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COMMENTARY

Translating epidemiology in psychiatry: the future is here

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Commentary on: Henderson S. (2012). Psychiatric epidemiology now. Some achievements. And prospects. *Epidemiology and Psychiatric Sciences* (doi:10.1017/S2045796012000042).

Scott Henderson, among the leading psychiatric epidemiology thinkers, has re-evaluated the contribution of epidemiology to understanding psychiatric disorders over the last 50 years. Beginning with Morris's use of epidemiology, he reviews contributions in classification as well as the understanding of morbidity, comorbidity and rates and the identification of pathogenic environmental exposures. He notes the new possibility of linking epidemiology to understanding biological pathways using molecular genetics and neurobiology. He also notes that the flat and featureless epidemiologic horizon has begun to show attractive contours and that we may be entering a new phase in the evolution. I would propose that this future is already here.

In June 2011, we published a review called Translational Epidemiology in Psychiatry, Linking Population to Clinical and Basic Sciences (Weissman *et al.* 2011). In the article, we noted that translational research generally refers to the application of knowledge generated by advances in basic science research, translated into new approaches for diagnosis, prevention and treatment of disease. This direction is called bench-to-bedside. Psychiatry has similarly emphasized the basic sciences as the starting point of translational research. We introduced the term translational epidemiology in psychiatry as a bidirectional concept, in which the knowledge generated from the bedside or the population can also be translated to the benches of laboratory science. Epidemiologic studies are primarily observational but they can generate representative samples, novel designs and hypotheses that can be translated into more tractable experimental approaches in the clinical and basic science laboratories. This bedside or population-to-bench concept has not been explicated in psychiatry, although there are an increasing number of examples in the research literature. Henderson notes that linkages with neurosciences will bring further progress in understanding the causes of psychiatric disorder. We agree and in the article describe epidemiologic designs, providing examples and opportunities for translational research from community surveys, as well as prospective, birth cohort and family-based designs which can further this effort.

Henderson has focused on community survey and screening studies to highlight the 50 years of advancement. I would agree but would push those studies now to include DNA collection, family history, as well as biomarkers. Community surveys can also provide samples for case control studies and can generate hypothesis about environmental risk. Finally, they can be useful for providing control groups for genetic and other studies (Goodyer *et al.* 2009; den Heijer *et al.* 2010).

The gateway hypothesis derived from community surveys is an excellent example of an epidemiologic observation translated into a molecular understanding of mechanism. It has long been shown in community surveys that cigarettes and alcohol serve as gateway drugs, which people use before progressing to the use of marijuana and then to cocaine and other illicit substances. This progression is called the 'gateway sequence' of drug use. Levine *et al.* (2011), provided the first molecular explanation for the gateway sequence. They showed that nicotine causes specific changes in the brain that make it more vulnerable to cocaine addiction – a discovery made by using a novel mouse model. Alternate exposure to nicotine and cocaine were examined. They found that pretreatment with nicotine greatly altered the response to cocaine in terms of addiction-related behavior and changes in synaptic strength in a brain region critical for addiction-related rewards. On a molecular level,

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nicotine also primes the response to cocaine by inhibiting the activity of an enzyme. This inhibition enhanced cocaine's ability to activate a gene which promotes addiction. They found that nicotine enhances the effects of cocaine only when it is administered for several days prior to cocaine treatment and is given concurrently with cocaine. These findings stimulated a new analysis of epidemiological data, which showed that the majority of cocaine users start using cocaine only after they have begun to smoke and while they are still active smokers. These findings are a superb example of translation of findings from population-to-bench and back to the population.

The value of community surveys, especially if they are longitudinal and follow a defined population over time, has already been amplied demonstrated in the Dunedin Multidisciplinary Health and Development study from New Zealand (Caspi *et al.* 2010). This study showed that a polymorphism within the promoter region of the serotonin transporter moderated the effects of early-life stress on subsequent depression. These epidemiologic findings required translation in the laboratory and this work is underway (Hariri *et al.* 2005). I would also extend the epidemiologic design to birth cohort studies. Here, the toxic effects of in utero esposure to infections, drugs, nicotine or famine, are being followed over time in countries where there exists medical case registers. Finland, Denmark, Norway, England because of their medical records and health-care system have provided the best examples.

Well-designed family and high-risk studies, all falling within the realm of epidemiology are also ripe for collaborations with investigators in genetics and imaging. The high-risk longitudinal design is particularly well suited for unraveling biomarkers since high-risk subjects are followed before the onset of symptoms so that risk factors pre-morbid rather than concomitant with the disorder may be found. These designs are useful in the search for biomarkers or endophenotypes as heritable phenotypes associated with the disease can be measured independently of the disease (Hall *et al.* 2008).

An example of the use of a high-risk design is a three-generation cohort study at high and low risk for major depression (Weissman *et al.* 2005). This cohort includes probands with or without a lifetime history of major depression and their biological children and later grandchildren, who were characterized and followed up blindly for over 20 years. The study found that depression was transmitted across the generations; that there was a similarity of the age-at-onset pattern across generations – with anxiety disorders beginning before puberty and mood disorders emerging at puberty, especially in girls. Subjects from families with two generations previously affected with major depression were at greatest risk for depression. At the 20-year follow-up, magnetic resonance imaging (MRI) measures were added to examine whether abnormalities in brain structure or function contributed to the familial transmission of depression. A robust association of familial risk for major depressive disorder with asymmetries in cortical thickness, including a 30% reduction in thickness observed in the lateral parietal, temporal and frontal cortices of the right hemisphere of the high-risk group, was found (Peterson *et al.* 2009). These MRI findings were consistent with electroencephalographic (EEG) results in the same sample that also demonstrated reduced activity over the posterior cortices of the right cerebral hemisphere (Bruder *et al.* 2007). Both the MRI and EEG findings were also present in high-risk individuals who never had major depression in their lifetimes, suggesting that these abnormalities could not be simply a consequence of previously having been depressed or treated for depression. Thinning of the cortical mantle and reduced electrophysiologic activity in the right hemisphere may constitute related endophenotypes for familial vulnerability to developing major depressive disorder.

Any major psychiatric journal now will have examples of translational epidemiologic studies in psychiatry, although perhaps not labeled as such. The key points for epidemiologists are that the past achievements, noted by Henderson, are a major strength of the studies but that epidemiologic designs require other approaches for sorting out mechanisms of the disease. This statement in no way diminishes the findings from epidemiologic studies. Often the epidemiologic findings alone can lead to considerable guides for the health of the public before the mechanisms are understood. Recall the association between smoking and lung cancer or diet and cardiovascular disease. But the next wave of epidemiology in psychiatry needs to take the next step. There are opportunities for new ways to communicate complex issues in interdisciplinary collaborations. Real partnership between the epidemiologist, the clinical and basic scientist needs to be formed. I contend that this is happening and that the future described by Henderson has begun.

Declaration of Interest

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