Individual Differences: Signal, Noise—Or Both?

Experimental research requires that the researcher control as many variables as possible. Individual differences among study subjects—variations in age, sex, genetic makeup, and past experience—have long been regarded as introducing "noise" that can obscure the effects of experimental manipulations on the outcome variables. Genetically uniform strains of rodents were developed for the express purpose of minimizing variability among the animals used in an experiment. For the same reason, animals to be used in a specific experiment are almost always housed under uniform conditions and tested at the same stage of life. Similarly, scientists conducting human clinical and experimental research have traditionally limited their studies to subjects of a specific age and gender (which is why we know so much about college freshmen). If confining the study to specific age or gender groups is not possible, these variables are controlled statistically.

In a countervailing research tradition, individual differences have been the phenomena of interest. Psychological studies have attempted to determine how individual states and traits influence behavior, and epidemiologic studies have assessed the factors that place particular groups of people at greater risk than others of experiencing specific diseases. That is, age, race, gender, genetic factors, and exposure to conditions such as smoking or stressful life events have been examined to determine their relationship to disease. Nevertheless, I believe it is fair to say that, in both traditions, the underlying paradigm has been that there is a single disease or behavioral outcome, and that individual differences simply modify the risk of developing the disease or displaying the behavior.

More recently, however, it has become clear that the very mechanisms of disease may differ by age and sex. I recently returned from the 1st World Congress on Gender-Specific Medicine in Berlin (February 23–26, 2006). At this conference, the underlying theme was that the anatomy, physiology, and hormonal status of men and women differ so substantially that, unless disease rates and manifestations show absolutely no differences between men and women, the default approach should be to consider the genders separately, rather as one would study various strains of mice. Similarly, we are not the same organisms physiologically or psychosocially at age 25 as at age 45 or age 65. Studies whose subjects cover a broad age spectrum need to consider that effects may differ by age.

In addition to disease mechanisms, outcomes of treatment or preventive interventions may vary depending on the patient's age and sex. To take 1 dramatic example, men who take 1 aspirin per day have lower risk of experiencing myocardial infarction (MI), but aspirin use does not influence rates of stroke for men. The same daily dose of aspirin in women lowers risk of stroke but not MI.[1] In another example, perhaps closer to home for pain clinicians and researchers, benzodiazepines have been found to be less effective as muscle relaxants in women with normal menstrual cycles than in women using oral contraceptives containing progesterone.[2]

In recent issues of the *Journal of Orofacial Pain,* various findings have been reported relevant to age and gender influences on pain related to temporomandibular disorders (TMD pain). Nilsson et al[3] reported a dramatic increase in the prevalence of TMD pain in girls around the age of 15. Prior to age 15, rates were similar in the 2 sexes or only slightly elevated in girls. After age 15, the prevalence curve for females rose steeply, while that for males remained relatively flat. By age 16, the rate in girls was roughly double that of boys. In human laboratory research, Cairns et al[4] found significant sex-related differences in pain in response to glutamate injections into the masseter, with women reporting higher pain levels. Lest we conclude that all gender differences are solely due to "lower pain thresholds" or differences in the willingness of men and women to report pain, Cairns and colleagues also found that baseline human jaw-stretch reflex responses evoked with a muscle stretcher were larger in women, while glutamate facilitated jaw stretch reflexes only in men. Finally, in the

current issue of this journal, Yu et al[5] report age and sex differences in the levels of aromatase in the rat temporomandibular joint.

These findings suggest, at minimum, that age and gender need to be considered seriously in investigations of orofacial pain mechanisms, disease presentation, and treatment. Clinicians have long recognized the importance of individual differences. It is time for researchers to be creative in designing studies that can aid our understanding not only of age and sex differences but also differences involving the interaction of age and sex (younger men versus older men versus younger women versus older women) and even the multiple interactions of age and sex with other individual differences. The knowledge gained from such studies will certainly have relevance to the clinical situation, where each patient presents as a complex individual.

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Errata

In the Spring 2004 issue of the *Journal of Orofacial Pain* (JOP), the degrees of Drs Michel H. Steenks and Mauro Farella were listed incorrectly. They should have been listed as follows.

Michel H. Steenks, DDS, PhD
Mauro Farella, DDS, PG Orthod

Furthermore, in the Winter 2006 issue of JOP, Dr Ephraim Winocur should have been listed as the third author of the article "Nasopharyngeal Carcinoma Mimicking a Temporomandibular Disorder: A Case Report."

The JOP staff regrets the errors.