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Estrogen, Testosterone, and Gender Differences

Dean E. Dluzen

Department of Anatomy, Northeastern Ohio Universities College of Medicine, (NEOUCOM), Rootstown, OH

The purpose of this report is to gain some current perspective on the definition, bases, and trends for research associated with gender differences. To accomplish this goal an analysis on the number of citations from a 1994–2004 Medline search with the terms estrogen, testosterone, gender differences, sex differences as well as the combinations of these terms was performed. Other combinations of terms included separate searches of estrogen, testosterone, and their combination within males or females, and an analysis of gender and sex differences with the terms human and animal. The salient results from this survey include: (1) An overall greater ratio of estrogen:testosterone citations when these terms were searched alone or in combination with gender differences; (2) an overall greater ratio of testosterone:estrogen citations when these terms were combined with sex differences or conducted separately within males or females, although this trend was shifting toward decreased testosterone and increased estrogen citation numbers toward the latter years of the survey; (3) a trend for increasing numbers of estrogen and gender differences citations over the period of the survey; (4) a clear indication for the term gender differences to be associated with the search term human; and (5) a very small number of citations when the terms estrogen and testosterone were combined. Interpretations and implications of these results are discussed.

Key Words: Sex differences; gonadal steroids; male; female.

Introduction

When discussing gender differences in health and disease, a major consideration is the dissimilarity in gonadal steroid hormones between females and males. Such a consideration will generally lead to the question of whether gender differences result from estrogen in females or testosterone in males. This question conceals a number of dormant issues regarding an evaluation of estrogen, testosterone, and gender differences, as well as relating to the core of the definition of gender differences. Are estrogen and testosterone assessed equally in studies on gender differences? How often are the combination of estrogen and testosterone considered as contributing to gender differences? Have these trends changed over the past decade? Do the terms gender differences and sex differences relate comparable information? The aim of the present report represents an attempt to gain some perspective on the current bases, trends, and definition of gender differences as encompassed within these questions.

Results

The results for the number of yearly citations when the terms estrogen, testosterone, and estrogen AND testosterone were searched are presented in Fig. 1. These data show that the overall number of citations for estrogen is larger than testosterone and demonstrate a relatively consistent increase over this sampling period. By contrast, the number of citations for testosterone remained fairly constant over this period. The other salient feature of these data was the extremely low and unwavering number of citations resulting from the combination of estrogen AND testosterone. As a complementary means of assessing these data, the numbers of citations were expressed as a percentage for each individual term as a function of the total number of citations within each year. For example, in 1994 there were a total of 3970 total citations (estrogen, testosterone, and estrogen AND testosterone) of which estrogen accounted for 2282 (57.5%), testosterone 1550 (39%), and estrogen AND testosterone 138 (3.5%). In Fig. 2A are shown the percentages that result for each year of the sampling period. This presentation illustrates a trend for an increasing preponderance of estrogen versus testosterone citations along with the low and steady percentage of citations from the combination of terms estrogen AND testosterone. Figure 2B contains a summary and analyses of these percentages as collapsed over the sampling period. This summary indicates that the total percentage of estrogen citations (63.2%) is nearly twice that of the testosterone citations (33.2%) and only a minuscule percentage of the citations consisted of a combination of estrogen AND testosterone (3.6%). An overall statistically significant difference is present ($F_{2,30} = 1639$, $p < 0.0001$) and individual pairwise comparisons reveal statistically significant differences ($p < 0.001$) between each of the three terms.

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Author to whom all correspondence and reprint requests should be addressed: Dean Dluzen, Department of Anatomy, Northeastern Ohio Universities College of Medicine (NEOUCOM), 4209 State Route 44, P. O. Box 95, Rootstown, OH 44272-0095. E-mail: ded@neoucom.edu

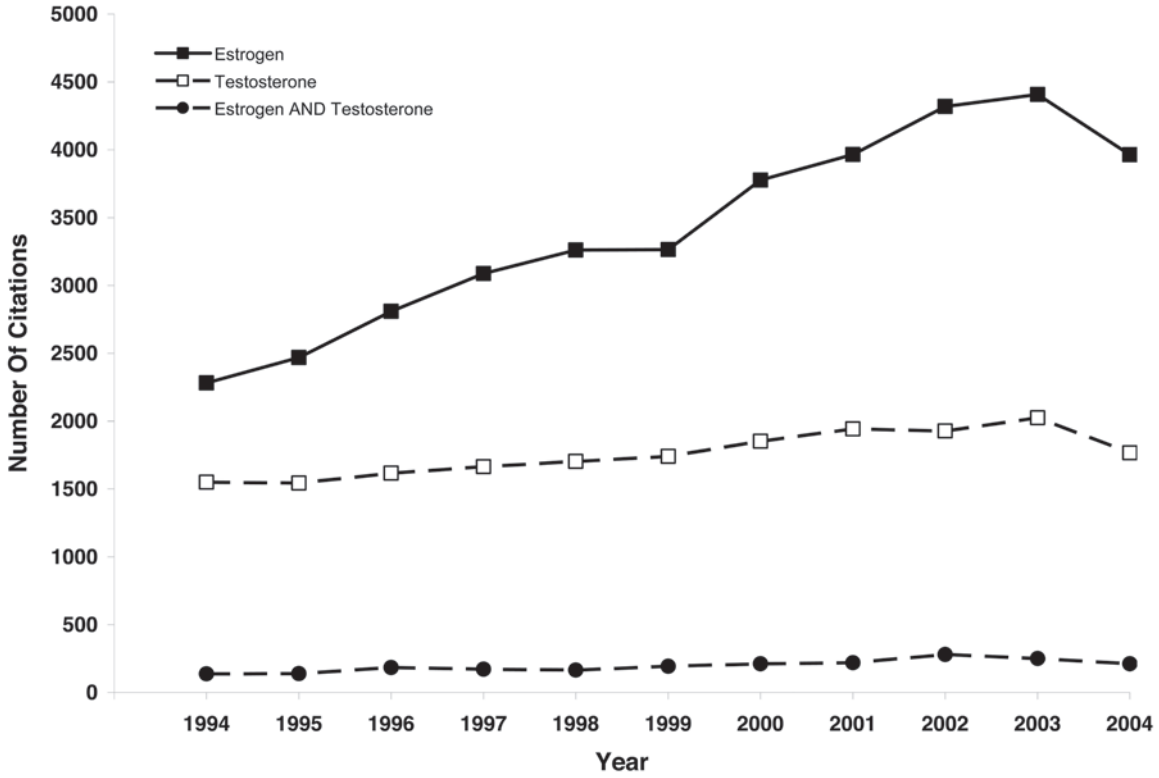

Fig. 1. The number of citations obtained from a Medline search as performed from 1994 to 2004 using the terms estrogen, testosterone, and the combination of these terms (estrogen AND testosterone).

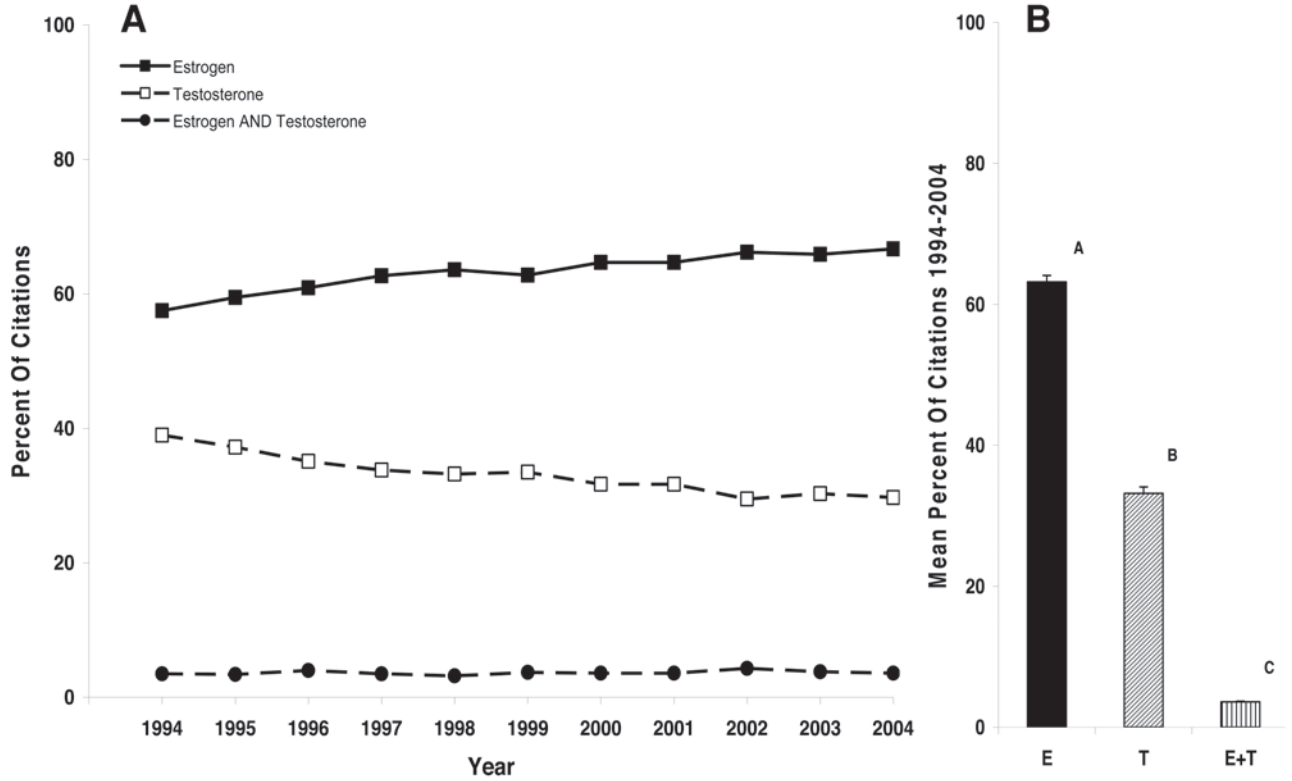

Fig. 2. (**A**) The percentage of citations obtained for estrogen, testosterone, and the combination of these terms over the 1994–2004 period of the survey as derived from the data of Fig. 1. The values presented represent percentages resulting from the number of citations for the individual terms over the total number of citations generated from the three terms. (**B**) The overall mean + SEM of these citation percentages as collapsed over the entire survey period for estrogen (E), testosterone (T), and the combination of estrogen AND testosterone (E+T). Superscript letters indicate statistically significant differences among the percentages obtained for each of the terms.

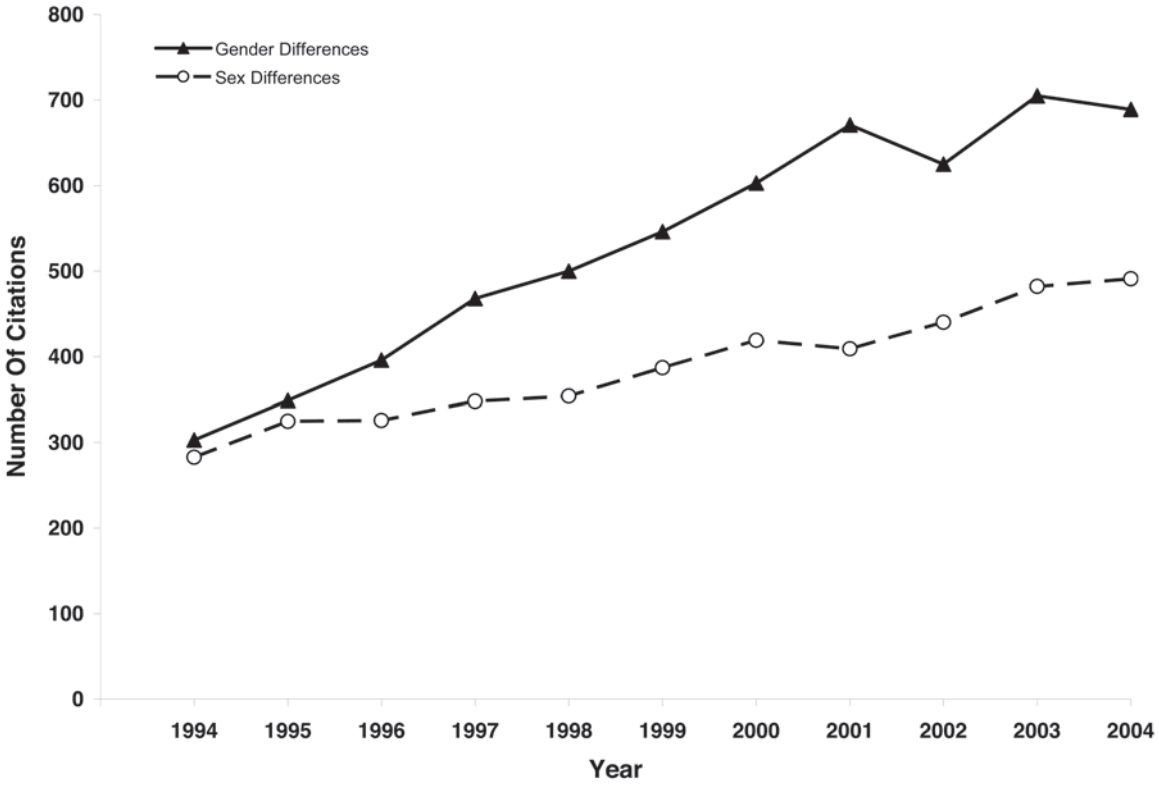

Fig. 3. The number of citations obtained from a Medline search as performed from 1994 to 2004 using the terms gender differences and sex differences.

The issue as to how this literature citation profile in Fig. 1 may be related to gender (and sex) differences can be evaluated from citations generated by the term gender differences over this period. Citations for the term sex differences are also included for purposes of comparison. An interesting difference in the citation number profile exists between these two terms as shown in Fig. 3. The number of citations for gender and sex differences was quite similar for the first two years (1994 and 1995) of the survey. Thereafter, they diverged markedly with citation numbers for gender differences climbing at a greater rate (slope = 0.45) than that for sex differences (slope = 0.22).

Although sex differences may be used interchangeably with gender differences by some investigators, others may make the distinction that the former primarily refers to laboratory/animal studies and the latter to clinical/human reports *(1)*. In an attempt to gain some vista on this eventuality, the terms gender differences and sex differences were each combined with the terms human or animal. These results are presented in Fig. 4 and show that use of the term gender differences is much more commonly associated with human versus animal studies (human:animal ratio = 2.9). By contrast, no such clear distinction is observed with the use of the term sex differences where citation numbers were equally divided between the terms human or animal (human:animal ratio = 1.03).

When comparing the data of Figs. 1 and 3, there is an interesting similarity in the relationship of citation profiles between estrogen and testosterone of Fig. 1 and gender and sex differences of Fig. 3. Specifically, the degree of increase in citation numbers over the survey period for gender differences (Fig. 3) is similar to that of the yearly citation number profile for estrogen (Fig. 1), while that of sex differences is comparable to that of testosterone. As a result, both profiles (estrogen/gender differences versus testosterone/sex differences) show a marked divergence by the latter years of the sampling period. The intriguing nature of this relationship suggested an evaluation of citation numbers for estrogen, testosterone, and estrogen AND testosterone as combined with the terms gender differences or sex differences.

A plot of the percentage of citations for the combination of estrogen AND gender differences, testosterone AND gender differences, and estrogen AND testosterone AND gender differences from 1994 to 2004 (calculated as that described for Fig. 2) is presented in Fig. 5A. While these plots show a more erratic and variable profile over the years sampled, the basic ordering of this relationship among these combinations of citation percentages is similar to that observed when these gonadal steroid hormone terms and their combinations were considered alone (Fig. 2). A summary of these citations collapsed over the entire sampling period as shown in Fig. 5B substantiates that the maximal percentage of citations is for gender differences AND estrogen (50.5%), followed by that for gender differences AND testosterone (35.9%) and gender differences AND estrogen

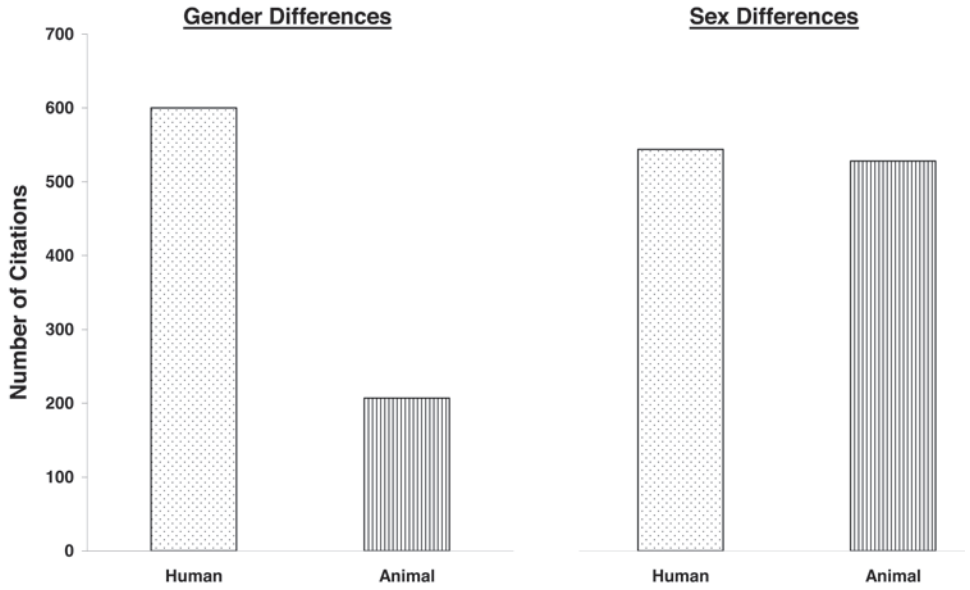

Fig. 4. The overall number of citations obtained over the period 1994–2004 when the terms gender or sex differences were combined with either the search terms human or animal.

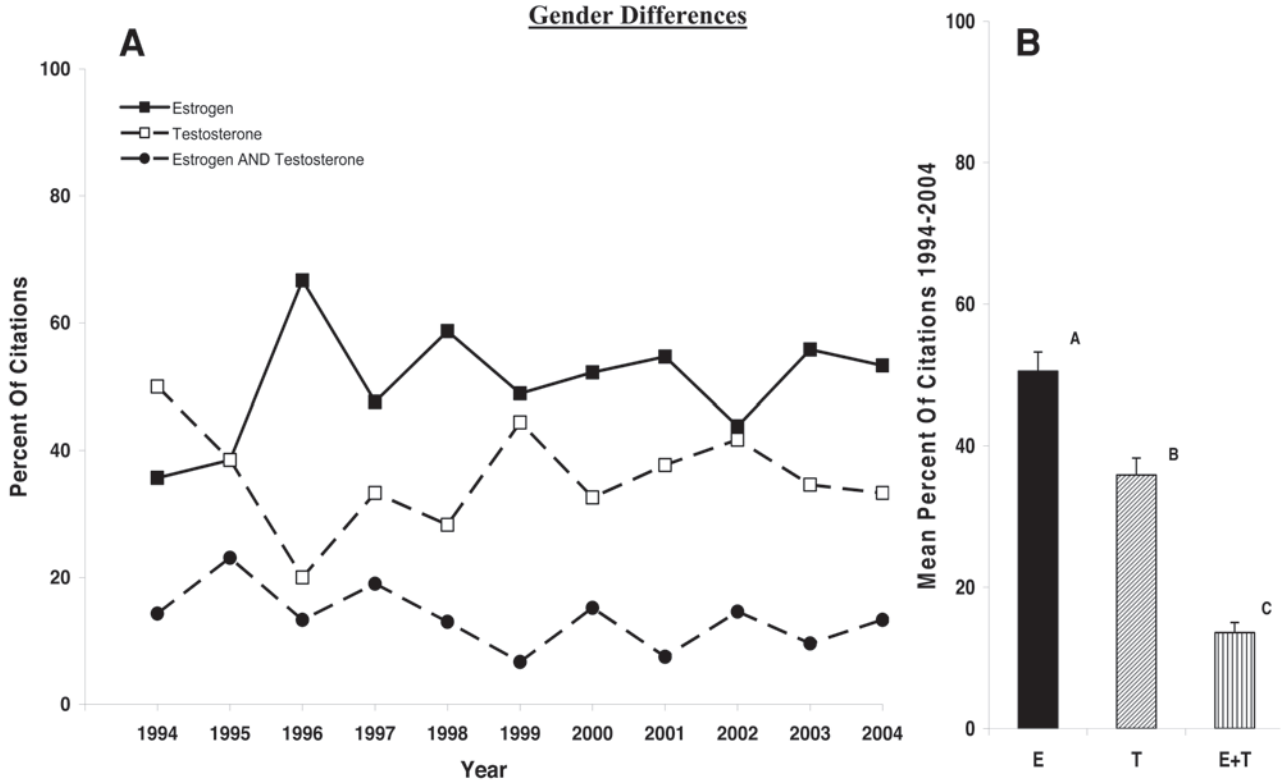

Fig. 5. (**A**) The percentage of citations obtained for the term gender differences as combined with estrogen, testosterone, and the combination of estrogen AND testosterone over the 1994–2004 period of the survey. The values presented represent percentages resulting from the number of citations for the individual terms over the total number of citations generated from the three terms. (**B**) The overall mean + SEM of these citation percentages as collapsed over the entire survey period for estrogen (E), testosterone (T), and the combination of estrogen AND testosterone (E+T). Superscript letters indicate statistically significant differences among the percentages obtained for each of the terms.

AND testosterone (13.6%). Analyses of these data as presented in Fig. 5B reveal that an overall statistically significant difference is present ($F_{2,30} = 67.9$, $p < 0.0001$). When individual pairwise comparisons were performed, statistically significant differences ($p < 0.0003$) were obtained between each of the three combinations of terms.

The data generated when the term sex differences was combined with estrogen or testosterone or estrogen AND

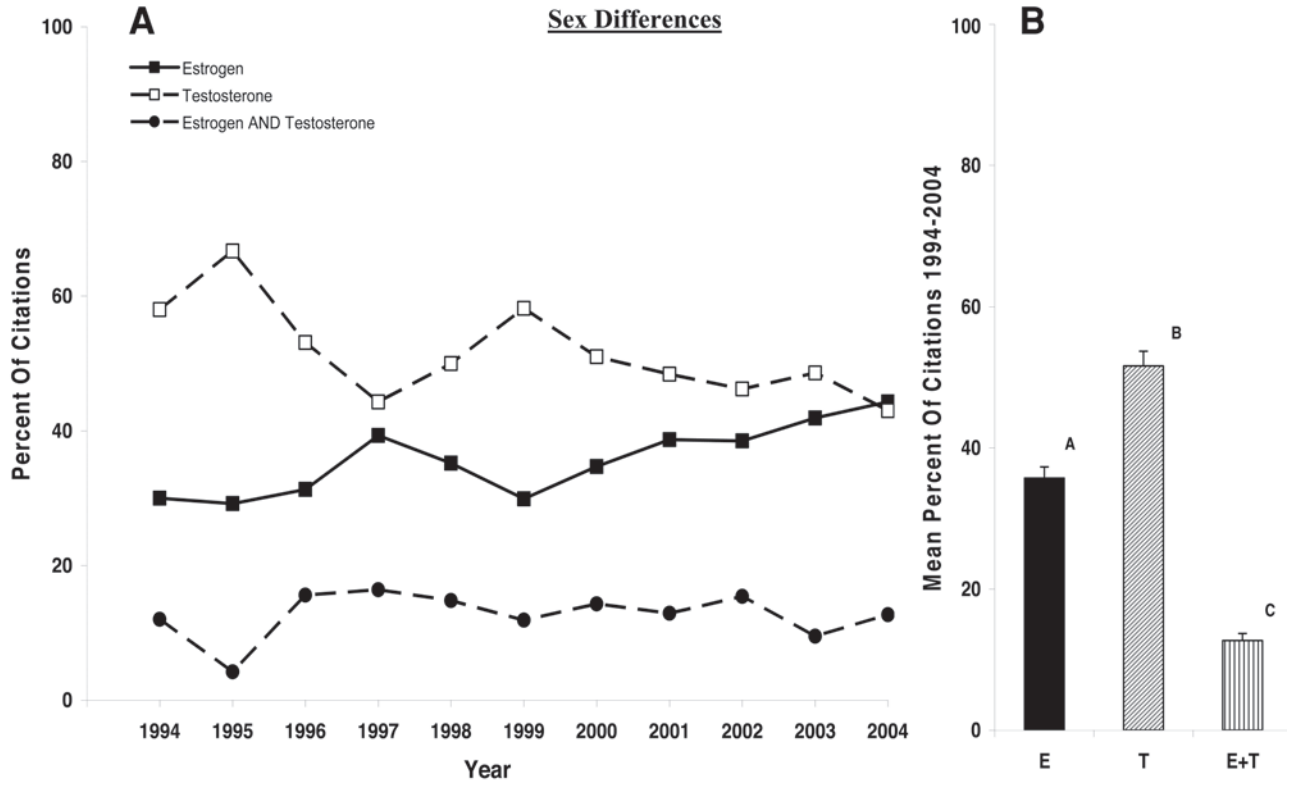

Fig. 6. (**A**) The percentage of citations obtained for the term sex differences as combined with estrogen, testosterone, and the combination of estrogen AND testosterone over the 1994–2004 period of the survey. The values presented represent percentages resulting from the number of citations for the individual terms over the total number of citations generated from the three terms. (**B**) The overall mean + SEM of these citation percentages as collapsed over the entire survey period for estrogen (E), testosterone (T), and the combination of estrogen AND testosterone (E+T). Superscript letters indicate statistically significant differences among the percents obtained for each of the terms.

testosterone are shown in Fig. 6. The combination of the term sex differences with these individual gonadal steroid hormone terms yields a reversal in the percentage of citations as compared with that of gender differences. As illustrated within the yearly profiles (Fig. 6A) and confirmed within the data summary (Fig. 6B), the percentage citations for the terms sex differences AND estrogen (35.7%) is lower than the terms sex differences AND testosterone (51.6%), while that for sex differences AND estrogen AND testosterone remain low (12.7%) and similar to that observed for the gender differences AND estrogen AND testosterone term (13.6%, Fig. 5B). Analyses of these data from Fig. 6B reveal an overall statistically significant difference ($F_{2,30} = 142.7$, $p < 0.0001$) and pairwise comparisons show that statistically significant differences ($p < 0.0001$) were obtained between each of the three combinations of terms assessed.

A final set of analyses were performed in which the terms estrogen, testosterone, and estrogen AND testosterone were evaluated separately for males or females. These data, as obtained for males and females, are presented in Figs. 7 and 8, respectively. In males, the percentage of citations for testosterone were maintained at a fairly high and consistent level over the sampling period (Fig. 7A) accounting for an overall value of 63% of the citations (Fig. 7B). The percentage citations for testosterone were over twofold greater than that for estrogen within males, which also showed a relatively consistent level over the sampling period and an overall total value of 28%, while that for the combination of estrogen AND testosterone accounted for only 9% of the citations.

Analyses of these data as presented in Fig. 7B reveal an overall statistically significant differences ($F_{2,30} = 818.8$, $p < 0.0001$) and pairwise comparisons show that statistically significant differences ($p < 0.0001$) were obtained between each of the three search terms assessed.

In females, the percentage of citations for testosterone tended to decline over the sampling period (mean of years 1994–1996 = 53.8% versus 2002–2004 = 45.1%), while that for estrogen rose slightly (mean of years 1994–1996 = 38.2% versus 2002–2004 = 45.3%) (Fig. 8). Citation percentages for the combination of estrogen AND testosterone were mostly stable and low over the sampling period (overall mean = 8%). Analyses of the summary data presented in Fig. 8B reveal an overall statistically significant difference ($F_{2,30} = 441.5$, $p < 0.0001$) and pairwise comparisons show that statistically significant differences ($p < 0.001$) were obtained between each of the three search terms. Interestingly, the overall percentage of citations for testosterone were

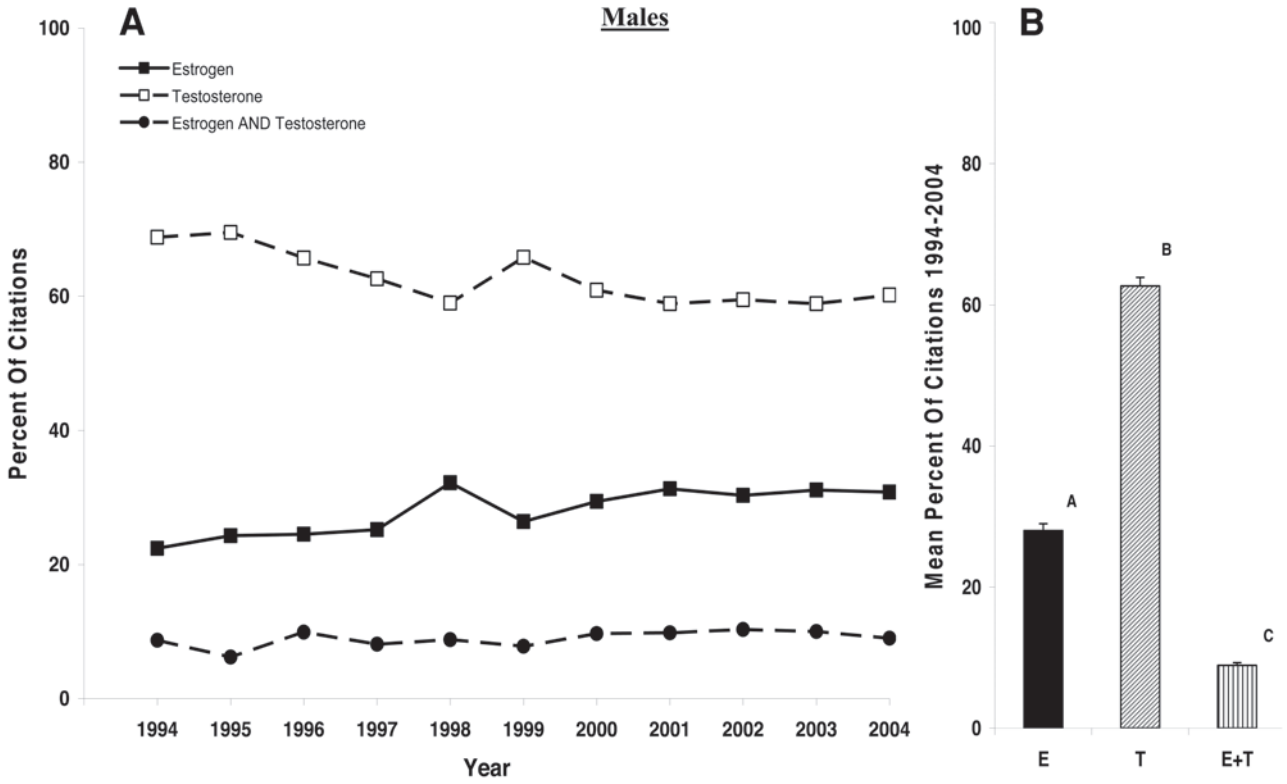

Fig. 7. (**A**) The percentage of citations obtained for estrogen, testosterone, and the combination of these terms when combined with the term males over the 1994–2004 period of the survey. The values presented represent percentages resulting from the number of citations for the individual terms over the total number of citations generated from the three terms. (**B**) The overall mean + SEM of these citation percentages as collapsed over the entire survey period for estrogen (E), testosterone (T), and the combination of estrogen AND testosterone (E+T). Superscript letters indicate statistically significant differences among the percents obtained for each of the terms.

significantly larger than that for estrogen within females (Fig. 8B).

Conclusions

The survey presented in this report relates some interesting information and implications regarding gender differences, sex differences, and gonadal steroid hormones. Across all the surveys performed, a very small number of citations were associated with the combination of terms estrogen and testosterone. This was particularly apparent for the survey conducted using just the terms estrogen, testosterone, and estrogen AND testosterone (Figs. 1 and 2), where only 3.6% of the citations involved the combination of terms estrogen AND testosterone. Similarly, when estrogen AND testosterone were combined within searches of gender and sex differences (Figs. 5 and 6) or conducted separately within males or females (Figs. 7 and 8), the citation percentage never exceeded 14%. These extremely low percentages reveal that investigators examining the general effects of gonadal steroids seem to focus on either estrogen or testosterone with little attention directed toward a potential interaction of estrogen and testosterone. From these results it would appear that only a diminutive concern exists regarding the possibility that differential effects of estrogen and testosterone may be present, such that an effect of estrogen may be in one direction while that for testosterone in another. Because the predominantly female gonadal steroid hormones, estrogen and progesterone, are capable of producing differential effects through their positive and negative feedback actions *(2,3)*, it seems possible that differential effects between estrogen and testosterone may also exist. In fact, there are data that suggest such a possibility, as it has been reported that estrogen can diminish the degree of neurotoxicity resulting from the psychostimulant, methamphetamine *(4)*, while testosterone increases these neurotoxicity responses *(5)*. In this way, the gender differences in neurotoxicity to methamphetamine *(6)* may result from a combination of decreased neurotoxicity due to relatively greater concentrations of estrogen in females and increased neurotoxicity due to relatively greater concentrations of testosterone in males. Such findings raise the question as to whether other paradigms in which gender differences are observed may result from an interaction or differential effects of actions from estrogen and testosterone.

As one approach to assess whether the terms gender differences may be primarily associated with clinical/human

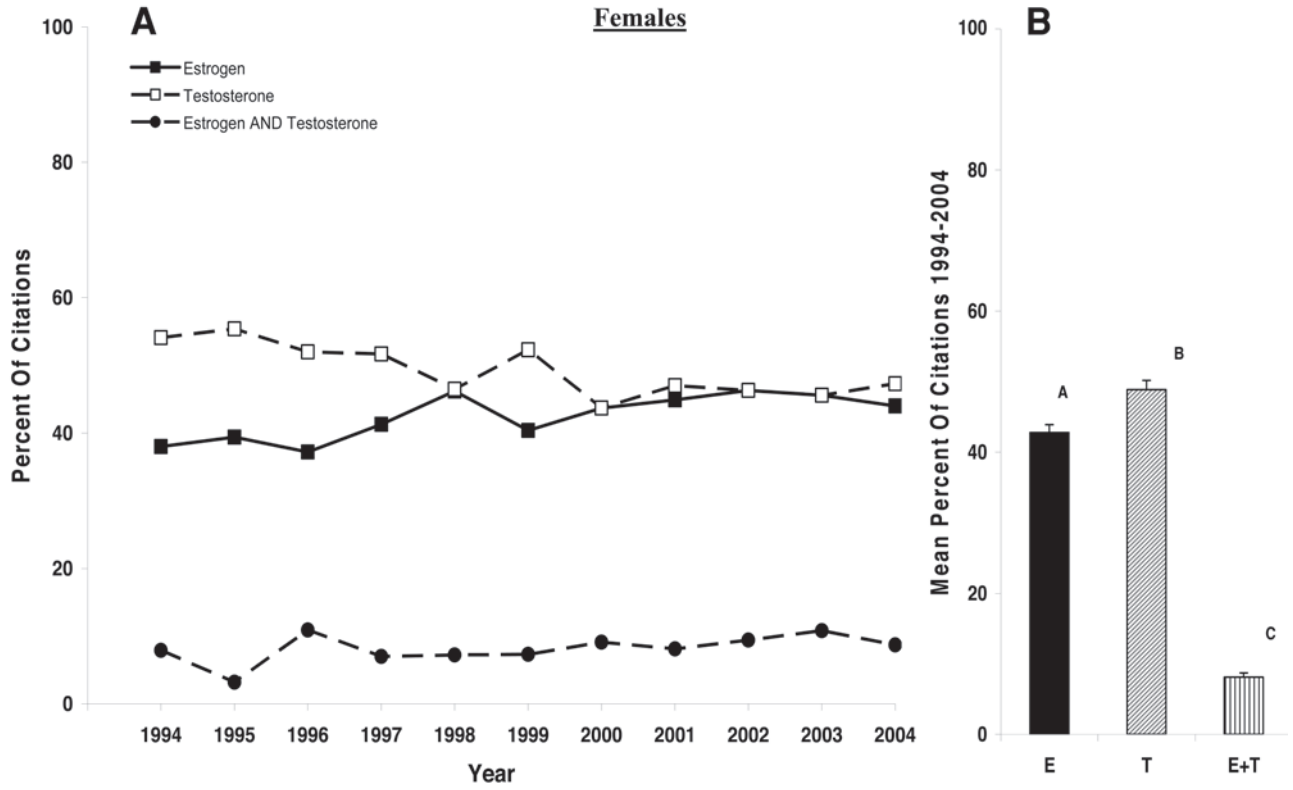

Fig. 8. (**A**) The percentage of citations obtained for estrogen, testosterone, and the combination of these terms when combined with the term females over the 1994–2004 period of the survey. The values presented represent percentages resulting from the number of citations for the individual terms over the total number of citations generated from the three terms. (**B**) The overall mean + SEM of these citation percentages as collapsed over the entire survey period for estrogen (E), testosterone (T), and the combination of estrogen AND testosterone (E+T). Superscript letters indicate statistically significant differences among the percents obtained for each of the terms.

reports, while that of sex differences with laboratory/animal studies *(1)*, the terms gender and sex differences were searched with either the terms human or animal. As shown in Fig. 4, there does appear to be a clear predominance for the term gender differences to be associated with the term human. No such salient distinction was present with regard to the relationship between sex differences as associated with the terms human or animal. Nearly identical numbers of citations were obtained when the term sex differences was combined with either human or animal. Taken together, these data suggest that use of the term gender differences may be more closely related with clinical/human studies. In contrast, the term sex differences was equally likely to be related with human or animal studies.

A major difference, in fact a complete reversal, in the relationship of citations between estrogen and testosterone for gender versus sex differences was obtained in this survey (Figs. 5 and 6). When considering the differences between gender versus sex differences, the percentage of estrogen citations decreased from 50.5% to 35.7%, while that for testosterone increased from 35.9% to 51.6% (Fig. 5B and 6B). It should be pointed out that such a relationship pertains to the overall collapsed results obtained over the 1994–2004 period. When examining the yearly profile for estrogen within the sex differences category, the estrogen citation percentages are clearly rising in the latter years of the survey and surpass that of testosterone in the last year (Fig. 6A). This change in emphasis from testosterone to estrogen within sex differences is highlighted when considering the results from the first 3 yr of the survey (1994–1996), where the mean percentage of testosterone citations was 59.3% and estrogen 30.2%, versus the last 3 yr of the survey (2002–2004), where the mean percentage of testosterone citations now decreased to 45.9% while estrogen increased to 41.6%. Therefore, while the current data generated from the past decade show that investigators working under the rubric of sex differences appear more interested in the influence of testosterone, the prevalence of testosterone is clearly declining of late and may not be maintained in the future.

When these searches were performed discriminately for males or females (Figs. 7 and 8), the number of citations for the combination of the terms estrogen AND testosterone was, again, very low and similar to that observed in previous searches. A somewhat surprising outcome of these sex-specific searches was the slightly, but significantly, larger

percentage of citations for testosterone (49%) versus estrogen (43%) within females (Fig. 8B). Within males, the percentage of testosterone citations were also significantly larger than that of the estrogen citations. However, unlike that of the females, the differences between the testosterone and estrogen citations within males were clearly defined (63% versus 28%, respectively, Fig. 7B). The larger percentage for testosterone citations in these separate male and female searches (Figs. 7 and 8) is similar to that of the greater testosterone citations obtained when testosterone and estrogen were searched within the category of sex differences (Fig. 6), but markedly different from that obtained within the category of gender differences (Fig. 5). Because there were (1) overall larger numbers (Fig. 1) and percentages (Fig. 2) of citations for estrogen, (2) more citations for gender versus sex differences (Fig. 3), (3) an indication that gender differences are more likely to be associated with clinical/human studies (Fig. 4), and (4) larger percentages of estrogen citations when examined within gender differences, it seems that there exists an increased emphasis upon clinical/human studies involved with estrogen. One possible explanation could be that estrogen represents a more generalized term, thereby generating more hits in such a survey. In this way, a comparison between the terms estrogen and the more general term related to testosterone, androgen, may alter the outcome of the survey. To mitigate against this possibility, the term androgen was substituted for testosterone within the survey results of Fig. 2. Such a substitution resulted in even fewer citations, with the overall citation percentage being 27.2% for androgen versus 33.2% for testosterone. Moreover, at no individual year of the survey did the number of citations for androgen exceed testosterone. Because estrogen is more closely related to clinical conditions (menopause) and syndromes (pre-menstrual syndrome) as well as pathology (breast cancer), the increased amount of attention to this gonadal steroid within clinical studies seems understandable. Moreover, an increased awareness of women's health issues and controversies regarding estrogen use in hormone replacement therapy would also contribute to a relatively greater concentration of work involving estrogen. In contrast, the greater incidence of testosterone citations within sex differences studies (Fig. 6) and under conditions when examined separately within males (Fig. 7) or females (Fig. 8) would suggest that these may represent studies more likely involving research with animal/laboratory paradigms. Since investigators working in the area of sex differences in laboratory/animal models may be more sensitive to the critical organizational effects exerted by testosterone, and/or its aromatization to estrogen *(7)*, a greater amount of attention may be directed toward testosterone in these studies.

The temporal divergence in citations between gender and sex differences (Fig. 3) are also quite engrossing. In 1994 there was only a slight difference in citation numbers between gender (303) and sex (282) differences for a gender/sex difference ratio of 1.07. In 2004, this difference was rather striking resulting in a gender (689)/sex (494) difference ratio of 1.40. A similar temporal divergence was present for number of citations between estrogen and testosterone (Fig. 1) with the 1994 estrogen (2282)/testosterone (1550) ratio of 1.47 climbing to 2.24 in 2004 (estrogen-3964/testosterone-1767). Whether or not the increase in gender differences citation numbers may be related to the increase in estrogen citations over the sampling period cannot be established from the present data, but remains an intriguing possibility.

Summary

The present results provide some interesting information on gender differences, its relationship with gonadal steroid hormones, sex differences, and some perspective on the defining characteristics of gender differences. The data from these surveys suggest that the term gender differences is more closely associated with clinical/human studies (Fig. 4), and there appears to be an increasing amount of clinical/human related work being performed as indicated by the greater rise in gender differences versus sex differences citation numbers (Fig. 3). Because there also exists a corresponding greater rise in estrogen versus testosterone citations (Fig. 1) and the overall percentage of estrogen citations, either listed alone (Fig. 2) or in combination with gender differences (Fig. 5), is greater than testosterone, it would appear that these increased number of clinical reports would be allied with estrogen indicating an increased emphasis on women's health-related issues. These clinical/human related findings (gender differences) may differ from laboratory/animal studies as defined by the term sex differences (Fig. 6) and/or when studies are isolated within males (Fig. 7) or females (Fig. 8), where an overall greater emphasis was directed to testosterone. However, this trend has been shifting from testosterone to estrogen over the latter years of the survey. The potential for differential interactive effects between estrogen and testosterone seems largely ignored within research performed in these areas.

Procedure

As one means to address the questions posed in this article, the number of citations obtained from a Medline search conducted from 1994 to 2004 was performed using the terms estrogen, testosterone, and estrogen AND testosterone. These terms were initially searched separately, searched following combinations with gender differences or sex differences, and also searched separately within males or females. In addition, the terms gender differences and sex differences were searched individually as well as when combined with the terms human or animal. Such an analysis provides a per-

spective on the extent to which each of these gonadal steroid hormones as well as their combination may be considered when evaluating gender or sex differences as well as the extent to which the terms gender and sex differences may be associated with either human or animal studies.

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