang, M. X., et al (1993) Genetic susceptibility and head injury as risk factors for Alzheimer's disease among community-dwelling elderly persons and their first-degree relatives. *Annals of Neurology*, **33**, 494–501.

Merikangas, K. R. & Swendsen, J. D. (1997) Genetic epidemiology of psychiatric disorders. *Epidemiologic Reviews*, **19**, 144–155.

Meyer-Lindenberg, J. (1991) The Holocaust and German psychiatry. *British Journal of Psychiatry*, **159**, 7–12.

Miki, Y., Swensen, J., Shattuck-Eidens, D., et al (1994) A strong candidate for the breast and ovarian cancer gene BRCA1. *Science*, **266**, 66–71.

Munk-Jørgensen, P. & Ewald, H. (2001) Epidemiology in neurobiological research: exemplified by the influenza–schizophrenia theory. *British Journal of Psychiatry*, **178** (suppl. 40), s30–s32.

Nalbantoglu, J., Gilfix, B. M., Bertrand, Y., et al (1994) Predictive value of apolipoprotein E genotyping in Alzheimer's disease: results of an autopsy series and several combined studies. *Annals of Neurology*, **36**, 889–895.

Neiderhiser, J. M. (2001) Understanding the roles of genome and envirome: methods in genetic epidemiology. *British Journal of Psychiatry*, **178** (suppl. 40), s12–s17.

Nicoll, J. A., Roberts, G. W. & Graham, D. I. (1996) Amyloid beta-protein, APOE genotype and head injury (review). *Annals of the New York Academy of Sciences*, **777**, 271–275.

Penrose, L. (1971) Psychiatric genetics (editorial). *Psychological Medicine*, **1**, 265–266.

Peltonen, L. & Lönnqvist, J. (1995) Human genome project: consequences for the search for predisposing genes in psychiatric disorders. *Baillière's Clinical Psychiatry*, **1**, 111–122.

Plomin, R. (1994) *Genetics and Experience: The Interplay Between Nature and Nurture*, pp. 1–40. Thousand Oaks, CA: Sage.

___ & Craig, I. (2001) Genetics, environment and cognitive abilities: review and work in progress towards a genome scan for quantitative trait locus associations using DNA pooling. *British Journal of Psychiatry*, **178** (suppl. 40), s41–s48.

Prescott, C. A. & Kendler, K. S. (1999) Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. *American Journal of Psychiatry*, **156**, 34–40.

Raiha, I., Kaprio, J., Koskenvuo, M., et al (1996) Alzheimer's disease in Finnish twins. *Lancet*, **347**, 573–578.

Reiss, D., Hetherington, M., Plomin, R., et al (1995) Genetic questions for environmental studies. Differential parenting and psychopathology in adolescence. *Archives of General Psychiatry*, **52**, 925–936.

Risch, N. (1997) Evolving methods in genetic epidemiology: genetic linkage from an epidemiologic perspective. *Epidemiologic Reviews*, **19**, 24–32.

Ritsher, J. E. B., Warner, V., Johnson, J. G., et al (2001) Inter-generational longitudinal study of social class and depression: a test of social causation and social selection models. *British Journal of Psychiatry*, **178** (suppl. 40), s84–s90.

Roberts, G. W., Gentleman, S. M., Lynch, A., et al (1994) β-amyloid protein deposition in the brain after severe head-injury: implications for the pathogenesis of Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **57**, 419–425.

Rosanoff, A. J., Handy, L. M., Plesset, I. R., et al (1934) The etiology of the so-called schizophrenic psychoses with special reference to their occurrence in twins. *American Journal of Psychiatry*, **91**, 247–286.

Rose, S. (1997) *Lifelines: Biology, Freedom, Determinism*. London: Penguin.

___ (2001) Moving on from old dichotomies: beyond nature–nurture towards a lifeline perspective. *British Journal of Psychiatry*, **178** (suppl. 40), s3–s7.

Roy, M. A., Neale, M. C., Pedersen, N. L., et al (1995) A twin study of generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Archives of General Psychiatry*, **52**, 374–383.

Royal College of Psychiatrists (1993) *Prevention in Psychiatry. Report of the Special Committee on the Place of Prevention in Psychiatry*. Council Report CR21. London: Royal College of Psychiatrists.

Rutter, M. & Plomin, R. (1997) Opportunities for psychiatry from genetic findings. *British Journal of Psychiatry*, **171**, 209–219.

Shaffer, D., Philips, I. & Enzer, N. B. (1989) *Prevention of Mental Disorders, Alcohol and Other Drug Use in Children and Adolescents*. OSAP Prevention Monograph 2. Rockville, MD: US Department of Health and Human Services.

Sharpley, M. S., Hutchinson, G., McKenzie, K., et al (2001) Understanding the excess of psychosis among the African–Caribbean population in England. Review of current hypotheses. *British Journal of Psychiatry*, **178** (suppl. 40), s60–s68.

Sherrington, R., Brynjolfsson, J., Petursson, H., et al (1988) Localization of a susceptibility locus for schizophrenia on chromosome 5. *Nature*, **336**, 164–167.

Smeraldi, E. & Macciardi, F. (1995). Association and linkage studies in mental illness. *Baillière's Clinical Psychiatry*, **1**, 97–110.

Strömgren, E. (1950) Statistical and genetical population studies within psychiatry. Methods and principal results. In *Psychiatrie Sociale* (ed. T. Sjögren),

International Congrès de Psychiatrie, Paris 1950, vol. 6. Paris: Herrman.

Susser, M. & Susser, E. (1987) Separating heredity and environment: research designs and strategies. In *Epidemiology, Health and Society: Selected Papers* (ed. M. Susser), pp. 114–128. New York: Oxford University Press.

Tambs, K. & Moum, T. (1993) Low genetic effect and age-specific family effect for symptoms of anxiety and depression in nuclear families. *Journal of Affective Disorders*, **27**, 183–195.

Thomas, P., Romme, M. & Hamelijnck, J. (1996) Psychiatry and the politics of the underclass. *British Journal of Psychiatry*, **169**, 401–404.

Toomey, T. L. & Wagenaar, A. C. (1999) Policy options for prevention: the case of alcohol. *Journal of Public Health Policy*, **20**, 192–213.

Tsuang, M. T., Stone, W. S. & Faraone, S. V. (2001) Genes, environment and schizophrenia. *British Journal of Psychiatry*, **178** (suppl. 40), s18–s24.

Vaillant, G. E. & Milofsky, E. S. (1982) The etiology of alcoholism. *American Journal of Psychology*, **37**, 494–503.

Van Duijn, C. M., Clayton, D. G., Chandra, V., et al (1994) Interaction between genetic and environmental risk factors for Alzheimer's disease: a reanalysis of case–control studies. *Genetic Epidemiology*, **11**, 539–551.

Van Os, J., Park, S. B. G. & Jones, P. B. (2001) Neuroticism, life events and mental health: evidence for person–environment correlation. *British Journal of Psychiatry*, **178** (suppl. 40), s72–s77.

Vieland, V. J., Susser, E. & Weissman, M. M. (1995) Genetic epidemiology in psychiatric research. *Baillière's Clinical Psychiatry*, **1**, 19–45.

Wahlberg, K. E., Wynne, L. C., Oja, H., et al (1997) Gene–environment interaction in vulnerability to schizophrenia: findings from the Finnish Adoptive Family Study of Schizophrenia. *American Journal of Psychiatry*, **154**, 355–362.

Weber, M. M. (1997) Ernst Rüdin, 1874–1952: a German psychiatrist and geneticist (editorial). *American Journal of Medical Genetics*, **67**, 323–331.

Whalley, L. J. (2001) Early-onset Alzheimer's disease in Scotland: environmental and familial factors. *British Journal of Psychiatry*, **178** (suppl. 40), s53–s59.

Wilkie, T. (1998) Genetics and insurance in Britain: why more than just the Atlantic divides the English-speaking nations. *Nature Genetics*, **20**, 119–121.

World Health Organization (1988a) *Prevention of Mental, Neurological and Psychosocial Disorders*. Report of Director-General. WHO/MNH/EVA.88.1. Geneva: WHO.

___ (1988b) *Prevention of Mental, Psychosocial and Neurological Disorders in the European Region*. EUR/PSF 88.1. Copenhagen: WHO Regional Office for Europe.

___ (1991) *Implications for the Field of Mental Health of the European Targets for Attaining 'Health or All'*. EUR/ICP/HSC 013. Copenhagen: WHO Regional Office for Europe.

Yang, Q. & Khoury, M. J. (1997) Evolving methods in genetic epidemiology. III: Gene–environment interaction in epidemiologic research. *Epidemiologic Reviews*, **19**, 33–43.

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