Longitudinal Influence of Age, Menopause, Hormone Replacement Therapy, and Other Medications on Parotid Flow Rates in Healthy Women

Elisa M. Ghezzi,1 Leslie A. Wagner-Lange,2 M. Anthony Schork,2 E. Jeffrey Metter,3 Bruce J. Baum,4 Charles F. Streckfus,5 and Jonathan A. Ship1

University of Michigan 1School of Dentistry and 2School of Public Health, Ann Arbor, Michigan.
3National Institute on Aging, National Institutes of Health, Gerontology Research Center, Baltimore, Maryland.
4National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, Maryland.
5University of Mississippi School of Dentistry, Jackson, Mississippi.

Background. Recent investigations have demonstrated that parotid salivary dysfunction is not a normal process of aging, but may be the consequence of systemic conditions and their treatment, including medications and menopause. The purpose of this study was to assess longitudinally the influence of age, menopausal status, hormone replacement therapy, and other medications on stimulated parotid flow rates (SPFR) in healthy women.

Methods. Medical diagnoses, menopausal status, medication utilization, and 2% citric acid stimulated parotid salivas were collected from 396 women, aged 21 to 96 years, from the Baltimore Longitudinal Study of Aging (National Institute on Aging, National Institutes of Health) over a 17-year span by three investigators.

Results. There was no overall longitudinal effect of time on SPFR. Age at first visit was a significant predictor of a decrease in SPFR when adjusted for time and xerostomic medications. However, the deleterious effect of taking one xerostomic medication was equivalent to approximately 14 years of aging. Menopausal status and hormone replacement therapy were not consistently associated with diminished SPFR.

Conclusions. These results suggest that menopause and hormone replacement therapy are not associated with parotid salivary dysfunction. Aging may have a statistically significant yet small deleterious influence on SPFR; however, the adverse influence of xerostomic medications is much larger.

Saliva plays a critical role in the maintenance of oral health. It is uniquely designed to aid in lubrication, mucosal protection, soft tissue repair, microbial control, alimentation, digestion, remineralization of teeth, and maintenance of pH in the oral cavity (1). A decrease in salivary output can lead to detrimental oral effects, including dental caries, oral mucosal infections, sensory disturbances, speech dysfunction, decreased nutritional intake, and difficulty in mastication, deglutition, and denture retention (2,3).

Salivary gland dysfunction was once thought to be a normal sequela of aging. However, researchers have found, in general, that parotid gland flow rates are age stable in healthy adults in cross-sectional (4—10) and longitudinal (11,12) studies. In addition, cross-sectional and longitudinal analyses of parotid saliva constituents demonstrate no overall differences between healthy young and older adults (13). Therefore salivary gland dysfunction is not considered a normal process of aging.

More recent research has attributed a decrease in salivary flow in the geriatric population to the effects of local and systemic diseases, immunologic disorders, head and neck radiation, chemotherapy, and multiple prescription and nonprescription medications (1,3,13,14). Of the most commonly prescribed medications in 1992, 80% were reported to cause xerostomia (15), with over 250 medications causing a side effect of salivary gland dysfunction (16,17). The intake of prescription medications increases with age, with greater than 68%—78% of persons over the age of 65 years taking at least one prescription medication (18,19). With the increased intake of prescription medications, many of which cause salivary gland dysfunction, the prevalence of medication-induced xerostomia is greater among the elderly (20).

It has also been speculated that menopause may cause salivary gland dysfunction and that salivary dysfunction may be the cause of a variety of oral problems commonly experienced in menopausal women (21—24). Menopause is defined as the cessation of menses for at least 6 months as a consequence of a decline in ovarian function by natural or surgical means (25,26). The average age of onset of menopause in the United States is 50 years. Hormonal changes include a decrease in estrogen production and the absence of progesterone. Menopause may be accompanied by acute symptoms of vasomotor instability, vaginal dryness and pruritis, and psychological disturbances as well as the chronic sequelae of postmenopausal osteoporosis (26). Complaints of oral discomfort and burning mouth have been reported as oral symptoms of menopause (23,24), and these have been attributed to salivary gland dysfunction. Salivary gland dysfunction in postmenopausal women has been reported (21,22), and one investigation found lower stimulated whole
salivary flow rates in postmenopausal women compared with perimenopausal women (27). However, others have found that, among healthy women, salivary gland function is not significantly influenced by menopause (7,28).

To relieve menopausal symptoms and sequelae, many postmenopausal women receive hormone replacement therapy (HRT) (29). HRT has been found to be efficacious in the prevention and treatment of osteoporosis, vaginal bleeding and dryness, and mood alterations (26). Approximately 32% of postmenopausal women are on HRT, with 26% taking estrogen alone, and the remaining 6% are on a combination formulation of estrogen and progesterone (30,31).

Because some postmenopausal women complain of a burning mouth and oral discomfort, it has been suggested that topical and systemic hormones may be of some benefit. However, there is no consensus on the efficacy of HRT for oral problems. A topical application of estrogen to buccal mucosal tissues was not found to improve oral symptoms significantly nor increase salivary flow rates (32). Alternatively, systemic ingestion of HRT has been shown to be beneficial for relief of postmenopausal oral discomfort (23,33,34). Some longitudinal studies reported that estrogen intake produced increases in salivary flow rates (27,35), whereas other cross-sectional studies demonstrated that menopausal status and estrogen intake did not have an effect on parotid flow rates in healthy women (7,28). In summary, the results of previous studies investigating the effects of menopause and HRT on oral discomfort and salivary flow rates are conflicting and inconclusive.

Therefore the purpose of this study was to assess longitudinally the influence of age, menopausal status, HRT, and other medications on parotid flow rates in healthy women.

METHODS

Subjects

Three hundred ninety-six women between the ages of 21 and 96 years (Table 1) were examined as participants of the oral physiology component (36) of the Baltimore Longitudinal Study of Aging (BLSA), Gerontology Research Center (National Institute on Aging [NIA] and National Institutes of Health [NIH]) (37). The study was approved by the John Hopkins Bayview Medical Center Institutional Review Board (IRB) and the National Institute of Dental and Craniofacial Research (NIH) IRB. Written informed consent was obtained from all subjects. All study subjects were healthy (American Society of Anesthesiologists I or II [38]), Caucasian, community-dwelling individuals who returned to the BLSA every 2–3 years, allowing for cross-sectional and longitudinal data collection. Subjects with a history of Sjögren’s syndrome, head and neck radiation for cancer, salivary gland neoplasm, or any disease known to cause salivary gland dysfunction were excluded from the study (2,3); however, none were identified with these conditions. Current and regular medication intake information was obtained at every subject visit (39), and medications were categorized as prescription (P) or nonprescription (NP) and xerostomic (X) or nonxerostomic (NX), according to accepted criteria (16,17,40). For each subject, medications were placed into the following categories as appropriate: total medications (Total Meds); total P medications (P-Total) or total NP medications (NP-Total); total X medications (X-Total) or total NX medications (NX-Total); xerostomic–prescription medications (X-P), xerostomic–nonprescription medications (X-NP), nonxerostomic–prescription medications (NX-P), or nonxerostomic–nonprescription medications (NX-NP). Medications that have been associated with salivary dysfunction (anticholinergics, antidepressants, antihistamines, antihypertensives, anti-Parkinsonians, antipsychotics, diuretics, and tranquilizers) are referred to as X drugs in this paper.

Menopausal status for each subject was determined as premenopausal (report of regular menses for 3 months or more before the visit), perimenopausal (report of menses in the 12 months before the visit, but with a period of amenorrhea and/or changes in regularity or flow), or postmenopausal (report of no menses in the 12 months before the visit or surgical removal of the ovaries). Seven subjects (10 visits) did not have menopausal status ascertained at any of their visits; therefore they were used only in time, age, and medication category analyses (Table 1). Intake of estrogen and progesterone HRT at the time of the visit was recorded for each subject. Blood specimens for assaying estrogen and progesterone levels were not available for this study. Standardized medical examinations were performed by a physician, trained nurse practitioner, or physician assistant (39).

Salivary Collection Procedures

All subjects refrained from eating, drinking, smoking, and oral hygiene for a minimum of 90 minutes before saliva collection. Saliva was collected from one parotid gland with a Carlson–Crittenden cup, as described previously (4). Salivary flow was stimulated with the application of 2% citric acid to the dorsal surface of the tongue every 30 seconds for 2 minutes be-

<table>
<thead>
<tr>
<th>Menopausal Status*</th>
<th>Number of Visits</th>
<th>Number of Subjects</th>
<th>Number of Longitudinal Subjects</th>
<th>ERT nt (%)</th>
<th>PRT nt (%)</th>
<th>ERT and PRT nt (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal</td>
<td>143</td>
<td>120</td>
<td>23</td>
<td>2 (1.7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Perimenopausal</td>
<td>86</td>
<td>54</td>
<td>23</td>
<td>16 (30%)</td>
<td>13 (24%)</td>
<td>13 (24%)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>271</td>
<td>215</td>
<td>45</td>
<td>78 (36%)</td>
<td>18 (8.4%)</td>
<td>17 (7.9%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10</td>
<td>7</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>510</td>
<td>396</td>
<td>94</td>
<td>96 (25%)</td>
<td>31 (8.0%)</td>
<td>30 (7.7%)</td>
</tr>
</tbody>
</table>

Notes: ERT = estrogen replacement therapy, PRT = progesterone replacement therapy.
*See Methods section for definitions.
†Number of subject visits.
fore collection, then stimulated at 30-second intervals during saliva collection for 2 minutes. Following collection, the salivary volume was determined gravimetrically. Stimulated parotid flow rates (SPFRs) are reported in units of milliliters per minute per gland. Cross-sectional and longitudinal parotid flow measurements reported in this study were collected over a 17-year span by three dentists in the oral physiology component of the BLSA (first investigator, 1978 to 1981; second investigator, 1989 to 1992; third investigator, 1992 to 1995).

Statistical Analyses

Usual descriptive statistics including means and standard deviations (SDs) were computed for SPFRs. Investigations of the distributions of the parotid values overall and by investigator subgroup were completed to assess requisite assumptions, including normality and equal variation. Original SPFR values were found to not follow a normal distribution, and therefore the square roots of the SPFR values were used in all statistical analyses reported in this paper, as this transformation was found to correct adequately for the nonnormality (41). Because of the longitudinal character of this study and because the same subject may have been seen by more than one investigator, correlation among the SPFR values may exist. Therefore all statistical analyses utilized procedures for correlated data (mixed model). Prospective calibration of the three investigators was not possible because the investigators participated in the study at different times over the 17-year duration of the study. Statistically significant differences in mean square-root SPFR values between investigators were observed (analysis of variance [ANOVA]; \( p < .0001 \)). Because of these investigator differences, the individual effects of age, menopausal status, and xerostomic medications on SPFR were initially assessed by each investigator (Figures 1–3).

All subsequent analyses adjusted for these investigator effects by standardizing the square-root SPFR. This standardization was effected by subtracting the mean and then dividing by the SD of the square root of the SPFRs of each investigator's measurements separately. This process thus made the measurements for each investigator have a mean of 0 and a SD of 1. As a result of this transformation, investigator measurement differences were not statistically significant (ANOVA, \( p = 1.0 \)). The skewness and kurtosis values were indicative of nonnormality before the square-root transformation (skewness, 1.48; kurtosis, 2.61), but were adequately corrected with this transformation (skewness, 0.46; kurtosis, 0.10) and remained consistent following standardization (skewness, 0.24; kurtosis, 0.70). Be-

Figure 1. The effect of aging and investigator on SPFRs: investigator 1, \( n = 155 \), mean = 0.8089, \( SD = 0.4747, r = -0.1583, p > .05 \); investigator 2, \( n = 126 \) (three subjects with two visits), mean = 0.4498, \( SD = 0.2997, r = -0.0969, p > .05 \); investigator 3, \( n = 226 \), mean = 0.3265, \( SD = 0.2423, r = -0.1429, p < .025 \). The linear regressions were determined from individual SPFR values.
cause of the effect of the square-root transformation and investigator standardization, the SPFR values used in the analysis do not represent actual values (in milliliters per minutes), and therefore are not provided in this paper. Rather, the values reported (Tables 2 and 3) represent the relative contribution of each independent variable (e.g., menopausal status, medications) compared with the influence of age (adjusted for time and X medications) on changes in the transformed and standardized SPFR. In the remainder of this paper when the term SPFR is used, it refers to the transformed and standardized SPFR unless otherwise stated.

The mixed-model analysis of covariance (PROC MIXED, release 6.11 of the SAS System, Cary, NC) in which time was used as a repeated measure was utilized to determine longitudinal effects on SPFR. Time was defined as the number of years between visits for individual subjects with longitudinal data (time = 0 for all subjects with only cross-sectional data). Using time as a covariate permitted assessment of the presence of both cross-sectional and longitudinal effects in the model as well as accounted for differences in the amount of time between visits among longitudinal subjects. In summary, the outcome was investigators’ standardized square root of the SPFR at each examination. All analyses accounted for time (by use of the length of time [years] between visits) and age (years) at the first visit as predictors in each model. Other predictors for the various analytic approaches at each visit included menopausal status, use of estrogen replacement therapy (ERT), use of progesterone replacement therapy (PRT), and medication intake.

All data were analyzed together in a series of models. Next, the subjects were divided into subgroups defined by menopausal status (premenopausal, perimenopausal, postmenopausal), and analyzed with the same modeling approach as that outlined above. To maintain the longitudinal analysis, subjects were placed into exclusive groups. The premenopausal category included those subjects with one visit who were premenopausal or those with multiple visits who were always premenopausal. Likewise, the postmenopausal category was defined as those subjects with one visit who were postmenopausal or those with multiple visits who were always postmenopausal. The perimenopausal category contained those subjects with one visit who were perimenopausal or those with multiple visits whose menopausal status varied from premenopausal, perimenopausal, and postmenopausal from visit to visit, thereby denoting a change in menopausal status. Finally, subjects were classified into decades of life by the age at the first visit as an additional method to assess the data longitudinally and then were evaluated in similar models. Each decade of life group spanned 10 years, with the last category containing subjects aged 80 years and above. Two covariates were included in these mixed models (length of follow-up [time] and age at first visit) because subjects were followed over time, and to account for variation in age at initial visit within each category (e.g., menopausal status, decade of life).

Last, a mixed model longitudinal analysis was performed solely on the women whose menopausal status changed during the course of the study (i.e., the longitudinal women in the perimenopausal group as defined above). A criterion of \( p < .05 \) was accepted for significance in all statistical tests.
RESULTS

A total of 510 subject visits was recorded from the 396 female participants in the study. The mean age of the subjects at the first visit was 54 ± 16.8 years (mean ± SD, range 21–96). Longitudinal data were collected on the 94 subjects who were examined at more than one visit. The mean length between visits for these subjects was 9.1 ± 3.6 (range 2–15 years).

A statistical analysis of investigator differences in the mean of the untransformed, unstandardized SPFR values was completed. Statistically significant ($p < .0001$) differences among investigators were found. Therefore the analyses to assess the effect of age, menopausal status, and intake of X medications were calculated by investigator. The SPFR slightly decreased with age, but significantly for only investigator 3 ($p < .025$, Figure 1), and there was no significant ($p = .4$) interaction between investigator and age. Premenopausal, perimenopausal, and postmenopausal women had similar SPFRs for investigators 1 and 2 ($p > .05$) and decreased slightly for investigator 3 ($p < .01$, Figure 2). An analysis of X medication intake (categorized as an intake of no or at least one X medication at time of visit) demonstrated lower SPFRs for subjects taking at least one X medication, but significant for only investigator 1 ($p < .01$, Figure 3).

Because of the parotid flow rate differences by investigator and the nonnormal distributions of these values, transformation (square-root) and standardization (to account for differences by investigator) procedures were completed as described in the Methods section. All subsequent analyses use these transformed and standardized flow rates.

A comparison of the cross-sectional (baseline data only) and longitudinal (baseline and at least one follow-up visit) cohorts was performed, and several statistically significant differences were observed between these two cohorts for the transformed and standardized SPFRs. The longitudinal cohort was younger (50 ± 15.7 years) than the cross-sectional cohort (56 ± 17.1, $p = .002$). Consistent with being an overall younger sample, the longitudinal cohort took fewer X medications (0.17 ± 0.52) than the cross-sectional cohort (0.32 ± 0.67, $p = .02$), was more likely to have a premenopausal status (longitudinal cohort 48%, cross-sectional cohort 32%, $p = .02$), and was less likely to be on ERT (longitudinal cohort 10%, cross-sectional cohort 23%, $p = .007$) and PRT (longitudinal cohort 1%, cross-sectional cohort 6%, $p = .05$).

The next analyses examined the longitudinal effect of time on SPFR of all subjects in the mixed model, and time was not found to be significant when adjusted for age at first visit (Table 2). Thus, for subjects with multiple visits, there was no statistically significant longitudinal change in salivary flow rates over time. Time was included in all subsequent models to assess possible longitudinal effects on SPFR in light of the extended length of time among visits for some women. X-Total medications were included in all subsequent models to detect potential deleterious medication effects on SPFR (2,3,13,16,17,40). Next, the effect of age on SPFR at first visit was evaluated and found
to be statistically significant when adjusted for time and X-Total medications (Table 2). Based on these analyses, time, age at first visit, and X-Total medications would always be used as covariates (the standard reference) for all subsequent analyses.

A series of three mixed-model ANOVAs was generated in which time, age at first visit, and then the effect of each of the predictors containing X medications (X-P, X-NP, X-Total) were considered separately to assess their effect on SPFR. A series of eight mixed-model ANOVAs was generated in which time, age at first visit, X-Total medications, and then the effect of each of the predictors (6–13 listed in Table 2) were considered separately to assess their effect on SPFR. Neither ERT nor PRT significantly influenced SPFR. In the medication intake analysis, X-P and X-Total approached significance as predictors of decreased SPFR (Table 2). When compared with the reference value (age at first visit adjusted for time and X-Total), the deleterious effect on SPFR that was due to the intake of these medications was equivalent to 13 or 14 years of aging (Table 2).

Each of these models described was initially performed with an interaction term between age at first visit and the individual predictor. Then each of the models was run with an interaction term between time and the individual predictor. There were no changes in main effect $p$ values that affected statistical significance, nor were any of the interaction terms found to be significant.

After adjustments were made for time and X-Total, both age at first visit and menopausal status were found separately to be statistically significant predictors of decreased SPFR. Menopausal status is directly associated with age, and therefore they are highly correlated. The strength of this multicollinearity was verified in a mixed model with age at the visit as the outcome and menopausal status as the predictor, which resulted in a statistically significant ANOVA ($p < .0001$). Because of this strong correlation between age at visit and menopausal status, subsequent analyses were performed to investigate further the effect of this relationship and the individual effects of these two predictors.

Subjects were placed into three categories: premenopausal, perimenopausal, and postmenopausal while the longitudinal framework was maintained (see Methods section). Time, age at first visit, and X-Total medications were initially analyzed together in a mixed model. Then a series of two mixed-model ANOVAs was generated in which time, age at first visit, and then the effect of each of the predictors (4 and 5 listed in Table 2) were considered separately to assess their effect on SPFR. Next, a series of eight mixed model ANOVAs was generated in which time, age at first visit, X-Total medications, and then the effect of each of the predictors (6–13 listed in Table 2) were considered separately to assess their effect on SPFR. The results of these ANOVAs revealed that age at first visit, ERT, PRT, and all medication categories did not significantly influence salivary flow in any of the three menopausal categories (data not shown).

Subjects were also divided into seven decades of life groups

### Table 2. Results from All-Female-Subjects Analysis; Predictors for Change in SPFRs (Repeated Measures Mixed-Model ANOVA)

<table>
<thead>
<tr>
<th>Predictor/Variable</th>
<th>$p$ value*</th>
<th>Effect on SPFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Time*</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>2. Age at First Visit†</td>
<td>.004</td>
<td>−1§</td>
</tr>
<tr>
<td>3. X-Total Medications†</td>
<td>.067</td>
<td>−13¶</td>
</tr>
<tr>
<td>4. X-P Medications †</td>
<td>.085</td>
<td>−14¶</td>
</tr>
<tr>
<td>5. X-NP Medications †</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>6. Estrogen Replacement Therapy#</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>7. Progesterone Replacement Therapy#</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>8. NX-P Medications#</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>9. NX-NP Medications#</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>10. NX-Total Medications#</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>11. P-Total Medications#</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>12. NP-Total Medications#</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>13. Total Medications#</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Notes: X = xerostomic medication, NX = nonxerostomic medication, P = prescription medication, NP = nonprescription medication.

* Only $p$ values < .1 displayed.
† Adjusted for age at first visit.
‡ Adjusted for time and X-Total medications.
§ Decrease in SPFR: relative effect of 1 year of aging (see the subsection on Statistical Analysis in the Methods section for description).
¶ Each variable analyzed separately and adjusted for time and age at first visit.

### Table 3. Decades of Life Categories

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number of Visits</th>
<th>Number of Subjects</th>
<th>Number of Subjects with 1 Visit</th>
<th>Number of Subjects with &gt; 1 Visit</th>
<th>Variable* Analyses†</th>
</tr>
</thead>
<tbody>
<tr>
<td>21–29</td>
<td>43</td>
<td>35</td>
<td>27</td>
<td>8</td>
<td>Time (−)</td>
</tr>
<tr>
<td>30–39</td>
<td>73</td>
<td>49</td>
<td>28</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>106</td>
<td>83</td>
<td>66</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>81</td>
<td>64</td>
<td>51</td>
<td>13</td>
<td>NX-P (+); NX-Total (+); P-Total (+); Total Meds (+)</td>
</tr>
<tr>
<td>60–69</td>
<td>113</td>
<td>83</td>
<td>59</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>64</td>
<td>54</td>
<td>45</td>
<td>9</td>
<td>NX-P (−); P-Total (−)</td>
</tr>
<tr>
<td>80–96</td>
<td>30</td>
<td>28</td>
<td>26</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>510</td>
<td>396</td>
<td>302</td>
<td>94</td>
<td></td>
</tr>
</tbody>
</table>

* Each variable analyzed separately and adjusted: time adjusted for age at first visit and X-Total medications; menopause adjusted for time and X-Total medications; X-Total, X-P, X-NP adjusted for time and age at first visit; estrogen replacement therapy, progesterone replacement therapy, NX-P, NX-NP, NX-Total, P-Total, NP-Total, and Total medications adjusted for time, age at first visit, and X-Total medications.
† $p$ values ≤ .05: (−) decrease in SPFR; (+) increase in SPFR.
based on their age at the first visit in order to maintain the longitudinal analysis in each age group (Table 3). Time, age at first visit, and X-Total medications were initially analyzed together in a mixed model. Then menopausal status, time, and X-Total medications were analyzed together in a mixed model. Next, a series of two mixed-model ANOVAs was generated in which time, age at first visit, and then the effect of each of the predictors (4 and 5 listed in Table 2) were considered separately to assess their effect on SPFR. A series of eight mixed model ANOVAs was then generated in which time, age at first visit, X-Total medications, and the effect of each of the predictors (6–13 listed in Table 2) were considered separately to assess their effect on SPFR. Finally, the results of these ANOVAs revealed that menopause, ERT, and PRT did not significantly influence salivary flow in any of the seven decades of life categories. Only in the fourth decade was time found to be a significant predictor of a decrease in salivary flow. Medication intake was not a significant predictor until the sixth decade of life. Intake of NX-P medications (p = .01), NX-Total medications (p = .04), P-Total medications (p = .01), and Total Meds (p = .04) were significant indicators of an increase in SPFR. In contrast, in the eighth decade, intake of NX-P medications (p = .02), and P-Total medications (p = .02) were significant predictors of a decrease in SPFR (Table 3).

Finally, an analysis was performed in which the longitudinal data of only perimenopausal women were used. At baseline 18 women were premenopausal and 37 were perimenopausal. When time, menopausal status at each visit, and X-Total were placed in the model, there were no statistically significant predictors of decreased SPFR.

DISCUSSION

SPFRs were examined cross-sectionally by three individual investigators to determine the effect of age, menopausal status, and intake of X medications. These results demonstrated that age caused a slight but inconsistent decrease in SPFR over time, and menopause did not appear to have a consistent adverse effect on flow rates. The decrease in SPFR caused by X medications was small, most likely attributable to the overall good health of the population and a low intake of X medications (a mean intake of 0.3 ± 0.6 X medications in the cross-sectional cohort). The longitudinal analysis of the SPFR revealed similar results. Age, menopause, and some medication categories were significant predictors of decreased SPFR, whereas HRT did not affect SPFR.

With the mixed model ANOVA, cross-sectional and longitudinal data were analyzed together. Time, a possible marker for longitudinal changes in SPFR, was not found to be a significant predictor of a change in SPFR in all analyses, except in the fourth decade of life (Table 3). These findings are also consistent with previous cross-sectional and longitudinal studies, demonstrating the age stability of parotid flow rates (4,6–12). However, age was a significant predictor of decrease in SPFR even when adjusted for time and X-Total. The pattern of age trends, however, was not consistent, and changes were low in magnitude. The changes in SPFR were small across the 75-year span examined in this study (mean = −0.1% per year for investigator 1, mean = −0.4% per year for investigator 2, mean = +0.1% per year for investigator 3), and well within the normal variance of SPFR (42). When compared with the effect of X medication intake, the decrease in SPFR by age is relatively small (Table 2). It is possible that the large sample size and the long age span of individuals investigated in this study were factors that contributed to a slight yet significant age-related change that may be consistent with histomorphometric and tomographic results (43,44; see below). Nevertheless, it is not clear at this time why there is a discrepancy between the time and the age results of this present investigation.

Statistically significant differences were observed among the three investigators for SPFR, despite the use of similar collection techniques (4). As described in the preceding section, prospective calibration of the three investigators over the 17-year span of the study was not possible, and the results are based on a retrospective analysis. However, cross-sectional and longitudinal evaluations by each investigator yielded similar trends based upon decade of life (Figure 1), menopausal status (Figure 2), and use of X medications (Figure 3). Although there is no clear explanation for investigator differences, the overall results and general conclusions based on cross-sectional and longitudinal data do not appear to be affected.

Histomorphometric (43) and tomographic (44) investigations utilizing parotid gland tissues showed a decrease in acinar (fluid-producing) cells with an increase in fat cells with increased age. Several of the small yet statistically significant age results (in contrast to the nonsignificant time results) in the present investigation may reflect these histomorphometric and clinical findings (e.g., 45). The average decrease in SPFR for the three investigators across the 75 years was 7.5%, which is still smaller than the 33% loss in acinar cells reported by Scott et al. (43). It has been hypothesized that a secretory reserve exists to account for the loss of cells in normal aging (43,45). However, if a secretory reserve exists, as the number of reserve cells decreases with age, it is possible that the adverse effects of drugs on salivary output will become more pronounced. This loss of reserve cells could account for the decrease in salivary flow observed in women taking medications in the eighth decade of life. The secretory reserve hypothesis has been previously examined by increasing salivary output in young and old healthy subjects over an extended period of time, but the results did not definitively establish an age-related secretory reserve because of the tremendous robustness of human parotid and submandibular glands (10).

The results of the menopause status analyses in the present investigation demonstrated no consistent trends of an effect on SPFR. This is consistent with previous cross-sectional reports (7,28), whereas other investigations have suggested that menopause may have adverse effects on salivary gland function (21,22,24,27). Both menopausal status and age at the first visit separately were found to be statistically significant predictors of decreased SPFR, yet they are highly correlated variables (ANOVA; p = .0001). When subjects were categorized by their menopausal status (Table 1), there were no statistically significant predictors of a change in salivary flow in any group. Therefore it appears that menopausal status does not have an influence on change in SPFR.

Significant changes in flow rates were observed that were due to medication intake. An interesting finding was that the deleterious effect of taking one X-P medication on SPFR was 14 times greater than the effect of 1 year of aging alone (Table 2). When subjects were also grouped by decade of life at baseline examination, medication intake was not an important pre-
dictor of a decrease in salivary flow until the eighth decade, when intake in some medication categories became statistically significant. These results suggest that medication intake has a much greater adverse influence on SPFR compared with the effect of age alone, especially in older, generally healthy women (ASA I and II [38]). Indeed, the typical X medications taken by the older women in the study (antihypertensives, antidepres-
sants, antihistamines) have been suggested to cause xerostomia and salivary dysfunction (16,17,40).

In the overall analyses, there was a trend toward decreased salivary flow that was due to X medication use. However, when analyzed by menopausal status and decade of life, the X medication effect was lost and NX drugs were predictors of a change in salivary gland function. It is interesting to note that the use of NX-P medications was a predictor of an increase in SPFR in the sixth decade and a decrease in SPFR two decades later (Table 3). These variable results from the overall analyses may be attributable to the smaller sample size resulting from the decade of life categorization (Table 3) and/or the low intake of these medications by this healthy population. Subjects over the age of 65 were taking an average of 1.4 ± 1.6 prescription medications, with 38% of these women taking no prescription medications. The 62% of subjects taking prescription medications was lower than found in published population surveys (18,19).

The present cross-sectional and longitudinal findings reveal that ERT and PRT do not have an adverse influence on parotid output. These findings are in agreement with those reported by Streckfus et al. (28) and Ship et al. (7), whereas Hietala et al. (35) found that salivary flow rates increased in subjects treated with estrogen. Laine and Leimola-Virtanen (27) also demonstrated higher salivary flow rates in subjects taking HRT. These conflicting results may be attributed, in part, to the large variability found in salivary flow rates among adults (42). Because there are many forms of HRT that vary greatly in their biological activities, this can also contribute to the discrepancy of results found among these studies (27).

In the United States, approximately 32% of postmenopausal women use HRT (30,31). Because 37% (78 ERT + 1 PRT not on ERT = 79/215; Table 1) of the postmenopausal women in this study population were using some combination of HRT (ERT, PRT, or both), the subjects in this study were slightly higher than national averages in their use of HRT. Because of the self-reporting nature of the HRT data collection, it was not possible to document the frequency of intake and reliability of responses. The retrospective nature of the study’s analysis did not allow for clarification of the type of HRT preparation beyond the distinction between ERT and PRT. Furthermore, no blood samples were drawn to determine hormone blood levels. Therefore, based on these methodological weaknesses in the present study, it is not possible to establish definitively a relationship between ERT and PRT and salivary function.

Subjective complaints of a dry mouth are not uncommon in the elderly population, especially in postmenopausal women (2). The differential diagnosis for salivary gland dysfunction includes local and systemic diseases, immunologic disorders, radiation, chemotherapy, as well as multiple P and NP medications. A thorough medical history and evaluation is necessary to rule out disease or medication intake as the cause of the salivary dysfunction.

In conclusion, these results demonstrate that although menopause and HRT are not associated with parotid salivary dysfunction in healthy women, medication intake can cause a decrease in salivary flow in healthy women, especially older women. These findings may have clinical ramifications. Complaints of a dry mouth and objective signs of salivary dys-
function should not be attributed directly to menopausal status or directly to the normal aging process. Therefore xerostomia must be clinically investigated, an accurate diagnosis established, and appropriate treatment provided in order to preserve oral health.

ACKNOWLEDGMENTS

We acknowledge the assistance of the University of Michigan Faculty Training Project in Geriatric Medicine and Dentistry (DHHS, HRSA #D31-AH90005-01). In addition, we appreciate the contributions of the BLSA participants who have generously volunteered for these studies, and the staff and collaborators of the Gerontology Research Center (NIA, NIH).

Address correspondence to Dr. Jonathan A. Ship, University of Michigan School of Dentistry, 1011 N. University, Room G-004, Ann Arbor, MI 48109-1078. E-mail: jship@umich.edu

REFERENCES

21. Kullander S, Sonesson B. Studies on saliva in menstruating, pregnant and 
23. Wardrop RW, Hailes J, Burger H, Reade PC. Oral discomfort at meno-
26. Evans MP, Fleming KC, Evans JM. Hormone replacement therapy: man-
27. Laine M, Leimola-Virtanen R. Effect of hormone replacement therapy on 
salivary flow rate, buffer effect and pH in perimenopausal and post-
30. Harris RB, Laws A, Reddy VM, King A, Haskell WL. Are women using 
taking postmenopausal estrogen supplementation. J Periodontol. 1993;64: 
957–962.
32. Pisanty S, Rafaely B, Polishuk WZ. The effect of steroid hormones on 
33. Volpe A, Lucenti V, Forabosco A, et al. Oral discomfort and hormone re-
34. Forabosco A, Cresciolo M, Coukos G, et al. Efficacy of hormone replace-
ment therapy in postmenopausal women with oral discomfort. Oral Surg 
35. Hiitala E-L, Heikkinnen J, Vaananen K, Larmas M. Effect of post-
menopausal estrogen treatment on some diagnostic salivary variables. Ann 
36. Baum BJ. Characteristics of participants in the oral physiology compo-
nent of the Baltimore Longitudinal Study of Aging. Community Dent Oral 
Baltimore Longitudinal Study of Aging. Washington, DC: U.S. Govern-
ment Printing Office; 1984. NIH publication 84-2450.
38. American Society of Anesthesiologists. New classification of physical sta-
tus. Anesthesiology. 1965;24:11.
Response stability and reliability in longitudinal evaluations. Aging Clin 
42. Ship JA, Fox PC. Baum BJ. How much saliva is enough?: normal func-
43. Scott J, Flower EA, Burns J. A quantitative study of histological changes 
44. Drummond JR, Newton JP, Abel RW. Tomographic measurements of age 
45. Baum BJ, Ship JA, Wu AJ. Salivary gland function and aging: a model for 
studying the interaction of aging and systemic disease. CRC Crit Rev Oral 

Received February 17, 1999
Accepted July 8, 1999
Decision Editor: William B. Ershler, MD