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THE YENTL SYNDROME

YENTL, the 19th-century heroine of Isaac Bashevis Singer's short story,[1] had to disguise herself as a man to attend school and study the Talmud. Being "just like a man" has historically been a price women have had to pay for equality. Being different from men has meant being second-class and less than equal for most of recorded time and throughout most of the world. It may therefore be sad, but not surprising, that women have all too often been treated less than equally in social relations, political endeavors, business, education, research, and health care.

Two studies published in this issue of the *Journal* provide evidence that there is sex bias in the management of coronary heart disease. In one study, Ayanian and Epstein[2] show that in Massachusetts and Maryland women were significantly less likely to undergo coronary angiography, percutaneous transluminal coronary angioplasty, or coronary surgery when admitted to the hospital with a diagnosis of myocardial infarction, unstable or stable angina, chronic ischemic heart disease, or chest pain. These differences were evident even after the investigators controlled for age, race, heart failure, diabetes, and economic status. Steingart et al.[3] used a prospective postinfarction intervention trial to examine a similar hypothesis. They determined that women had angina before myocardial infarction as frequently and with more debilitating effect than men, yet women underwent cardiac catheterization only half as often — again, after the investigators controlled for variables such as age and coexisting disease. It is noteworthy that when women who had undergone cardiac catheterization were studied, there were no differences between the sexes in the likelihood of coronary surgery. Similarly, once a woman had a myocardial infarction, she was as likely as a man to undergo cardiac catheterization and revascularization. The latter two findings demonstrate the Yentl syndrome at work. That is, once a woman showed that she was just like a man, by having severe coronary artery disease or a myocardial infarction, then she was treated as a man would be.

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The problem is to convince both the lay and the medical sectors that coronary heart disease is also a woman's disease, not a man's disease in disguise. Neither women nor their physicians fully recognize that myocardial infarction is the leading cause of death among women in the United States. Moreover, all too many research studies of prevention, diagnostic methods, and intervention for coronary heart disease have been conducted in exclusively male populations. The Veterans Administration Cooperative Study,[4] one of the earliest to show the benefits of coronary surgery in subgroups of patients with angina, the Multiple Risk Factor Intervention Trial, a study of risk-factor modification to prevent adverse cardiac events,[5] and the U.S. Physicians Study,[6] demonstrating the benefits of prophylactic aspirin in decreasing the risk of myocardial infarction, are all examples of major clinical research studies with widespread influence on the treatment of patients with cardiovascular disease that have excluded women from the study population. It should be noted, however, that two of these three studies were conceived approximately two decades ago, during an epidemic of coronary disease among middle-aged men. Improvements in prevention and treatment, partly resulting from these sex-exclusive studies, have reduced coronary death rates by nearly 50 percent since the epidemic peaked in 1963; this decline occurred in both men and women. Coronary disease is now most evident in older people and at a time in life when men and women are affected with equal frequency, but the full legacy of these studies must be recognized.

Decades of sex-exclusive research have reinforced the myth that coronary artery disease is a uniquely male affliction and have generated data sets in which men are the normative standard. The extrapolation of these male-generated findings to women has led in some cases to biased standards of care and has prevented the full consideration of several important aspects of coronary disease in women. The importance of estrogen in women as an antiatherogenic agent and its role in both the primary and secondary prevention of coronary disease in women are examples. With an "androgenic" research focus, estrogen would be unlikely to be tested as a treatment for coronary disease. We must be challenged by the example of coronary artery disease to examine critically the extent to which the Yentl syndrome pervades medicine and medical research and to respond promptly whenever its influence is evident.

Indeed, it is now time for a general awakening. Women have unique medical problems. They have greater morbidity than men and are affected by more chronic debilitating illness. Although women live longer than men — by as much as seven years, on average — the quality of life of those extra years is exceptionally burdened by cancer, particularly of the breast, lung, and colon, by heart disease and stroke, osteoporosis, Alzheimer's disease, depression and social isolation, and general frailty. These conditions, which tend to afflict women in the last third of their lives, are not the inevitable ravages of age but are in many cases highly preventable and eminently treatable. We must awaken fully to these facts and address the diseases of women as different from the diseases of men but of equal importance, even when they also affect men.

Toward that end, the National Institutes of Health (NIH) has made a major commitment to research on women's health and illness. A host of conditions that affect women exclusively or uniquely are receiving more attention: infertility and the need for contraception, complications of pregnancy, menopause, breast cancer, ovarian and uterine cancer, carcinoma of the cervix, and sexually transmitted diseases. Moreover, diseases that affect both men and women will consistently be addressed with an eye to uncovering relevant sex differences that influence pathophysiologic features, diagnosis, or treatment. Just recently, the NIH has mounted a multidisciplinary, multi-institute intervention study, the Women's Health Initiative, that will address the major causes of death, disability, and frailty among middle-aged and older women, including cardiovascular disease, cancer, and osteoporosis. The goal of this study is to gather data that will provide women and their health care providers with vitally needed information on the prevention and treatment of these diseases and their risk factors, with the ultimate goal of improving the quality of life of women. The study will have three components: a large-scale prospective epidemiologic surveillance study involving several hundred thousand women followed over a period of 10 years, a randomized clinical trial, and a trial of prevention and intervention in the community. The intervention strategies to be studied include diet modification, including substantial reduction in fat; vitamin and calcium supplementation; exercise; smoking cessation; and hormone-replacement therapy as a means of keeping women healthy. For the most part, these interventions have overlapping effects on the illnesses to be prevented. This study, the largest of its kind ever conducted, will draw on the resources of nine NIH institutes and centers and involve scientists, clinicians, and health care providers across the United States.

The Women's Health Initiative is part of an overall strategic commitment of the NIH to make women's health a priority, not just in the interest of women but for the well-being of the American people. And it is our hope that the bold and charming heroine Yentl will survive, but that her syndrome will slip back into history as a curiosity of times gone by.

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COGNITIVE DEFICITS IN PREMATURE INFANTS

EACH year approximately 45,000 infants with very low birth weights are born in the United States, and approximately 80 to 85 percent survive the neonatal period. All too often, these survivors have overt motor deficits (cerebral palsy) or substantial cognitive disturbances that lead to learning difficulties in school.[1,2] This group of infants, numbering in the many thousands yearly, now constitute an enormous burden on the tangible and intangible resources of families and educational systems.

The interesting report of Hack et al. in this issue of the *Journal*[3] focuses particularly on the cognitive function at school age of very-low-birth-weight children and specifically on the prognostic value of subnormal head size, defined as a circumference more than 2 SD below the mean, at eight months of age (corrected for premature delivery). The cohort studied represented approximately 80 percent of the survivors among infants of very low birth weight who were born between 1977 and 1979 and admitted to the neonatal intensive care unit at Rainbow Babies and Children's Hospital in Cleveland. The survival rate of the original population was approximately 65 percent — only slightly less than current survival rates.

The major motor deficits in very-low-birth-weight infants, occurring in 5 to 15 percent of this group, are spastic diplegia and spastic hemiparesis. Spastic diplegia is a distinctive motor disability of premature infants, involving primarily the legs, though usually with some involvement of the arms as well. Spastic hemiparesis of the premature infant is a distinctive type of hemiparesis, with prominent involvement of the lower as well as the upper extremities. Also important, however, are cognitive and related disturbances (those involving, for example, attentional skills and specific learning skills), which lead to appreciable school difficulties in 25 to 50 percent of very-low-birth-weight children. Indeed, in the study by Hack et al., IQ was less than 85 in 25 percent of the infants followed, and an index of academic skills was less than 80 in 34 percent.[3]

Data derived primarily from studies correlating ultrasonographic, neuropathological, and clinical information lead to the conclusion that spastic diplegia is the clinical expression of periventricular leukomalacia and its variants. Periventricular leukomalacia appears to be caused, at least in large part, by ischemic injury to the periventricular white matter, the locus of presumed arterial border zones and end zones. However, the increasing recognition of more diffuse injury to the periventricular white matter in such infants, outside of the presumed arterial border zones and end zones,[4,5] raises the possibility of other pathogenetic factors, related to the intrinsic metabolic properties of the periventricular white matter rather than to vascular factors as such. Moreover, the recent demonstration that the cerebral metabolism of oxygen in periventricular white matter is nearly undetectable in human premature infants suggests that the long-held notion that oxygen deprivation is the final common pathway in injury to the periventricular white matter may be incorrect.[6] Much more needs to be learned about the biology of the cellular target of injury to the periventricular white matter in human infants — i.e., the differentiating oligodendroglial cell — if we are to understand more clearly the pathogenesis of this characteristic form of brain injury in very-low-birth-weight infants. The neuropathologic cause of the distinctive spastic hemiparesis seen in premature infants is a unilateral periventricular hemorrhagic infarction that occurs in association with and presumably as a result of substantial asymmetric intraventricular hemorrhage.[1,7]

The injury that leads to the cognitive disturbances that result in school failure in very-low-birth-weight children remains unclear, however. The available data suggest that in these infants, unlike full-term infants, cortical neuronal injury is not the crucial occurrence. Rather, the underlying cause of the deficits in premature infants may be a lasting disturbance of one or more of the major events in brain development during the neonatal period, a disturbance initiated by ischemia or other insults. These developmental events include the elaboration of the ramifications of cerebral cortical neuronal dendrites and axons, the formation of synapses, cell death and the selective elimination of neuronal processes and synapses, the proliferation and differentiation of glial cells, and myelination.[8] We know little about the deleterious effects of neonatal insults on these processes in premature infants. However, a neuropathological study recently demonstrated a decreased number of synapses in the brains of premature infants who were dependent on ventilators,[9] and recent reports of magnetic resonance imaging in children born prematurely and studied later in infancy and childhood indicate a delay in cerebral myelination after neonatal injury to the white matter.[10,11]

Hack et al. suggest that determination of the head circumference at eight months of age is a useful means of predicting subsequent cognitive deficits and difficulties in school.[3] Indeed, the head and brain grow most rapidly from the third trimester of pregnancy through the first year of life. The main anatomical reasons for this increase in brain size are probably the elaboration of dendritic and axonal ramifications,