Sex-based physiology prior to political correctness

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This essay examines the historical significance of an APS classic paper that is freely available online:


Except for reproductive function, human physiology traditionally was defined in textbooks of physiology in terms of responses of the “typical 70-kg man.” Furthermore, most basic science studies and human clinical trials were conducted on male animals. The rationale that researchers used to justify excluding female animals from basic science studies and women from clinical trials was that ovarian cyclicity complicated the data and inclusion of another group increased the cost of the study (6). However, in 1990, the Government Accounting Office audited the National Institutes of Health policy for inclusion of women in clinical trials (7). The result of this audit, as well as a series of other governmental and activist initiatives, culminated in a report by the Institute of Medicine in 2001, Exploring the Biological Contribution to Human Health: Does Sex Matter? (11). This Institute of Medicine report concluded that sex does matter in prevention, diagnosis, and treatment of disease and that barriers to the advancement of knowledge about sex differences in normal physiology and disease must be eliminated (11). Thus, in the 21st century, there are governmental regulations and political pressures to explore physiological differences between males and females.

However, in 1963 there were no political directives to investigate sex-based differences in physiology when Critchlow and colleagues (2) performed a rigorous series of experiments directed at resolving a controversy of whether or not there were differences in pituitary-adrenal function between male and female animals under resting conditions (Fig. 1). These investigators were driven by an innate curiosity to understand differences in findings from various laboratories regarding adrenal function in male and female animals. A greater adrenal cortical secretory response to stressors in female compared with male animals was a well-documented finding from several laboratories (3, 5, 8) and not under dispute. However, the difference in adrenal cortical function between male and female animals under resting conditions was not a consistent finding, and some evidence suggested that anesthetics normalized responses between the sexes (3). To resolve these controversies and to establish reliable data obtained under nonstressed or control conditions, Critchlow and colleagues undertook three series of experiments that defined the circadian pattern of corticosterone, adrenocorticotropic (ACTH), and leukocyte activation in prepubescent, sexually mature, and gonadectomized male and female rats. To validate circadian cyclicity of responses, animals were light-phase shifted or blinded, and circadian measurements were repeated. Blood was collected from each group of animals at 4-hour intervals for periods of 24–32 hours either by rapid decapitation or while animals were anesthetized with pentobarbital sodium. These arduous protocols reflect the dedication and energy the young Dr. Critchlow expended in order to obtain quality data.

One key assay required for linking the pituitary-adrenal axis, i.e., measurement of ACTH, was a bioassay. Bioassays today are not usually regarded as a sophisticated approach to quantification of biological activity. However, such assays, based on a sound physiological rationale, stand the test of time regardless of their level of refinement and are still useful in defining physiological activity of new molecules.

Results of the Critchlow experiments provided the classic validation that the pituitary-adrenal axis is sexually dimorphic under resting (control) conditions and can be modulated both by hormonal status and by neurological processes inhibited by barbiturates. One wonders how many interesting observations are missed today because of lack of attention by investigators to the circadian patterns of activity or hormonal status of the
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experimental subjects. In addition, investigators often do not know the extent to which various analgesics or anesthetics required by animal regulatory panels may interact with or modulate particular physiological responses of interest.

Readers of this classic paper will immediately notice differences in the structure of that paper compared with reports of today. One obvious difference between the two groups of papers separated by almost half a century is the minimalistic statistical analysis of the data. Unlike requirements for some journals today for “independent statistical review,” statistics of the Critchlow study were described with one sentence: “All statistical probabilities were derived from analysis of variance.” Figures and text, unlike today’s papers, were not peppered with the prerequisite asterisks, crosses, and $P$ values to the nth decimal level of statistical significance. Differences between responses of male and female animals are obvious to the reader and as such emphasize that statistics are a tool, like other scientific assays, and statistical significance should not override common sense.

A second difference between papers of today and the Critchlow study is the lack of translational relevance or applied rationale for the study. In a recent interview with Dr. Critchlow, he indicated that his group simply needed reliable baseline information from which to design future experiments. Although their investigative team had considered possible clinical relevance of their observations, he and his colleagues were simply not aware of any. Needless to say, observations from these basic experiments have clinical relevance today. Indeed, it has taken over 40 years for sexual dimorphic responses to cortisol to be observed and validated in pubertal humans (10), and today it is recognized that estrogen-modulated release of ACTH has implications for sex disparities in incidence of depression, reproductive disorders (4), and perhaps acute stress-induced Tako-Tsubo cardiopathy (1).

By today’s standards, the study by Critchlow and colleagues could perhaps be labeled “descriptive,” an adjective that often pronounces a death sentence for publication of papers in so-called “high-impact” journals. Fortunately, physiologists recognize the value of definitive, descriptive, integrative experiments that provide insight into controversial findings. It is just such descriptive observations that are still cited after 40 years (9) because they provide the background information that is necessary to explore more mechanistic approaches to understanding how physiological systems are modulated.

In the 21st century world of genomics and political correctness in science, sexual genotype or sex-based differences in physiological responses coupled with definition of hormonal status of the experimental subject are important variables to consider in the development of novel preventive, diagnostic, and treatment strategies in medicine. In addition, students of physiology would do well to follow Dr. Critchlow’s advice, that is, “to be curious and to have fun with the discovery process.” This timeless advice overshadows political correctness and, when followed, results in classic discoveries.

REFERENCES