Psychological Medicine, 2002, **32**, 1145–1148. © 2002 Cambridge University Press
DOI: 10.1017/S0033291702006542 Printed in the United Kingdom

EDITORIAL

Genetic epidemiology in a molecular age[1]

In this issue we publish three genetic epidemiology papers (Agrawal *et al*. 2002; Johnson *et al*. 2002; Wichers *et al*. 2002). *Psychological Medicine* in recent years has had genetic epidemiology as one of its major themes. We also publish some molecular genetic papers. This is a time when the development of molecular genetic technologies, which have already enabled the sequencing of the entire human genome, has been widely and appropriately hailed as a major advance, promising to generate a revolution in the understanding of causes of all human disease, including psychiatric, and in the discovery of new drugs. *Psychological Medicine* now has a distinguished American Editor from the world of genetic epidemiology in the person of Kenneth Kendler. This editorial, by his British editorial counterpart, is deliberately non-expert, and a view of the psychiatric future of genetic epidemiology from outside the field.

The basic findings for heritability of major psychiatric disorders have become well established and replicated in some decades of research. Family studies were followed by twin studies and adoption studies which established on a much firmer basis that a substantial element in the familiality was genetic. Disappointingly, the genes still remain to be identified with certainty. That is the task of molecular genetics. It is becoming increasingly clear that the task will not be an easy one, because for the most part we seem to have multi-gene disorders, with a number of or many genes of small effect, requiring large samples and quantitative trait methods to elucidate (Plomin *et al*. 1994).

If the broad findings regarding heritability are well established, what is left for genetic epidemiology? First, there is a good deal of tidying up to do. It is essential, if not always headline-grabbing. Johnson *et al*. (2002) in this issue make use of a Danish twin study to analyse heritability for self-reported depression in subjects aged 45 to 95. Over this wide age range, although the frequency of depressive symptoms increased with age, heritability remained constant. It has sometimes been argued that higher genetic loading will lead to earlier onset of depression and other disorders. By inference, later onsets of the disorders should show greater environmental effects. On the other hand there has been some published evidence suggesting that genetic contribution to depression may increase with age (McGue & Kristensen, 1997; Carmelli *et al*. 2000). Most studies have limited age ranges. The findings of Johnson *et al*. (2002) indicate that from middle to old age, heritability does not change.

In other recent papers dealing with depression Kendler and colleagues have been particularly interested in sex differences. Last year they presented evidence that using broader but not narrow criteria, genetic factors play a greater role in the aetiology of major depression in women than men (Kendler *et al*. 2001), confirming earlier non-significant trends (Kendler & Prescott, 1999). Stronger findings indicating greater heritability in women were reported by Bierut *et al*. (1999). In similar work on anxiety disorders, Kendler *et al*. (2002*a*) have found some differences between different kinds of phobias. The sex differences in rates for mood and anxiety disorders are well known. There has so far been little study of sex differences in genetic aspects outside these disorders.

Other worthwhile work involves disorders not so far well studied. Fu *et al*. (2002), have reported on suicidal behaviour in male veterans from the Vietnam Era Twin Registry. They found genetic elements in suicidal ideation and attempts, not simply explained by inheritance of underlying major psychiatric disorders. Treloar *et al*. (2002), using an Australian twin register, have found genetic elements in premenstrual symptoms but have also raised the possibility of reporting factors.

[1] Address for correspondence: Professor E. S. Paykel, Editor, *Psychological Medicine*, University of Cambridge, Department of Psychiatry, Douglas House, 18E Trumpington Road, Cambridge CB2 2AH.

Lynskey *et al*. (2002) in male Australian twins have found consistent evidence of genetic elements in cannabis dependence. Similar findings have been reported from a US national sample (Kendler *et al*. 2002*b*) and from a broader study of substance use and abuse (Kendler *et al*. 2000). Nadder *et al*. (2002) using the Virginia Twin Study of Adolescent Behavioural Development found evidence that the co-occurrence of attention deficit hyperactivity disorder and conduct disorder was due to a shared genetic liability acting directly or via gene–environment interaction. Kortegaard *et al*. (2001) in Danish twins have found a genetic element in self-reported eating disorder.

This is useful and important work. The paradigm has many more years to play. However, one day when the disorders have all been studied and the tidying up done, the vein will start to run out. The most valuable ore will be harder to mine, and the work will gradually become more and more replicatory, secondary, and of lesser interest. What then?

At one level all geneticists, even the molecular, need the epidemiologist. Most informative genetic studies are in selected populations. Findings need to be applied to gene frequencies and disease frequencies in the general population, before the magnitude of genetic effects can truly be quantified. Major applications of genetics to human disease, for instance in cancer, seem increasingly to come from research units and institutes that combine molecular geneticists, genetic epidemiologists and classical epidemiologists (Kuschel *et al*. 2002).

Increasingly important for the future are likely to be studies that simultaneously examine genetic and environmental effects and the relationship between them. Twin and family studies, although classical models for genetic questions, also provide good settings in which to study the detailed environmental factors that contribute to disorders. In a study of parents and children a relationship was found between number of parents with major affective disorder and occurrence of psychiatric disorder in offspring (Nomura *et al*. 2001). The design of this study could not distinguish genetic from environmental effects, but it did indicate important dose–response consequences of the combination. Kendler & Gardner (2001) used monozygotic twins discordant for major depression to study environmental differences between the affected twin and the unaffected co-twin, and found differences on a wide range of factors from childhood environments to recent stressful events. Fu *et al*. (2002) included data collection on life history antecedents of suicidal behaviour in a genetic twin study. These are first steps, following which in future studies the detailed relationship between each environmental cause and the genetic factors will need to be examined.

Genetic and environmental effects may be additive, as assumed in the usual genetic models, but they may not be straightforwardly so. Wichers *et al*. (2002) in this issue in a Belgian twin study examine effects of pregnancy and birth complications, and of genetic factors, on child problem behaviour. They find problem behaviour in the child influenced both by genetic effects and by an effect of being small for gestational age. They also find a negative interaction, with a decreased genetic influence in twins who were small rather than large for their gestational age. There is other good evidence that genetic effects can vary with environment. For instance, heritability of regular tobacco use in Swedish females increased greatly in the first half of the twentieth century as opportunities for women to smoke rose from minimal to easy (Kendler, 2001). Conversely, the actual phenotypic disease of phenylketonuria showed increasingly incomplete penetrance with widespread introduction of low phenylalanine diet. Heritability estimates of other disorders and behaviours are not necessarily stable and need to be retested in different populations and at different times.

Causative pathways are complex and the most interesting studies for the future will be those that recognize this complexity. Fascinating and subtle are studies of genetic influences on environmental factors, or on behaviours that produce later consequences via the environment. Considerable genetic influences have been found on initiation of smoking, and on the progression to nicotine dependence (Kendler *et al*. 1999; Sullivan & Kendler, 1999). A wide range of physical diseases can then result, and thereby show heritability. Agrawal *et al*. (2002) in this issue, find in a twin study that genetic factors influence a variety of aspects of social support. This is not surprising, when one thinks about the qualities and skills in individuals which foster social relationships, and the different patterns of socialization in everyday life, which in one's own experience characterize individuals

with different personalities. A little less expected, but only at first sight, is the confirmation from twin studies of genetic elements in recent life events, particularly events not independent of illness (Plomin *et al.* 1990; Kendler *et al.* 1993; Kendler & Karkowski-Shuman, 1997). Our personalities can help to create our events. Part of the link between genetic vulnerability and psychiatric disorder may be via such life events. The event is part of the causation, and if the disorder is less likely to occur because the event can be avoided or its consequences modified, there may be important practical implications. Parental discipline, a potent influence for the child and the future adult, has also been found to be influenced by genotype both of parent and of child (Wade & Kendler, 2000). The genes related to these elements need to be elucidated, by molecular genetic studies, which include good measurements of these social and behavioural aspects. Also, genes act over time and the field is likely to move from static statistic of heritability to clarification of the dynamic developmental pathways through which genes, by interaction and covariation with the environment, result in phenotypes.

Both social and genetic researchers are learning to be more sophisticated in their thinking about causation. Genetic epidemiology seems to be alive and well, with a good future before it. *Psychological Medicine* looks forward to continued publication of genetic studies, both from genetic epidemiology and molecular genetics.

EUGENE PAYKEL

REFERENCES

Agrawal, A., Jacobson, K. C., Prescott, C. A. & Kendler, K. S. (2002). A twin study of sex differences in social support. *Psychological Medicine* **32**, 1155–1164.

Bierut, L. J., Heath, A. C., Bucholz, K. K., Dinwiddie, S. H., Madden, P. A., Statham, D.-J., Dunne, M. P. & Martin, N. G. (1999). Major depressive disorder in a community-based twin sample: are there different genetic and environmental contributions for men and women. *Archives of General Psychiatry* **56**, 557–5563.

Carmelli, D., Swan, G. E., Kelly-Hayes, M., Wolf, P. A., Reed, T. & Miller, B. (2000). Longitudinal changes in the contribution of genetic and environmental influences to symptoms of depression in older male twins. *Psychology and Aging* **15**, 505–510.

Fu, Q., Heath, A. C., Bucholz, K. K., Nelson, E. C., Glowinski, A. L., Goldberg, J., Lyons, M. J., Tsuang, M. T., Jacob, T., True, W. R. & Eisen, S. A. (2002). A twin study of genetic and environmental influences on suicidal behaviour in male veterans. *Psychological Medicine* **32**, 11–24.

Johnson, W., McGue, M., Gaist, D., Vaupel, J. W. & Christensen, K. (2002). Frequency and heritability of depression symptomatology in the second half of life: evidence from Danish twins over 45. *Psychological Medicine* **32**, 1175–1185.

Kendler, K. S. (2001). Twin studies of psychiatric illness: an update. *Archives of General Psychiatry* **58**, 1005–1014.

Kendler, K. S. & Gardner, C. O. (2001). Monozygotic twins discordant for major depression: a preliminary exploration of the role of environmental experiences in the aetiology and course of illness. *Psychological Medicine* **31**, 411–423.

Kendler, K. S. & Karkowski-Shuman, L. (1997). Stressful life events and genetic liability to major depression: genetic control of exposure to the environment? *Psychological Medicine* **27**, 539–547.

Kendler, K. S. & Prescott, C. A. (1999). A population-based twin study of lifetime major depression in men and women. *Archives of General Psychiatry* **155**, 1016–1022.

Kendler, K. S., Neale, M., Kessler, R., Heath, A. & Eaves, L. (1993). A twin study of recent life events and difficulties. *Archives of General Psychiatry* **50**, 789–796.

Kendler, K. S., Neale, M. C., Sullivan, P., Corey, L. A., Gardner, C. O. & Prescott, C. A. (1999). A population-based twin study in women of smoking initiation and nicotine dependence. *Psychological Medicine* **29**, 299–308.

Kendler, K. S., Karkowski, L. M., Neale, M. C. & Prescott, C. A. (2000). Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. *Archives of General Psychiatry* **57**, 261–269.

Kendler, K. S., Gardner, C. O., Neale, M. C. & Prescott, C. A. (2001). Genetic risk factors for major depression in men and women: similar or different heritabilities and same or partly distinct genes? *Psychological Medicine* **31**, 605–616.

Kendler, K. S., Jacobsen, K. C., Myers, J. & Prescott, C. A. (2002*a*). Sex differences in genetic and environmental risk factors for irrational fears and phobias. *Psychological Medicine* **32**, 209–217.

Kendler, K. S., Neale, M. C., Thornton, L. M., Aggen, S. H., Gilman, S. E. & Kessler, R. C. (2002*b*). Cannabis use in the last year in a US national sample of twin and sibling pairs. *Psychological Medicine* **32**, 551–554.

Kortegaard, L. S., Hoerder, K., Joergensen, J., Gillberg, C. & Kyvik, K. O. (2001). A preliminary population-based twin study of self-reported eating disorder. *Psychological Medicine* **31**, 361–365.

Kuschel, B., Auranen, A., McBride, S., Novik, K. L., Antoniou, A., Lipscombe, J. M., Day, N. E., Easton, D. F., Ponder, B. A., Pharoah, P. D. & Dunning, A. (2002). Variants in DNA double-strand break repair genes and breast cancer susceptibility. *Human Molecular Genetics* **11**, 1399–1407.

Lynskey, M. T., Heath, A. C., Nelson, E. C., Bucholz, K. K., Madden, P. A. F., Slutske, W. S., Statham, D. J. & Martin, N. G. (2002). Genetic and environmental contributions to cannabis dependence in a national young adult twin sample. *Psychological Medicine* **32**, 195–207.

McGue, M. & Kristensen, K. (1997). Genetic and environmental contributions to depression symptomatology: evidence from Danish twins 75 years of age and older. *Journal of Abnormal Psychology* **106**, 439–448.

Nadder, T. S., Silberg, J. L., Rutter, M., Maes, H. H. & Eaves, L. J. (2002). Genetic effects on the variation and covariation of ADHD and ODD/CD symptomatologies across informant and occasion of measurement. *Psychological Medicine* **32**, 39–53.

Nomura, Y., Warner, V. & Wickramaratne, P. (2001). Parents concordant for major depressive disorder and the effect of psychopathology on offspring. *Psychological Medicine* **31**, 1211–1222.

Plomin, R., Lichtenstein, P., Pedersen, N., McClearn, G. E. & Nesselroade, J. R. (1990). Genetic influences on life events during the last half of the life span. *Psychology and Aging* **5**, 25–30.

Plomin, R., Owen, M. J. & McGuffin, P. (1994). The genetic basis of complex human behaviors. *Science* **264**, 1733–1739.
Sullivan, P. F. & Kendler, K. S. (1999). The genetic epidemiology of smoking. *Nicotine and Tobacco Research* **1**, S51–S57.
Treloar, S., Heath, A. C. & Martin, N. G. (2002). Genetic and environmental influences on premenstrual symptoms in an Australian twin sample. *Psychological Medicine* **32**, 25–38.
Wade, T. D. & Kendler, K. K. (2000). The genetic epidemiology of parental discipline. *Psychological Medicine* **30**, 1303–1313.
Wichers, M. C., Purcell, S., Danckaerts, M., Derom, C., Derom, R., Vlietinck, R. & Van Os, J. (2002). Prenatal life and postnatal psychopathology: evidence for gene–birth weight interaction. *Psychological Medicine* **32**, 1165–1174.