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WOMEN'S MENTAL HEALTH RESEARCH: The Emergence of a Biomedical Field*

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■ **Abstract** This review surveys the field of women's mental health, with particular emphasis on its evolution into a distinct area of biomedical research. The field employs a biomedical disease model but it also emphasizes social and cultural influences on health outcomes. In recent years, its scope has expanded beyond studies of disorders occurring in women at times of reproductive transitions and it now encompasses a broader study of sex and gender differences. Historical and conceptual influences on the field are discussed. The review also surveys gender differences in the prevalence and clinical manifestations of mental disorders. Epidemiological findings have provided a rich resource for theory development, but without research tools to test theories adequately, findings of gender differences have begged the question of their biological, social, and cultural origins. Clinical depression is used to exemplify the usefulness of a sex/gender perspective in understanding mental illness; and major theories proposed to account for gender differences are critically evaluated. The National Institutes of Health (NIH) is the primary federal funding source for biomedical women's mental health research. The review surveys areas of emphasis in women's mental health research at the NIH as well as some collaborative activities that represent efforts to translate research findings into the public health and services arenas. As new analytic methods become available, it is anticipated that a more fundamental understanding of the biological and behavioral mechanisms underlying sex and gender differences in mental illness will emerge. Nonetheless, it is also likely that integration of findings predicated on different conceptual models of the nature and causes of mental illness will remain a challenge. These issues are discussed with reference to their impact on the field of women's mental health research.

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INTRODUCTION

This review surveys women's mental health as it has evolved into a biomedical research field. To a great extent, this evolution reflects the ascendancy of a disease model of mental illness as well as the ascendancy of a model of mental illness as a "brain disorder." The latter model is founded on advances in neuroscience over the past several decades. Neuroscience, augmented by genetics and imaging methods, currently promises to usher in a new era of molecular diagnosis and treatment of the disorders. Nonetheless, biomedical women's mental health research also retains elements of social and cultural causation perspectives formerly applied broadly to the understanding of mental illness, and increasingly it reflects a public health perspective as well.

The National Institutes of Health (NIH) is the primary federal funding agency for biomedical research. Three NIH institutes have primary responsibility for research on the mental and addictive disorders.[1,2] They are the National Institute

[1]The author wrote this review in her capacity as an NIH employee. The review is based in part on knowledge gained while she served as Chief of Women's Mental Health Programs at the National Institute of Mental Health (NIMH). The views expressed in the paper, however, do not represent official positions of the NIMH, National Institutes of Health, or the Department of Health and Human Services.

[2]Hereafter, in this review, the term "mental disorders" is used as shorthand to refer to the conditions studied through the research programs of NIMH, NIDA, and NIAAA. Diagnostic

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of Mental Health (NIMH), the National Institute of Drug Abuse (NIDA), and the National Institute of Alcohol Abuse and Alcoholism (NIAAA). These institutes differ in the specific conditions falling within their program scope. Nonetheless, the conditions share important commonalities. They evidence a degree of co-occurrence, which suggests that they share in common some etiological and risk factors. Furthermore, neuroscience provides a model for understanding the conditions as fundamental disturbances in brain neurochemistry and function, despite differing clinical manifestations. Within the past decade, social and cultural influences on the conditions have also come to be viewed through a health disparities perspective. The following sections provide an overview of historical and conceptual influences on the content of women's mental health research today.

HISTORICAL AND CONCEPTUAL INFLUENCES ON WOMEN'S MENTAL HEALTH RESEARCH

The women's health research movement emerged from a wave of grassroots feminism that swept the United States in the 1960s. This movement focused attention on perceived gender inequities in social systems such as the exclusion of women from male-dominated professions. In the biomedical realm, this focus on inequity was translated into a call for the "empowerment" of women so that they could have direct access to information about their reproductive health and sexuality rather than relying on "paternalistic" medical practitioners. For example, the first edition of *Our Bodies, Ourselves* (Boston Women's Health Collective 1972) served to provide such information to "baby boom" women.

"Women are not Small Men": Gender Issues and Biomedical Research

In the 1980s, women's health moved into the sphere of mainstream biomedical research when a group of researchers, clinicians, and other advocates raised objections to the perceived dominance in research of the "male norm"—a belief that men and women were biologically equivalent except for differences in their reproductive organs and secondary sexual characteristics. In their view, the male norm had served to justify the exclusion of women from clinical research. This exclusion had been further rationalized by ethical concerns over possible adverse effects of drugs on fetal health if a woman should become pregnant during a drug trial and practical concerns over resultant legal liability. Nonetheless, the exclusion was seen by women's health advocates as a form of biomedical paternalism, which had placed the health of American women at risk by limiting knowledge of the effects of treatments on them.

In 1985, a Public Health Service Task Force on Women's Health released a report that provided evidence of underrepresentation or exclusion of women in

criteria for these conditions are found in the *Diagnostic and Statistical Manual of Mental Disorders* (Am. Psychiatr. Assoc. 1994).

federally funded clinical studies and therapeutic trials for such serious and disabling conditions as cardiovascular disease. As a result, the NIH issued guidelines urging grant applicants to include women in their studies unless a compelling rationale for their exclusion could be presented. In 1989, the Society for Women's Health Research was founded by scientists who continued to be concerned that measures taken were inadequate to ensure that research attend to women's health issues. This concern was a major reason why in 1989 the Congressional Caucus on Women's Issues requested that the GAO report on the success to date of NIH efforts to include women in research. Results of that report (US GAO 1990) did little to allay concerns. The report provided evidence of continuing underinclusion of women in biomedical research as well as inconsistent efforts to track their inclusion in studies at NIH. Public and congressional reaction to the findings led to legislation establishing the NIH Office of Research on Women's Health (ORWH) and to explicit requirements for tracking the inclusion of women in NIH research (NIH Revitalization Act 1993).

The 1991 appointment of Bernadine Healy, a cardiologist, as NIH director, also gave rise to funding of the Women's Health Initiative (WHI), a large-scale multisite study addressing the role of hormone replacement therapy (HRT), lifestyle, diet, and vitamin supplements in major health outcomes of midlife and older women, including cardiovascular disease, cancer, and osteoporosis. Recent findings from the WHI have changed clinical practice. Results of a randomized clinical trial (Writing Group Women's Health Initiative Invest. 2002) indicated that HRT, routinely prescribed for women on a long-term basis following menopause, did not have preventive benefits, as had been commonly believed. Decreased risk for osteoporosis and colon cancer among study women taking hormones for several years did not outweigh their increased risk for heart disease, stroke, and breast cancer. Another WHI publication (Rapp et al. 2003) found no evidence that long-term use of HRT preserved cognitive function in postmenopausal women as they aged. In fact, long-term HRT use was associated with increased risk for cognitive impairment. The findings of the clinical study were perplexing since they failed to support the neuroprotective benefits of estrogen—previously found in preclinical research and widely thought to be generalizable to clinical samples.

Renewed Emphasis on the Biology of Sex Differences

An Institute of Medicine report underscored the scientific value of studying sex differences at multiple biological levels. The report *Exploring the Biological Contributions to Human Health: Does Sex Matter?* (Wizemann & Pardue 2001) cited substantial evidence of the role of sex hormones in male-female differences[3] in the brain, sex-typed behavior, cognitive abilities, and gender identity.

[3]The report also called for clarification of language used to conceptualize male-female differences. This review uses the term "sex differences' to refer to variables for which substantial evidence exists of biological influences. The term "gender differences" is used to refer to descriptive information and for findings for which there is substantial evidence of social and cultural learning. It is acknowledged that these distinctions are far from clear

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(See Kimura 1996 for a review of this area.) But the report also pointed to evidence for the existence of many sex differences at the cellular and molecular levels. Sex differences, which had significant impact on health and development, were present in chromosomes, somatic cells, and organ systems. Not all sex differences could be attributed solely to male-female differences in sex hormones.

Recent examples of the value of studying biological sex differences can be seen in the field of genetics. At the cellular level, aging is thought to involve a progressive shortening of telomeres in chromosomes of cells, leading to apoptosis (Nawrot et al. 2004, Stindl et al. 2004). On average, this process is hypothesized to be accelerated in males in part due to sexual dimorphism in body size. Since males are, on average, larger than females, they have increased demands on cellular metabolism, leading to earlier cellular exhaustion. Sex differences in estrogen levels are also thought to provide females with enhanced protection against telomere damage due to oxidative stress. Another genetic factor hypothesized to underlie the female advantage in longevity is the availability of genes from their inactivated X chromosome. On average, 15% of X chromosome genes escape inactivation on the "inactivated" X chromosome, and Carrel & Willard (2005) have noted substantial variability among females in this percentage. It is hypothesized that the "availability" of genes from the partially inactivated X chromosome in later life may provide women with a source of biological resilience that is not available to men and that contributes to the sex difference in longevity (Aviv et al. 2005).

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The Changing Model of Mental Illness

In 1992, the research functions of the NIMH, NIDA, and NIAAA moved to the NIH from the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) (PL.102–321, the ADAMHA Reorganization Act, 1992). The ADAMHA had been established in 1973 as a component of the public health service charged with primary federal responsibility for ensuring community treatment and services for the disorders. As part of the ADAMHA Reorganization Act, the public health services component of the ADAMHA institutes was reorganized into a new entity, the Substance Abuse and Mental Health Services Administration.

The research programs of the former ADAMHA institutes were strengthened by placing them within the NIH community. A major impetus for the movement of these programs to the NIH was a growing consensus that neuroscience was the cornerstone of fundamental research on the psychiatric and addictive disorders. Such research would benefit from inclusion in the NIH environment. This consensus was itself a result of a paradigm shift set into motion by the serendipitous discovery in 1953 of the antipsychotic effects of chlorpromazine. This discovery and subsequent demonstrations that the drug's mechanism of action involved a blockade of dopamine receptors in the brain marked the beginning of a biological era for the disorders focused on brain neurochemistry. Subsequent developments,

in the human case, since all human behavior results from interactions of biological and environmental influences.

including the further characterization of the role of the catecholamines in addictive and depressive disorders (Axelrod & Kopin 1969) and the development of drugs to alleviate depression and anxiety, severed mainstream mental health research from its early roots in Freudian psychodynamic models. Complex behavior, it was thought, could be understood by—and possibly reduced to—more fundamental molecular biological elements.

The integration of the ADAMHA institutes within the NIH also ensured that women's mental health research would be coordinated with other NIH women's health research by the ORWH, which was situated in the office of the NIH director. The influence of the ORWH on women's mental health research has been significant. Since their 1992 move, the former ADAMHA institutes have adopted the ORWH framework for defining the field. The ORWH definition of the scope of women's health research includes not only conditions affecting women exclusively but also conditions more prevalent in women and ones in which males and females differ in clinical manifestation, course, and treatment response.

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Women's Mental Health Research: A Biomedical Definition

Consistent with the general biomedical disease-oriented model, biomedical women's mental health research in fact focuses primarily on disorders. Also consistent with the general model are emphases in the women's mental health field on predisposing biological factors within the individual and on treatments (usually pharmacological) to correct neurochemical imbalances in the brain that manifest in behavioral disturbances. In the biomedical model, behavioral treatments are increasingly viewed as alternative methods to achieve similar corrections in brain function (Roffman et al. 2005).

The role of sex steroids in the etiology, manifestation, and course of mental illness remains an important emphasis area. However, the area has moved beyond observational and correlational studies of mental disorders in women during reproductive transitions to one increasingly informed by knowledge from preclinical neuroscience of the role of sex steroids in modulating the function of neurotransmitters and altering gene expression (e.g., McEwen 2002, McEwen et al. 1998). Preclinical research has established that sexually dimorphic hormonal exposures have enduring organizational influences on brain development beginning prenatally and continuing through early childhood. These organizing events set the stage for later sex and gender differences in brain and behavior and for the cyclic influences of hormones in sexually mature individuals. There is substantial evidence from preclinical studies for estrogen-induced changes in serotonin transmission, binding, and metabolism in brain regions implicated in affect regulation. A report by Nishizawa et al. (1997) found rates of serotonin synthesis to be 52% higher in the brains of normal men than in normal women. Other clinical studies, such as those in menopausal women undergoing estrogen treatment, have provided some support for the role of serotonin-estrogen synergism and hormonal changes in clinical phenomena. However, further research is needed to understand neural

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processes involved in the complex interplay between estrogen and serotonin and their behavioral effects (Amin et al. 2005).

Another focal area in biomedical women's mental health research concerns sex and gender differences and treatment outcomes. Despite the fact that women are twice as likely as men to use prescription drugs for the treatment of mental disorders, historically there has been a lack of attention to possible sex differences in pharmacokinetics and toxicity. Historically, in phase III and postmarketing trials, there had been little research addressing possible differences in efficacy, drug-drug interactions, and side effects. (See Jensvold et al. 1996 for a review of this area.) Increasingly, ethical concerns about the inclusion of childbearing-age women in therapeutic trials, based on the possibility of unforeseen drug teratogenicity, are counterbalanced by concerns over a failure to address the treatment needs of childbearing women with serious health conditions (Mastroianni et al. 1994). The failure to attend to possible sex differences in preclinical studies and early phase trials has been criticized as well. Attention to biological sex differences at the earliest phases of drug development is seen as critical since evidence in these phases can suggest the presence of clinically significant sex differences. In turn, such evidence can alert clinical trialists to the need to monitor drugs for sex differences in efficacy, toxicity, or side effects. Furthermore, evidence of sex differences in early-phase research can be useful in determining whether phase III trials need to be designed so as to be able to detect clinical significant sex differences (US GAO 1992, 2001).

Recent reports of differences between men and women in response to pharmaceutical agents have begun to demonstrate the clinical value of a gender-based approach to therapeutics. Differences between males and females in irritable bowel syndrome (IBS) and in the efficacy of treatment agents provide clear examples. Although IBS is not considered a mental disorder, it has substantial psychological aspects and substantial comorbidity with anxiety, depression, and a history of sexual abuse. Twice as many women as men seek treatment for severe IBS. Factors influencing the gender ratio include sex differences in visceral sensitivity and central nervous system pain processing, the specific effects of estrogen and progesterone on gut function, and differences in neuroendocrine, autonomic nervous system, and stress reactivity related to bowel function and pain (Chang & Heitkemper 2002).

Sex differences in treatment efficacy have also been reported. Serotonin and its receptors in the intestines control how pain is felt (sensation) and gastrointestinal motility. Two drugs that act upon different types of serotonin receptors have been approved for IBS. In 2000, the FDA approved alosetron, a selective *5-HT-3* receptor antagonist, for the treatment of diarrhea-predominant IBS. In 2002, tegaserod, a *5HT-4* receptor agonist was approved for the treatment of constipation-predominant IBS. In both instances, the results of clinical trials upon which approval was based indicated efficacy in women but not in men.

Evidence is mixed for clinically significant sex/gender differences in the efficacy of drugs used to treat mental disorders. Kornstein et al. (2000), in a study of chronic

depression, compared the effects of imipramine, a tricyclic antidepressant, and sertraline, a selective serotonin reuptake inhibitor (SSRI). Women in the study were more likely to respond positively to sertraline than to imipramine, and men were more likely to respond positively to imipramine. Menopausal status was a factor in female preferential response to sertraline, since it was found in premenopausal but not in postmenopausal women. However, another report (Parker et al. 2003) that compared SSRIs to tricyclic antidepressants did not find a gender difference. The approval of sertraline for the treatment of posttraumatic stress disorder (PTSD) was based on results of clinical trials in which the drug showed little effect in men, but clear benefit over a placebo in women (Brady et al. 2000). The efficacy difference was attributed by the authors to differences between men and women in their sample in clinical characteristics of PTSD, but the possibility of a biological advantage of the SSRIs for women with PTSD could not be ruled out. There is a clear need for further studies to determine the possible benefits of "gender-specific" medicine in the treatment of mental disorders.

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SOCIAL AND CULTURAL PERSPECTIVES IN WOMEN'S MENTAL HEALTH RESEARCH

Social and cultural perspectives remain influential in many clinical approaches to women's mental health. Social causation approaches examine features of women's lives that enhance or undermine well-being. These approaches also tend to be less disease-oriented and more focused on health promotion and prevention. Social constructionist perspectives (Foucault 1973) involve critical analyses of conceptions of mental health and illness. These perspectives are common in academic psychology and women's studies departments (e.g., Stoppard 1999, Unger 2001). They can also be seen reflected in writings focused on medical practice and biomedical research (Hahn & Kleinman 1983, Lyotard 1993).

More recently, a health disparities perspective has become highly influential in biomedical research. The perspective, as applied to women, views them as members of different racial/ethnic groups. Differences among women in their racial/ethnic group values, experiences of discrimination, and barriers to education, job opportunities, and health services are seen as major contributors to variability in health outcomes. Thus, understanding the communities in which women are reared and live is important to reducing disparities among them. In 1999, the U.S. Surgeon General, David Satcher, broke ground by issuing a report focusing on mental disorders. The report was followed by a supplemental report in 2001 on mental health in racial/ethnic minority groups. The supplement identified social and economic disparities and barriers to access to mental health services.

Public health perspectives typically emphasize social and cultural factors as influences on biomedical disease outcomes. The value of biomedical research can be measured by its ultimate benefit to the public health. However, exclusively biomedical data is not adequate to inform an understanding of disease-based morbidity. To understand women's mental health, there is a need to take into account

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their economic status, social position, educational and career opportunities, family roles, legal rights, and likelihood of experiencing gender-based violence.

A public health perspective provides a basis for conveying to policymakers the magnitude of the burden imposed on the population by disease. The *Global Burden of Disease* study (Murray & Lopez 1996) reported on the disability burden of disease in the population worldwide. The study used a quantitative measure of disease burden that allowed cross-disease comparisons, thereby providing a method for ranking of diseases and conditions according to disability burden.

The *Global Burden of Disease* study portrayed the disability burden of mental and neurological disorders as a major and heretofore unrecognized public health issue. These conditions accounted for 10.5% of the disability burden of disease worldwide and were estimated to increase their share of the burden to 15% by 2020. The report also provided a way of framing women's mental health as a public health issue. Unipolar depression was identified as the fourth leading cause of disability worldwide in 1990 and was projected to move to second place by 2020. But for women in 1990, depression was already the leading cause of disability among all diseases, and it accounted for 41.9% of their disability burden from neurological and psychiatric disorders as compared to 29.3% among men.

Adverse social conditions worldwide were viewed as having a disproportionate impact on females. For instance, over three quarters of the 50 million people worldwide affected by violent conflicts, civil wars, disasters, and displacement were women and their children. Estimates of lifetime prevalence of partner violence against women have ranged from 15% to over 50% in studies based in 36 different countries (Heise et al. 1999). Such experiences can be viewed as significant environmental influences on variability in women's health outcomes.

THE EPIDEMIOLOGY OF MENTAL DISORDERS: GENDER DIFFERENCES

Prevalence data on mental disorders for U.S.-based population samples have been provided from three major surveys, the Epidemiological Catchment Area (ECA) study (Robins & Regier 1991), the National Comorbidity Survey (NCS), and the NCS-replication (Kessler et al. 1999, 2005a,b). Overall, these studies provide little support for the superiority of one sex over the other in mental health, as defined by the likelihood of being diagnosed with a mental disorder. Nevertheless, the sexes are strikingly different in prevalence and manifestations of many disorders. Females are overrepresented among those diagnosed with unipolar depressive, somatoform, and eating disorders. Females are also overrepresented among those diagnosed with most anxiety disorders, including posttraumatic stress disorder. Females also are more likely than males to be diagnosed with highly comorbid (three or more) mental disorders and mental disorders comorbid with chronic medical conditions. By contrast, males are overrepresented among those diagnosed with substance abuse disorders and with alcoholism and alcohol abuse disorders and conduct disorder. From childhood onward, males have higher rates than females of

attention deficit disorder with hyperactivity, autism, and severe learning disabilities and developmental delays.

There are fewer population-based studies of the personality disorders. However, most studies find evidence that females are more likely than males to be diagnosed with dependent, histrionic, and borderline personality disorders. Males are more likely than females to be diagnosed with obsessive-compulsive, narcissistic, and antisocial personality disorders (Golomb et al. 1995, Paris 2004).

Clinical manifestations of mental disorders also differ between the sexes. Depression is the best-studied disorder in this regard. For instance, a majority of studies find that women are more likely than men to experience the symptoms of depression on a seasonal basis (Rosenthal & Blehar 1989). Women with depression are more likely than men with depression to have "atypical" symptoms of hypersomnia, overeating, leaden paralysis, and rejection sensitivity (Benazzi 2003). Women with depression are also more likely than men with depression to have comorbid anxiety, somatoform, and eating disorders, and men are more likely to have comorbid substance abuse disorders.

The course of depression provides evidence of differences in risk factors. In men with comorbid depression and alcoholism, depression is more likely to be chronologically secondary to alcoholism than primary. For women, the opposite pattern is found (Kessler et al. 1996). A history of a childhood anxiety disorder is associated with increased risk for depression in adulthood for women but not for men, in whom a history of childhood conduct disorder confers increased risk for adult depression (Kessler 2003). Unlike in unipolar depression, most studies have found no difference in the population prevalence of bipolar disorder. However, in clinical samples, more females than males are diagnosed with bipolar II disorder and rapid cycling bipolar disorder (Arnold 2003).

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GENDER DIFFERENCES: THEORIES IN SEARCH OF EVIDENCE

Gender differences are among the most widely reproducible findings in psychiatric epidemiology, present across age cohorts and most cultures surveyed. But beyond this consistency lies a widely varying set of explanatory theories with only weak or partial validation. A comprehensive review of theories to explain gender differences in mental disorders is beyond the scope of this paper. Instead, the following section provides examples of the most common classes of theories that have been put forth to explain differences. To limit the review further, those aspects of theories that focus on clinical depression and other affective disorders twice as common in females as in males are highlighted.

Psychodynamic Theories

Arguably the most historically influential theorist of the origins of gender differences in mental disorders was Sigmund Freud. Freud had many original and

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valuable insights into mental processes, but his views on women reflected prevailing cultural stereotypes of them as inferior to men intellectually and morally. Freud's well-known statement that "anatomy is destiny" underscored his belief that universal childhood experiences based on differences in sexual organs had enduring effects on personality and neurosis (Freud 1898, 1905, 1929). According to Freud, the most formative experience in female children for personality development was that of "penis envy." In early childhood, females realized that their mothers, like themselves, did not possess male genitalia. This led them to repress their infantile masturbatory activity out of a sense of their own genital inferiority and to experience feelings of ambivalence and anger toward the mother, with whom they nonetheless identified. Although their childhood sexual energy was transiently directed toward the father, ultimately females substituted a desire to have the father with a more general desire to have children. Male children, on the other hand, experienced intense castration anxiety based on their fear that their sexual desire for the mother would lead the rival father to castrate them. This anxiety was the basis for the reactive development of a strong and abstract superego in males. Without the experience of castration anxiety, females developed less abstract superegos. Throughout life, females were more likely to use more primitive defense mechanisms such as repression and less likely to use higher-order mechanisms such as sublimation, a defense thought to redirect thwarted libido into intellectual and cultural achievements. Furthermore, intellectuality in women was suspected of being a manifestation of unresolved penis envy.

In today's light, the misogyny in Freud's writings is breathtaking. Yet his influence on early psychological theories and practice was enormous. It persisted in clinical practice well into the mid-twentieth century. When a wave of feminism swept over the United States in the 1960s, Freud was still an intellectual force to contend with. Freudian disciples such as Karen Horney (1967) built upon Freud's conceptual framework but substituted other culturally and socially based concepts for penis envy and castration anxiety. Many other psychologists developed new experiential theories of gender role development in reaction to Freudian psychodynamic psychology.

Social Learning Theories

Experimental psychology in the mid-twentieth century provided behavioral science with learning theories based originally on controlled animal studies. These theories were readily translated to the human case. Operant conditioning theorist B.F. Skinner (1938) wrote the landmark book *Behavior of Organisms: An Experimental Analysis*, in which he applied identical principles of learning to human and nonhuman organisms, with little attention to interspecies differences in structures of cognition. Social learning theorists (Bussey & Bandura 1999) emphasized observational and imitative learning. But like Skinner, such theorists tended to view personality as shaped by environmental contingencies. Appropriate gender role acquisition was a special case of imitative learning, and the principles upon which it was based were no different than were other forms of imitative learning.

Children learned their appropriate gender roles through observing and imitating the actions of others, as well as by being rewarded or punished for acting appropriately or inappropriately.

One well-known social learning theorist, however, viewed gender socialization through a more critical lens of cultural concepts reflecting institutional and social bias (Bem 1993). According to Bem, cultural beliefs about men and women were based on three major culturally reinforced concepts: androcentrism, a belief that men are inherently the dominant or superior sex; gender polarization, a belief that men and women have fundamentally different psychological and sexual natures; and essentialism, a belief that male-female differences and male dominance are natural. These beliefs maintained socially accepted gender roles and perpetuated female social disadvantage.

Overall, through the late twentieth century, developmental psychologists tended to view gender development as a special case of unidirectional socialization of the child by parents. There was little room in such theories for the child's own temperamental contributions to gender socialization or for a biological basis for gender differences. Maccoby & Jacklin (1974) reviewed more than 1600 studies of gender differences in infant and early childhood cognitive and social behaviors. These studies provided evidence of differences in such behaviors as orientation to faces and rough-and-tumble play, but the authors summarized findings by noting that boys differed from girls primarily in their tendency to display higher levels of aggression. However, unlike the majority of developmental researchers of the era, they also reached the conclusion that by and large parents did not treat children differently except for their responses to emotional displays. That is, there was little evidence to support the theory that children behaved in gender-appropriate ways because of differential reinforcement and molding by parents and other socialization agents. More recently, Harris (1998) has challenged unidirectional environmental models of child development and behavioral outcomes. In particular, she has criticized the unexamined bias of "nurturism" in behavioral psychology, which, she asserts, is not well supported by evidence and which excludes a consideration of constitutional and genetic influences.

Differences in causative models notwithstanding, the majority of empirical findings of gender differences in normal and psychopathological behavior consistently place males and females on opposite poles of externalizing and internalizing dimensions. Across different cultures, females score higher than males on an internalizing cluster of traits called socio-emotional, expressive, and interpersonally oriented, whereas males score higher on an externalizing cluster of task-oriented and instrumental behaviors (Costa et al. 2001). This polarization also characterizes gender differences in psychiatric diagnosis.

Stressful Life Events Theories

Stressful life events often precede the onset of depressive and anxiety disorders. Some explanations for gender differences in stress-related mental disorders suggest that females are differentially susceptible to stressful events by comparison

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with males. It is also theorized that the greater orientation of women toward the concerns and care of others increases their exposure to adverse life events in their social network, thereby contributing to higher rates of event-related depression (Maciejewski et al. 2001).

Other theories have emphasized the role of traumatic events. Epidemiology studies indicate that males experience more events that could be considered as potentially traumatizing than do females. Nonetheless, females are more likely to be diagnosed with stress-related mental disorders, including posttraumatic stress disorder, a condition originally developed to explain the reaction of male soldiers to the stress of battlefield conditions. To explain this epidemiological pattern, some (Weiss et al. 1999) have suggested that early experiences of sexual abuse, more common in females than males, are especially traumatic and thereby sensitize sexually abused females to respond to subsequent stressful life events more adversely than nonabused females or men. Furthermore, a history of clinical depression is seen as a risk factor for a subsequent event-related stress disorder (Breslau et al. 1997, Kessler et al. 1999).

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Cognitive Vulnerability Theories

Following the intellectual excesses of behavioral psychology, experimental cognitive psychology reintroduced mental structures to the field. Internal cognitive structures are conceived of as stable trait-like predispositions, formed in development based on learning, at times latent but capable of being primed throughout life by new emotionally salient experiences. These constructs were seen as mediating between the current environment and the individual's responses to it. They were necessary to explain individual differences in vulnerability to or resilience in the face of environmental stresses. These constructs have been applied to understanding differences in cognitive vulnerability to depression. Somewhat surprisingly, they have been applied much less frequently to the understanding of gender differences in depression, with the exception of researchers such as Nolen-Hoeksema (1987, 1991) and Hammen (2003). These researchers have proposed integrative developmental theories of gender differences in depression, which include differences in socialization and stresses as well as in gender-typical cognitive structures.

Nolen-Hoeksema (1991, 2000; Nolen-Hoeksema & Morrow 1991) has proposed that gender differences in susceptibility to stressful life event–based depression have a cognitive basis in a tendency to ruminate or dwell upon affectively negative life events. Rumination prolongs negative affect, thereby increasingly the likelihood of clinical depression. Ruminative thinking is more characteristic of females than of males and may therefore be a major factor in the gender disparity in the occurrence of depression.

Methodological Artifact Theories

Methodological artifact theories, such as one that men and women do not differ in true rates of depression but that alcohol abuse or irritability are depressive equivalents in males, have been proposed but rarely tested. There is considerable

face validity to the notion that males and females react to stress differently and with behaviors consonant with their gender roles. Nonetheless, the few genetic studies that have addressed the issue of shared diathesis for alcoholism and depression have failed to provide evidence of etiological identity (Heath et al. 1997, Kopnik et al. 2004). A redefinition of diagnoses according to genetic and other biological markers will no doubt do much to inform this debate. However, the idea that male alcohol abuse and irritability eliminate gender differences in depression must be considered speculative. Another methodological artifact theory, that women are more likely than are men to endorse symptoms, thus leading them to meet diagnostic criteria for depression more often, has not been supported (Angst & Dobler-Mikola 1984, Bogner & Gallo 2004).

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Diagnostic Artifact Theories

Psychiatric diagnosis continues to be a controversial issue for a number of reasons. The explosive growth in the number of mental disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), from 60 in the 1952 DSM I to 361 in the DSM IV, has made the DSM process of generating new diagnoses by expert consensus a subject of considerable criticism. Findings of a recent epidemiology survey (Kessler et al. 2005a,b) indicated that 40% of adult Americans develop a mental disorder over the course of a lifetime. This finding was taken by some social critics as further evidence of the mental health field's increasing tendency to pathologize variations in normal behavior (Carey 2005).

Other critics have pointed to evidence of gender bias and victim blaming in the diagnosis of mental disorders in women. Feminist psychologists in particular have been critical of a lack of attention in diagnostic criteria to context and of a seeming tendency to blame the victim for responses to distressing social conditions (Enns 1997). Therapeutic approaches, stemming from the biomedical model, which seek to fix problems within the individual are seen as turning a blind eye to social contexts. Brown (1992), a feminist psychologist, characterized some diagnoses commonly applied to women as "oppression artifact disorders."

DIAGNOSTIC CONTROVERSIES AND WOMEN'S MENTAL HEALTH Three diagnoses—one of a personality disorder and two others of mood disorders related to reproductive transitions—have been particularly controversial in the field of women's mental health. In 1989, members of a DSM subcommittee considering revisions to the section on personality disorders, proposed the inclusion of "masochistic personality disorder" in the diagnostic canon. In particular, this proposal met with strong criticisms for diagnostic criteria that were perceived to blame the (female) victim of gender-based violence for the actions of her partner. Because of such criticisms, a compromise was reached. The criteria for the personality disorder deleted reference to masochism and the name was changed to "self-defeating personality disorder." The association of the disorder with women was further lessened by making the criteria inapplicable to known victims of physical or sexual abuse.

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The diagnosis of mental disorders in relation to the female menstrual cycle has been criticized for pathologizing normal female biological functions. A condition known as "late luteal phase dysphoric disorder" was included in the 1986 DSM III-R manual, but it was placed in the appendix, indicative of its provisional status. The condition identified women who experienced strong mood changes premenstrually. In the DSM-IV revision (1994), the name of the disorder was changed to its current one of Premenstrual Dysphoric Disorder, or PMDD. The diagnosis continued to be placed in the DSM-IV appendix. However, in 2000, the FDA added legitimacy to the diagnosis with its approval of a remarketed drug, fluoxetine, for the treatment of PMDD.

More recently, controversy has arisen over the validity of a diagnosis of postpartum depression as an exculpatory defense for a Texas woman, Andrea Yates, who was accused of drowning her five children in the bathtub of her home. The DSM-IV does not classify postpartum depression as a distinct diagnostic entity. Rather it is considered under the category of major depression, with the added qualifier of "postpartum onset." In the United Kingdom, but not in the United States, special infanticide laws allow for probation and psychiatric treatment for mothers with mental illness who commit infanticide (Oberman & Meyer 2001, Spinelli 2004). The infanticide legislation is based in part on U.K. studies that have shown the postpartum period to be a time of peak prevalence for serious psychiatric illness in women, as reflected in statistics on psychiatric hospitalizations (Kendell 1981).

There is little doubt that the diagnoses of PMDD and postpartum depression characterize a number of women who experience significant psychosocial disability related to the conditions. Nonetheless, critics point out that diagnoses based on hormonal changes in women may contribute to gender stereotypes. On the other hand, compelling arguments can be made for the utility of these diagnoses based on the potential alleviation of disability through appropriate treatment. This issue continues to be a controversial one in the field of women's mental health.

Reproductive Transition Theories

Findings of consistent gender differences in mental disorders across cultures (Weissman et al. 1996) suggest the involvement of biological factors. Sex hormonal causal explanations developed based on the observed co-occurrence of mood changes with periods of reproductive transition have considerable face validity. The adolescent emergence of gender differences in depression suggests a role for sex hormones, although findings of hormone-mood correlations during the pubertal transition are inconclusive (Angold & Worthman 1993).

The postpartum period is a time of greatly increased risk for affective psychosis (Kendell et al. 1981), including psychotic depression and bipolar disorder. The absence of significant associations between postpartum-onset psychotic conditions and psychosocial stressors strongly suggests that biological factors are operative. Nonetheless, there is little evidence that replacement estrogen in affected women treats these conditions. Attempts to isolate specific hormonal factors in

nonpsychotic postpartum depression have met with relatively little success to date. Risk factors for postpartum nonpsychotic depression include personal or family history of depression or substance abuse, marital problems, and lack of social support (Gaynes et al. 2005).

A prospective case control study (O'Hara et al. 1990) found no significant differences between childbearing women and their nonchildbearing controls in incidence of depression. Other research has not found increased incidence of depression postpartum as compared to pregnancy, and it is estimated that up to half of all depressions diagnosed postpartum have in fact had their onset during pregnancy or prior to conception. The existence of a subgroup of women with postpartum-onset depression who are especially sensitive to falling levels of sex steroids has been hypothesized, but evidence in support of this hypothesis is sparse. There is little doubt that the onset of maternal depression during pregnancy and in the first weeks or months after the birth of an infant raises special issues for treatment of the mother as well as issues concerning child health and development. Based on such considerations, many researchers have begun to use the more inclusive term of "perinatal depression" to refer to mood disorders occurring during pregnancy or in the postpartum year.

There is evidence that approximately 60% of depressed women experience premenstrual exacerbation of their depression (Kornstein et al. 2005). In addition, 4% to 8% of reproductive-age women are estimated to be affected by a premenstrual syndrome of sufficient severity to meet criteria for premenstrual dysphoric disorder (PMDD) (Halbreich et al. 2003). There is evidence that the SSRIs are uniquely effective among antidepressants in alleviating PMDD. However, attempts to identify direct causal links between abnormalities in sex hormones and PMDD have not been successful to date. It is hypothesized that hormonal changes affect mood by altering underlying biological vulnerability factors that are as yet incompletely understood (Schmidt et al. 1998).

The role of hormonal factors in midlife depression in women remains an open question as well. In 1979, Weissman reported that epidemiology provided no support for "involutional melancholia" as a distinct form of postmenopausal depression in women. More recently, there has a shift from menopause to perimenopause as a time of possible increased susceptibility to mental disorders. There is evidence that perimenopausal hormonal changes influence the course of schizophrenia, as can be seen in worsening of psychotic symptoms (Seeman & Lang 1990). For depression, the evidence is mixed. A population study of midlife women (Avis et al. 1994, 2001) did not find evidence that perimenopause was a time of increased risk for depression except for a subgroup of women who had reported high levels of depressive symptoms prior to entering the perimenopausal transition. Elsewhere, there have been reports from small sample studies of increased risk for recurrent depression and depressive symptoms in perimenopausal women with prior histories of depression (Rasgon et al. 2005) and one report of new onsets of depression in women during perimenopause (Soares 2003). A controlled trial has provided evidence of the efficacy of estrogen in treating perimenopausal depression

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(Soares et al. 2001). The relationship between the menopausal transition and the course of depression remains an open question.

In summary, the preponderance of epidemiological evidence indicates relationships between reproductive transitions and mental disorders. However, with the exception of postpartum-onset affective psychosis and bipolar disorder, there is relatively little evidence for a causal role of sex steroids in clinical disorders. The evidence for the role of psychosocial stressors in perinatal mood disorders is strong. A limiting factor in studies of hormones may be methodological. In the near future, sensitive technologies to image in vivo brain function may allow researchers to test hormone hypotheses more directly.

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Theories of Stress Hormone and Sex Hormone Interactions

Integrative theories linking stress and stress and sex hormones to indices of behavioral depression have emerged from preclinical neuroscience research. Increasingly these theories are applied heuristically in clinical research. In addition to the organizing and cyclical effects of sex steroids on brain (McEwen et al. 1998), other preclinical research has indicated that sex steroids modulate the biobehavioral effects of stress. In an animal model, Leuner et al. (2004) found opposite-effect sex differences in the impact of an uncontrolled stress on male and female animals. The stress had a detrimental impact on learning in females but enhanced learning in males. The sex difference was eliminated by changing the stressor to a controllable one. The detrimental effects of uncontrolled stress were also eliminated by chronic treatment of females with fluoxetine. However, fluoxetine did not affect the males' responses to the stressor. Other findings indicated that the male-female difference in stress response depended on the presence of estrogen and changing levels of estrogen in the female (Shors & Leuner 2003).

In general, the biological impact of stress in animals and humans is seen as resulting from its activation of the "fight or flight" response, which in turn has a cascading impact on multiple biological systems, including the neuroendocrine and nervous systems. Stress axis hormones produce multiple, variable, and interconnected effects, such as loss of normal feedback mechanisms in the neuroendocrine system, dysregulation of circadian hormonal rhythms, and changes in brain receptor number and sensitivity. Depending on variables such as intensity, duration, and developmental timing, stress is thought to bring about both reversible and potentially irreversible changes.

In clinical depression, these changes are manifested behaviorally as alterations of memory, affect, motivation, sleep, reproductive cycling, cognition, appetite, sociability, and activity level. However, direct causal studies of the influence of sex steroids on the modulation of the stress axis in humans are sparse. One exception is a recent report by Rubinow et al. (2005). In a small study of normal males, the investigators found that hypothalamic-pituitary-adrenal axis hyperactivity, resulting from pharmacologically induced hypogonadism, was attenuated by replacement testosterone.

Human males and females have been hypothesized to differ in their characteristic behavioral styles of coping with stress. Taylor et al. (2000) noted that at times of stress, females are more likely than males to "tend and befriend," and males are more likely than females to fight or flee. In turn, such differences are hypothesized to have their origins in sex differences in the biological impact of oxytocin on stress responses. Oxytocin, occurring at higher levels in females than in males, plays a key role the initiation of labor, but it has also been studied for its impact on the initiation of maternal behavior and the establishment of social attachments such as mother-to-infant bonding. Oxytocin, which has a behaviorally calming effect, is secreted in both males and females in stressful situations, but it is hypothesized that its effect on male physiology and behavior is reduced by testosterone.

In addition to their influences on behavior, hormonal levels are also influenced by behavior and the social environment. Stress hormones and sex steroids have been shown to change rapidly within the individual in relation to changes in relative position in the social group. In nonhuman primate males, the individual's demotion in a social dominance hierarchy is associated with increased levels of stress hormones and decreased levels of testosterone (Sapolsky 2004). The impact of changes in social dominance on hormone levels may also differ between male and female members of the social group.

Genetic Theories

Recently other research has suggested a role for genetic factors or their differential expression in explaining gender differences in the prevalence of depression. For example, in a genetic linkage study of 81 families, Zubenko et al. (2002) identified 19 regions of chromosomes that were especially common in the families and therefore likely to contain genes that promote depression. Four of these regions were found linked to depression only in women and one region was found linked to depression only in men. These findings suggest that there may be a greater number of distinct genetic mechanisms in the causal path to depression in women. In the Zubenko study, more than 80% of women who inherited a particular variant of the CREB1 gene developed depression. CREB1 is a gene that encodes a regulatory protein responsible for the expression of large numbers of other genes that play important roles in memory and other brain functions. In other research, CREB1 expression has been found to be altered in postmortem brain tissue of depressed and suicidal individuals and in animals treated with antidepressants. One form of estrogen (17-beta-estradiol) synergizes the expression of CREB-related transcriptional events. In a rodent study, 17-beta-estradiol increased the numbers of gonadotropin-releasing hormone neurons expressing phosphorylated CREB (indicative of increased cellular metabolism) in females but not in males (Abraham & Herbison 2005). These findings suggest ways by which sex hormones could contribute to observed gender differences in prevalence of depression.

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Differential Sensory Sensitivity Theories

Another area of increasing research attention is that of gender differences in sensitivity to affective and pain stimuli and their role in gender manifestations of mental disorders, particularly those linked to environmental stress. Because affective dysregulation is a prominent component of many mental disorders, research on sex and gender differences in emotional processing has potential widespread implications for understanding differences in mental disorders. There is evidence of gender differences in brain-based processing of positive and negative emotions in males and females (Gur & Gur 2002). George et al. (1996) found evidence of heightened female orientation to negative stimuli during self-induced positive and negative affective states. Recent evidence indicates that females are more reactive than males to a number of distressing visual stimuli and to pain. Two recent studies of regional brain activation to fear stimuli (Butler et al. 2005, Williams et al. 2005) found enhanced brain activity in women as compared with men. Such findings suggest a possible neural basis for gender differences in vulnerability to phobias, anxiety disorders, posttraumatic stress disorders, and clinical depression.

NIH WOMEN'S MENTAL HEALTH RESEARCH: THE FORMER ADAMHA INSTITUTES

Much of the research cited in this review has been conducted with support from the National Institutes of Health, in particular the former ADAMHA institutes. A number of ongoing programs and program announcements demonstrate considerable interest in women's mental health research. NIMH has two program announcements (PAs) issued in the area. The first, *Women's Mental Health and Sex/Gender Differences Research* (available online at http://grants.nih.gov/grants/guide/pa-files/PA-03-143.html), calls for gender/sex differences research in basic and clinical neuroscience, epidemiology and risk factors, and intervention and services research. A second PA, *Women's Mental Health in Pregnancy and the Postpartum Period* (http://grants.nih.gov/grants/guide/pa-files/PA-03-135.html) focuses on perinatal depression, postpartum psychosis, and postpartum bipolar disorder. The PA calls for clinical and epidemiological research on the course of disorders in pregnancy and postpartum, as well as basic and clinical neuroscience to understand the sex hormone–related biology of the disorders. A third major focus is on studies to develop appropriate pharmacological and behavioral interventions that are acceptable to childbearing women. An NIDA PA (http://grants1.nih.gov/grants/guide/pa-files/PA-03-139.html), *Women, Gender Differences and Drug Abuse, Consequences, Prevention, and Treatment and Services*, calls for research on the mechanisms of gender differences in drug abuse and biological and social consequences of differences, and on gender-appropriate preventive interventions, treatments, and services. It is anticipated that the announcements will be reissued in 2006.

NIAAA emphasizes research on the differential neurological and social impacts of alcohol abuse in women and men. Although NIAAA does not currently have a PA focused on women's health, a recent survey conducted by ORWH (Simon et al. 2005) ranked NIAAA as first among all NIH institutes in the proportion of its research relevant to women's health issues.

Coordinated Interagency Activities

In addition to ongoing programs at individual NIH institutes, over the past five years, a number of coordinated women's mental health activities have taken place, reflecting shared interests of NIH institutes, other agencies throughout the Department of Health and Human Services (DHHS), and nonfederal mental health organizations. In 2000, the American Psychological Association and multiple NIH institutes participated in the Summit on Women and Depression (Mazure et al. 2002). The summit reflected awareness in the clinical and research communities of the public health impact of depression on women. The summit brought together a diverse group of experts from psychiatry, psychology, pharmacology, epidemiology, and health services research. A summary of knowledge and a list of key research, clinical, public health, treatment, and services recommendations were developed.

In 2005, an evidence-based review from the Agency for Health Care Research and Quality reported on the prevalence and treatment of perinatal depression. The report (Gaynes et al. 2005) was the outcome of activities of the "Safe Motherhood" work group, whose representatives from multiple DHHS agencies had met regularly throughout 2003–2004 to identify shared interests. The group, which was coordinated by the Office on Women's Health of the DHHS, identified perinatal depression as an important and cross-cutting condition affecting multiple aspects of maternal and child health. The Agency for Health Care Research and Quality report emphasized the importance of considering depression in pregnancy as well as postpartum depression and underscored this point by its use of the term "perinatal depression" to encompass mood disorders occurring at both times. The report noted the lack of systematic knowledge of effective treatments for perinatal depression. According to the report, 1 in 20 American women who are pregnant or have given birth in the past 12 months suffers from major depression. If minor depression is included in the estimate, prevalence increases to 13%. There is some evidence to support the efficacy of psychotherapy and/or antidepressants as treatments for women with perinatal depression, but the number of controlled studies is insufficient to support the development of treatment guidelines.

SUMMARY

The past several decades have seen increased differentiation of the field of women's mental health research. Gender as a demographic variable is a stronger statistical "predictor" of risk for major depression than any other variable except personal history of depression. Increasingly, research attention has focused more and more

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on the underlying processes for which the term "gender" serves as a proxy. No longer is it sufficient to note the predictive value of gender as a risk factor for the development of a mental disorder such as depression. Increasingly, models of mental illness are challenged to distinguish between sex and gender as biological and social variables, to consider both social and biological aspects, and to understand interactions. Scientists not attending to these distinctions risk failing to take advantage of a powerful heuristic tool for understanding mental illness. Further progress in identifying the bases of sex and gender differences in mental disorders will require social, clinical, and basic research scientists to conceptualize sex and gender at causal levels and to devise sensitive methods to measure underlying biological and biobehavioral processes.

Reproductive transitions continue to be of major interest to the field of women's mental health for their psychological significance and for the attainment of major new social roles as well as for the biological changes they mark. The onset of puberty brings a range of new social expectations and gender roles to bear on the individual, along with rapid hormonal and physical changes. A negative impact of expectations and roles for females can be seen in reports of eating disorders in adolescent females, as young women seek to reconcile their changing bodies and increased body fat with twentieth-century Westernized cultural ideals of slimness.

Social role, psychological, and hormonal changes together make pregnancy and childbirth unique times of change and adjustment for women and their partners. The resolution of stress and the avoidance of depression enhance the likelihood of successful mother-infant bonding and healthy child development. Pregnancy and the postpartum period are also times when women regularly access primary care systems for themselves and their children. This fact points to the potential public health benefit of preventive services and depression screening and treatments for childbearing women.

By virtue of its attempt to understand the nature of differences between the sexes—in particular those differences touching upon behavior and personality—the field of women's mental health has often found its premises and content to be controversial. By virtue of its status as a specialized area within mental health research, women's mental health research also reflects more general societal, scientific, and philosophical controversies of our times. They include controversies such as those concerning the validity of neuroscience as the predominant paradigm for understanding mind and behavior (Pinker 2002) and debate over the reducibility of mind to neurochemical events in the brain and the extent to which behavior and personality reflect the impact of nature and nurture.

Postmodernist constructionist critiques have served as a reminder to biomedical scientists of the need to examine their own "objective" scientific models for the presence of implicit and critically unexamined assumptions and bias. In this way, cultural feminist movements such as those that arose in the early 1960s can be seen as having provided the energy for the women's health movement to develop into a mature field of biomedical research. Today research on sex and gender differences in mental disorders is an active area. That the mental health community has taken

seriously the value of studying sex and gender can be readily evidenced by the proliferation and variety of journal reports on the topic. The community has clearly answered in the affirmative the question, Does sex matter?

With increased attention directed to women's mental health as a public health issue, it is not surprising that research has also started to interface with services and policy considerations, especially in such areas as maternal and adolescent mental health. Cross-agency collaborations represent new ways to produce more rapid translation of biomedical research findings into evidence-based health communications, policies, and services priorities. Emphasis on women's mental health in screening, services, and prevention is an effective public health strategy to reduce the burden of mental illness in the community.

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