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Depression

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Introduction

In 2009 most of this is taken for granted, but so as to never forget, let me begin. I was asked to write about how my career unfolded. I would never have any career unfolding if not for the Civil Rights movements of the 1970's. By family circumstances, I found myself in New Haven, Connecticut. Yale University was vocally the center of every rights movement of the time: race, gender, and sexual orientation. I applied to the Ph.D. program in the 1970s as a young, married mother of 4 children under the age of 7. I did not fit the historical picture of a Yalie. I was skeptically accepted by the admissions committee and had a wonderful graduate school experience. I joined the faculty at Yale where I later received tenure. In 1987 I moved to Columbia, as a tenured Professor, where I am now.

The decision to enter the Yale University Ph.D. program, and my future career path studying depression, was determined by the two day a week research assistant position. Working on the first clinical trial of the treatment of major depression (MDD), using drugs and psychotherapy, my role was to help develop the psychotherapy manual which would be used in training the therapists for the clinical trial. This psychotherapy, after efficacy was established in two clinical trials, became known as Interpersonal Psychotherapy (IPT) (Klerman et al., 1984). The focus was on the psychosocial triggers of a depressive episode, regardless of genetic vulnerability. There was good evidence that depressive episodes were increased in a background of life events, primarily loss of attachments in vulnerable individuals. This framework was compatible with the later emerging information on the genetics of depression and with the use of medications. The follow up of the patients in this clinical trial became my doctoral dissertation. This job gave me experience with many depressed patients during and after depressive episodes.

My graduate program at Yale University was in chronic disease epidemiology, not in psychiatry. I had the chance to learn from some of the most talented epidemiologists in cardiovascular disease and cancer. I was struck by the absence of psychiatric assessments in the Framingham study and the absence of community based epidemiologic data on depression. A lecture on family studies in cardiovascular disease suggested to me that similar approaches could be used for depression. Epidemiologic community studies to identify rates and risks; family studies, to look at familial clustering and transmission; and testing psychosocial treatments became the focus of my research on depression.

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Epidemiology: Rates and Risks

When I finished my degree, my advisor, Jerome Myers had just been funded to begin another wave of the New Haven community survey of psychosocial factors related to mental health impairment (not diagnosis), and he invited me to be the project director. I asked if I could try out a new idea to make clinical psychiatric diagnoses in a community survey. After decades when psychiatric epidemiology was influenced by sociology, anthropology and the other social sciences, there was now an opportunity to bridge the gap with clinical psychiatry applying the diagnosis we had used in the clinical trial (Weissman & Kierman, 1978). Robert Spitzer and Jean Endicott at Columbia were developing standardized measures of multiple, discrete psychiatric disorders which were quite different than the unitary dimension of mental health and illness, which had been used in the previous surveys, included the New Haven survey. These new methods were largely influenced by the developments in psychopharmacology. Spitzer and Endicott had just completed the Schedule for Affective Disorders and Schizophrenia (SADS) for current and 5-year prevalence. I thought we should use current and lifetime prevalence. I asked if they would mind if I made this modification. They rightfully didn't want anyone tampering with their scales, but agreed to make the modification themselves. Dr. Myers agreed to hold up the survey six months, to add the SADS to the survey. The results became the first published rates of psychiatric disorders in a U.S. community using diagnostic criteria that could be translated into clinical research (Weissman & Myers, 1978).

The availability of the New Haven survey data was fortuitous. President Carter and his wife Rosalyn were interested in mental health and established the President's Commission of Mental Health to determine mental health services and research needs. Secretary of Health, Joseph Califano was an empiricist, and said: "Where are the data?" I recall sending him hand-written drafts, via Gerald Kierman, with the early results of the New Haven Community Survey. These results, fueled by the President's interest in mental health, led to funding of the first major epidemiologic community survey in the United States, the Epidemiologic Catchment Area Study (ECA). The New Haven Survey had serious limitations: a single community, a sample of 511, and attrition; yet it provided good pilot data. Myers applied for and was awarded a grant for the first site of the ECA. This was soon followed by four other sites. Over 1 8,000 people were surveyed in 5 communities with oversampling of the elderly and of African Americans. The first results were introduced with an editorial by Danny Freedman in 1984: "Psychiatric Epidemiology Counts." My focus was on affective disorders. The key findings from the ECA on affective disorders were the high rates of MDD in the community; the epidemiologic distinction between MDD and bipolar disorder; higher rates in women than in men, and high comorbidity with anxiety disorders. The most important findings were on age and birth cohort: It was very clear from the 5-site data that the age of onset for major depression was far earlier than had been believed. The onset was often in adolescence and not in menopause (Weissman et al., 1988). There seemed to be a birth cohort effect or secular changes, with cohorts born since World War II having increasingly higher rates. These secular changes were not found in the ECA for other disorders, suggesting that these were not merely reporting errors, but possibly real.

The ECA received world-wide attention and investigators in other countries undertook similar surveys. The diagnostic assessment was the common denominator among these international studies. I developed a consortium of investigators from ten countries who provided their data sets. We looked for cross-national trends in MDD and bipolar disorder (Weissman et al., 1996). We found that the rates of MDD varied greatly across different countries. The Asian countries, Korea and Taiwan, had the lowest rates and, unexpectedly, New Zealand and France had the highest rates. Lebanon also had high rates, but it had a small sample and the study had been done in the midst of a civil war. The patterns of illness for depression were similar across countries. The rates were higher in women than in men, and the age of first onset was in youth;

there was evidence for secular changes (Cross-National Collaborative Group, 1992). We concluded that while the expression of MDD varied considerably by culture, the patterns were similar across cultures.

Following the publication of the ECA and the Cross-National study, I turned my attention away from large surveys. These were most aptly taken over by Ronald Kessler at Harvard University who did a national survey, then a replication of the national survey and, currently is publishing on cross-national surveys which include many more developing countries. The findings for MDD in these new surveys have not changed dramatically from the original ECA.

Family/Genetic Studies

In parallel with the epidemiologic studies, I began studies of the familial transmission of depression. I took advantage of the systematic diagnostic assessments that were available and applied them to designing a large family study of MDD, carried out in collaboration with Elliot Gershon then at The U. S . National Institute of Mental Health (NIMH), whose focus was on bipolar disorder. Our studies showed that MDD was highly familial and that onset under age 30 was the most familial (Weissman et al., 1984). We showed the distinction between MDD and bipolar disorder in terms of familial risk, and developed a number of methodologies which could be used by others in family genetics studies (Weissman et al., 1986; Weissman et al., 2000). Both the epidemiologic and the family studies showed the importance of focusing on early onset MDD.

The age of onset findings led to a study of offspring at high and low risk for MDD. Now in its 25th year, the study includes three generations: the probands, their children and grandchildren. I was able to take advantage of the new developments in **diagnostic** assessments of children and adolescents, which were way behind those of adults, and incorporate them into the study. The probands came from the original clinic where the psychotherapy studies had been carried out. The control groups came from the New Haven site of the ECA. Therefore, we had cases and controls from the same community. The control groups had already been assessed once in the ECA survey and showed no evidence of psychiatric disorders. We assessed them again before entering them into the high risk study as controls. These results showed the high familial transmission of MDD in children. We had earlier shown, in the epidemiologic survey, that the rates of MDD were high in young people by adolescence, and from the adult family studies, that early onset depression was the most familial. The high risk study allowed us to hone in on the children, when the disorders would first emerge, to learn about the pattern and sequence of disorders and eventually develop more targeted interventions. We found the same sex difference in youth, with rates higher in females than males beginning in adolescence. Major depression rarely occurred before puberty. The first onsets were phobias, which around adolescence developed into MDD, especially in girls. As the offspring aged, rates of substance abuse increased, particularly in the boys. We conducted 2-, 10-, and 20-year follow-ups, which showed the impact of parental depression on the offspring. In the 20-year follow-up we showed transmission across the third generations with similar patterns (Weissman et al., 2006a). Grandchildren who came from 2 generations affected by depression had a 60% chance of having a psychiatric disorder by the time they were at the average age of 12 years (Weissman et al., 2005).

A deeper understanding of MDD required a collaboration with the neurosciences, neurobiology, genetics, among other disciplines. I developed a collaboration with Bradley Peterson at Columbia University for the 25-year follow-up to carry out structural and functional imaging studies on these 3 generations. This had been arduous work, but it is beginning to bear fruit. The first findings showed that right hemisphere cortical thinning produces disturbances in arousal, attention to and memory of social stimuli, which in turn may increase the risk for

developing depressive illness (Peterson et al., in review). We are also studying the genetics of these families along with the neural processes to understand what makes these families vulnerable to depression, and have electroencephalographic and startle reaction data (Bruder et al., 2005; Grillon et al., 2005).

This work has taken two diverse paths, a multi-site genetic study and interventions. The ECA and the adult family and longitudinal high risk studies, confirmed by others, showed that early onset MDD with recurrent episodes was an important subtype of MDD. We became part of a 7-site collaborative study on the genetics of early onset recurrent MDD with the overall leadership of Douglas Levinson at Stanford University. Phenotype data and DNA on about 1,000 sibpairs with early onset recurrent depression were collected and deposited in repository at the U.S. National Institute of Health (NIH), for use by qualified scientists throughout the world. The first publications of this work have begun to appear (Holmans et al., 2007), and a genome-wide association study is underway. In collaboration with 6 other sites, an additional 900 sibpairs with this phenotype are being collected. We are also collaborating with Howard University to rectify the under-representation of African Americans (AA) in genetics studies. Eleanor Murphy at Columbia University is studying the obstacles for participation of AA and also conducting the first family study of major depression with AA. Had we had the AA family data available at the planning of the genetics study, we might have made a more informed judgment on how to recruit AA.

Intervention

Understanding the biological vulnerability of MDD is a long term project. We became interested in looking for ways to test interventions and break the cycle of depression across generations. Psychosocial events are the triggers of depression in genetically vulnerable individuals. We hypothesized that a depressed parent might be one of the more stressful situations for the child. If we could reduce the parent's symptoms, we might be able to reduce the child's symptoms and behavior problems. We developed, designed, and conducted the first study to examine the impact of parental remission from depression on a child's behavior and symptoms (Weissman et al., 2006b). We demonstrated that if a depressed parent could achieve remission at the end of 3 months with medication, her offspring showed a significant reduction in depression and conduct disorder (Weissman et al., 2006b). These results were sustained for mothers who remitted over one year (Pilowsky et al., 2008). This work is ongoing in a new study to attempt to understand the mediators of change, and includes both depressed mothers and fathers.

My work on IPT for depression has been an avocation. During most of my career I have been a cheerleader for the next generation who have carried out these trials (Mufson et al., 2004), (Verdeli et al., 2003). IPT, now a fully evidence-based treatment, has been translated into seven languages including, Japanese, Korean, and Chinese (Weissman et al., 2007). It has been tested in numerous clinical trials with depressed adults, adolescents and the elderly, and with primary care patients. There is now an international society of interpersonal psychotherapy (www.interpersonalpsychotherapy.org).

The most interesting adaptation and efficacy trial of IPT was conducted in Uganda for a population devastated by HIV and high rates of depression. The first clinical trial of a psychotherapy in Africa showed positive results of IPT in reducing depression in adults (Bolton et al., 2003). A second study of adolescents in Northern Uganda yielded similar findings.

I have returned recently to work on IPT (Weissman et al., 2007). In the treatment of depressed mothers, depressed, poor, single mothers had the worst outcomes (Talati et al., 2007). Helena Verdeli and I have developed a brief version of IPT that can be taught to health workers for triaging depressed patients in primary care in the U.S.

Conclusion

Currently, I am continuing the genetic studies of early onset, recurrent MDD, working with Bradley Peterson and Steven Hamilton from the University of California, San Francisco (UCSF), on genetics and imaging data from the three generations at high and low risk for depression, working on the new study of the effects of parental remission from depression on their children, and seeking funding to test out a brief triage version of IPT for low income patients in a family practice. Essentially, my interests remain the same, but the technology has improved tremendously. Priya Wickramaratne has been the statistician, and an important conceptualizer behind nearly all of this work. Philip Adams has developed systems to track and monitor our massive data, including DNA samples.

I feel strongly that epidemiologists must be aware of the potential of neuroscience, genetics, and molecular biology for understanding the processes that underlie behavior. It is useful for students of human disease, including scientists who model human behavior in animals, to understand the potential of epidemiology for good design, for providing the context, and for unraveling the triggers and course of illness. The collaboration between population and bench science should be bidirectional.

These are times of enormous scientific opportunity and frustration. I was fortunate to begin my career at a time when there was a flourishing in research funding, a paucity of studies, and a small stool at the table for women. There is no longer a paucity of studies and, there are very exciting tools, but the research funding is drying up. The opportunity to implement studies of novel ideas is diminished by repeated grant resubmissions. The U.S. NIH priority scores, which would have assured funding in my generation, assure non-funding in theirs.

I began with the great opportunities provided by the Civil Rights Movement in the 1970's. I see these opportunities now, in fruition, in the racial, ethnic, gender, and gender orientation diversity of the young people with whom I work. While they represent enormous diversity, they have been chosen for their enormous talents and their ideas. I hope that they will have some of the opportunities to carry out their research, as did I.

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