Changes in the central nervous system of alcohol dependent patients [ZEREBRALE VERANDERUNGEN BEI ALKOHOLABHANGIGEN]

Mann, K. , Dengler, W.

Psychiatrische Universitatsklinik, Osianderstr. 22, D-72076 Tubingen, Germany

Abstract

During the last decade, our understanding of the specific effects of alcohol on the brain has changed fundamentally. Controlled neuropathological studies found a reduction in the volume of white matter and a partial degeneration, or even a loss of specific neurons in humans. Using Magnetic Resonance Imaging and CAT-scans, the decrease in volume of white and grey matter was demonstrated in vivo. The degree and the time course of brain damage seems to be influenced more by age and gender than by drinking history. There is evidence that female alcoholics develop brain damage more readily than men. When abstinent, an increase in the volume of white and grey matter can be observed. This is not due to the rehydration of brain tissue alone. Future research will need to deal with the question of whether the central nervous system is capable of partial regeneration. For the study of neuroplasticity, the neurobiological model of alcohol dependence seems to be particularly well suited.

Author Keywords

Changes in the central nervous system of alcohol dependent patients

[ZEREBRALE VERANDERUNGEN BEI ALKOHOLABHANGIGEN]

Mann, K. , Dengler, W.

Psychiatrische Universitatsklinik, Osianderstr. 22, D-72076 Tubingen, Germany

Abstract

During the last decade, our understanding of the specific effects of alcohol on the brain has changed fundamentally. Controlled neuropathological studies found a reduction in the volume of white matter and a partial degeneration, or even a loss of specific neurons in humans. Using Magnetic Resonance Imaging and CAT-scans, the decrease in volume of white and grey matter was demonstrated in vivo. The degree and the time course of brain damage seems to be influenced more by age and gender than by drinking history. There is evidence that female alcoholics develop brain damage more readily than men. When abstinent, an increase in the volume of white and grey matter can be observed. This is not due to the rehydration of brain tissue alone. Future research will need to deal with the question of whether the central nervous system is capable of partial regeneration. For the study of neuroplasticity, the neurobiological model of alcohol dependence seems to be particularly well suited.

Author Keywords

Alcoholism: Clinical & Experimental Research

Volume 29(5), May 2005, pp 896-901

Neuroimaging of Gender Differences in Alcohol Dependence: Are Women More Vulnerable?
[Alcohol Effects on the Fetus, Brain, Liver and Other Organ Systems]

Mann, K; Ackermann, K; Croissant, B; Mundle, G; Nakovics, H; Diehl, A
From Central Institute of Mental Health (KM, KA, BC, HN, AD), University of Heidelberg, Mannheim, Germany; and Department of Psychiatry and Psychotherapy (GM), University of Tubingen, Tubingen, Germany.
Received for publication September 2, 2004; accepted February 24, 2005.
Supported by Grant BMBF 01 EB 9422 from the German Ministry of Education and Research.
Reprint requests: Karl Mann, MD, Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, University of Heidelberg, 68159 Mannheim, Germany; Fax: 49-621-1703-3505; E-mail: sucht@zi-mannheim.de

---

Outline

Graphics

Abstract

Background: Alcoholic brain damage has been demonstrated in numerous studies using neuropathology and brain imaging techniques. However, gender differences were addressed only in a few studies. Recent research has shown that development, course, and consequences of alcohol dependence may differ between female and male patients. Our investigation was built upon earlier research where we hypothesized that women develop alcoholic brain damage more readily than men do. To further compare the impact of alcohol dependence between men and women, we examined brain atrophy in female and male alcoholics by means of computed tomography (CT).

Methods: The study group consisted of a total of 158 subjects (76 women: 42 patients, 34 healthy controls; 82 age-matched men: 34 patients, 48 healthy controls). All patients had a DSM-IV and ICD-10 diagnosis of alcohol dependence. CT with digital volumetry was performed twice in patients (at the beginning and end of the 6-week inpatient treatment program) and once in controls.

Results: Patients of both genders had consumed alcohol very heavily. Although the average alcohol consumption in the year before the study was significantly lower in female alcoholics, this gender difference disappeared when controlled for weight. However, women had a significantly shorter duration of alcohol dependence. Despite this fact, both genders developed brain atrophy to a comparable extent. Brain atrophy was reversible in part after 6 weeks of treatment; it did not reach the level in the control groups.

Conclusions: Gender-specific differences in the onset of alcohol dependence were confirmed. This is in line with the telescoping effect, where a later onset and a more rapid development of dependence in women were described. Under the assumption of a gradual development of consequential organ damage, brain atrophy seems to develop faster in women. As shown in other organs (i.e., heart, muscle, liver), this may confirm a higher vulnerability to alcohol among women.

In the past, research articles concerning alcoholism referred predominantly to men dependent on alcohol. Frequently, women were not considered in published studies, or no gender-specific evaluations were conducted. Results of research were thought to be generally applicable to both genders. More recent studies argue for a separate analysis of female and male alcohol-dependent patients because epidemiological studies demonstrate sex differences in the behavior related to alcohol consumption and the course of alcohol dependence. Women typically start to drink later in life, consume less per occasion, and are, in general, less likely to develop alcohol dependence (Kessler et al., 1994). However, several studies indicate that there is a faster progression of the developmental events leading to dependence among female alcoholics (telescoping effect) and an earlier onset of adverse consequences of alcoholism (Ashley et al., 1977; Hesselbrock et al., 1985; Loft et al., 1987; Fernandez-Sola et al., 1997). These findings suggest that women may be more vulnerable to chronic alcohol consumption. Several recent studies focused on the gender-related

impairment of the central nervous system (Hommer et al., 2001; Pfefferbaum et al., 2001). Earlier studies revealed significant deficits in the brain volume of male alcoholics (Pfefferbaum et al., 1992; Jernigan et al., 1991), which confirms studies using computed tomography (CT) to report analog enlargement of intracranial CSF (cerebrospinal fluid) volume among female and male alcoholics in comparison with control subjects, despite a shorter exposure to excessive drinking in the female alcoholic subjects (Jacobson, 1986; Mann et al., 1992). Using magnetic resonance imaging, Hommer et al. (2001) demonstrated that the brain volume differences between alcoholic and nonalcoholic women were considerably larger than those found between alcoholic and nonalcoholic men, even though the female alcoholics reported fewer years of heavy drinking. However, Pfefferbaum et al. (2001) detected smaller brain volume differences between alcoholic and nonalcoholic women than between alcoholic and nonalcoholic men.

In this study, we examined alcohol-related brain atrophy by means of CT in women and men in relation to duration of alcohol dependence and average alcohol consumption of the last year. We hypothesized brain atrophy to be of the same degree in female alcoholics as in male alcoholics, despite a shorter duration of alcohol dependence in women. Provided that alcohol consumption is not higher in female alcoholics than in male alcoholics, this would be in line with results supporting a telescoping effect of alcoholism with an earlier onset of alcohol-related consequences in women.

MATERIALS AND METHODS

Subjects

The study group consisted of 76 women (42 alcoholic women, 34 healthy control women) and 82 age-matched men (34 alcoholic men, 48 healthy control men). All patients met DSM-IV and ICD-10 criteria for alcohol dependence.

All alcoholics were recruited while admitted to a 6-week inpatient treatment. Control group subjects were recruited by advertisement. Recruitment and examinations were performed within a 3-year period in the 1990s. All subjects underwent detailed clinical assessment that included demographics, medical history, and family status. The assessment of addictive behavior was carried out by means of a structured interview with proofed reliability and validity (Mann et al., 1995). We carried out physical examinations, blood tests, Beck Depression Inventory (BDI; Beck and Beamesderfer, 1974), and an assessment of verbal intelligence to determine premorbid intelligence (MWT-B; Lehrl, 1989).

Exclusion criteria for alcoholics included past or current dependence on drugs other than alcohol or nicotine, schizophrenia, bipolar or major depressive disorder, current or chronic medical or neurological illness unrelated to alcoholism, history of head injury involving loss of consciousness for more than 5 min, current medication that could affect the central nervous system, or pregnancy. For healthy controls, study exclusion criteria were the same as for alcoholics but included past or current alcohol abuse or dependence. [gamma]-Glutamyltransferase

level was determined for all healthy controls and alcoholics. Control subjects were excluded if the values exceeded the clinical norm. All subjects provided written informed consent before participation in the study, which was approved by the Institutional Review Board of the University of Tubingen, Tubingen, Germany.

Computed Tomography and Volumetry (Image Acquisition, Image Analysis)

CT scans were acquired with a Siemens Somatom DRH Head Scanner (Erlangen, Germany) at the beginning and end of the patients 6-week treatment program. Controls were scanned only once. Except for two female patients who had to be examined at day 26, the second examination took place between the 33rd and the 38th day after the first examination. Thus, all patients had 5 weeks of controlled abstinence between the scans. Median duration of abstinence at the first scan was 9 days for female and male patients. Because a few subjects had a very long duration of abstinence before admission, numerical value of the mean duration of abstinence +/- SD before the first CT examination was high (women, 20.33 +/- 28 days; men, 20.18 +/- 29.38 days).

CT scans were made parallel to the orbitomeatal line with at total of 30 to 35 slices depending on the individual. The images were acquired with a 256 x 256 matrix. A field of view of 213 resulted in a pixel size of 0.83 mm x 0.83 mm. Using very thin slices of 2 mm gives a high spatial resolution especially for the brain tissue/CSF differentiation. This allowed us to demonstrate the changes of the sulcal CSF spaces. For volumetry, we started with the first slice above the petrous bone to avoid volumetric problems due to beam hardening effects in the posterior fossa. This results in smaller volumes than reported in the literature (e.g., Pfefferbaum et al., 1997). Follow-up scans were performed identically; a digital topogram was made to secure an identical second scanning. We chose the following segmentation thresholds (all numbers in Hounsfield units): intracranial volume, -50 to +80; brain volume, +16 to +79 for the first 18 slices and then +26 to +79 until the apex. Changing the segmentation for the brain was performed to reduce the artifacts by shrinking the calotte toward the apex. Pixels between -22 and +15 Hounsfield units were defined as CSF apical of the basal cisterns, excluding the fourth ventricle if occasionally encompassed. Interrater reliability was tested with 0.99 for ventricles and 0.98 for sulcal CSF volumes (Finn coefficient; Asendorpf and Wallbott, 1979). Image analysis was done by means of digital volumetry of intracranial volume, total brain volume, and CSF volume. Volumetric evaluation was performed by a trained rater in a UNIX-environment with the commercial software Prominence (ISG Technologies, Inc., Toronto, Canada). Prominence is a semiautomated computer interactive thresholding technique to classify each pixel whether representing the specific tissue of interest that provides a three-dimensional data set for volume calculation. The ratio of brain volume over intracranial volume was calculated as the "global atrophy index." Expressing brain volume as a percentage of head volume corrects for the variation due to head size.

Statistical Analysis

The sample characteristics were analyzed by means of separate two-factor (sex

and diagnosis) analyses of variance (ANOVAs). Bonferroni adjustment for multiple comparisons was performed to test for differences in the single group comparison.

To show the impact of sex effects, diagnosis effects, and duration of alcohol dependence effects on the degree of brain atrophy, we also performed separate two-factor (sex and diagnosis; sex and duration of alcohol dependence) ANOVAs for volumetric data analysis. By means of a mean split, duration of alcohol dependence was transformed into a dichotomous variable. In addition, we wanted to show the impact of sex effects and duration of alcohol dependence effects on the reversibility of brain atrophy in alcoholics. We evaluated sex effects and time effects between first (week 1) and second (week 6) examinations with and without duration of alcohol dependence as a covariate in an ANOVA for repeated measures. We predicted main effects for sex due to anatomical differences between women and men in intracranial volume and brain volume and for diagnosis due to earlier results of alcohol-related brain atrophy (Jacobson, 1986; Mann et al., 1992). Alcoholics' intracranial volume at the beginning and end of the patients 6-week treatment program was considered as constant and served as an indicator of measurement reliability.

RESULTS

All subjects were white. Premorbid verbal intelligence (MWT-B) did not show any sex effect but did show a group effect with higher IQs in healthy controls. After Bonferroni adjustment for multiple comparisons, there was only one significant difference in premorbid intelligence between male controls and male patients (Table 1).

Table 1. ANOVA on Subjects Characteristics for Sex Effects, Diagnosis Effects (Alcoholics vs. Healthy Controls), and Single Group Comparison

---

Female alcoholics had more depressive symptoms (BDI) at admission than did male alcoholics. Alcohol consumption in the year before the study showed sex and diagnosis effects as expected. Although the average alcohol consumption was significantly lower in female alcoholics, gender differences disappeared when controlled for weight (Tables 1 and 2). The mean corpuscular volume (fl) and the mean [gamma]-glutamyltransferase level (units/l) showed a diagnosis effect as expected and did not show significant gender differences. However, elevation of the [gamma]-glutamyltransferase level was 4.5-fold in female patients versus 3.5-fold in male patients in relation to the gender-specific upper limit. The mean duration of abstinence before the first CT scan was significantly higher than the median duration of abstinence because of some outliers, but the mean and median duration of abstinence before the first CT scan were not different

for female and male patients.

Table 2. Description of Alcohol-Dependent Patients and Healthy Control Subjects (n = 158)

We found a significantly shorter duration of alcohol dependence for female alcoholics (mean, 5.55 years) than for male alcoholics (mean, 10.41 years), despite the same mean age at first CT examination.

Brain Atrophy by Means of Computed Tomography:

ANOVA for the first examination (week 1) showed significant sex effects on the intracranial volume and brain volume, with larger volumes in men (Table 3 and 4). Intracranial volume did not differ by diagnosis as expected. Brain volume, CSF volumes, and global atrophy index showed diagnosis effects, with smaller brain volume, larger CSF volumes, and lower global atrophy index (ratio of brain volume over intracranial volume) in alcoholics. Brain atrophy in alcoholics was confirmed separately in the Bonferroni-adjusted single group comparison (Table 4). Alcoholic women had significantly larger CSF volumes than did healthy control women. Alcoholic men had larger CSF volumes than did healthy control men.

Table 3. Regional Brain Volumes for Alcoholic Women, Alcoholic Men, Healthy Control Women, and Healthy Control Men

---

Table 4. ANOVA of Sex Effects, Diagnosis Effects (Alcoholics vs. Healthy Controls), and Single Group Comparison on Regional Brain Volumes in Alcoholic Women, Alcoholic Men, Healthy Control Women, and Healthy Control Men for the First Examination at Week 1

To evaluate the impact of sex effects and duration of alcohol dependence effects on brain atrophy, we performed a median split of the duration of alcohol dependence. The median was 6.5 years: 14 alcoholic women and 24 alcoholic men had a longer duration and 28 alcoholic women and 10 alcoholic men had a shorter duration of alcohol dependence. ANOVA revealed effects for the duration of alcohol dependence on total CSF and sulcal CSF volumes. Alcoholics with a longer duration of alcohol dependence had larger CSF volumes, what remained in the single group comparison for alcoholic men on total CSF and sulcal CSF volumes (Table 5).

Table 5. ANOVA of Sex Effects and Alcohol Dependence Effects (Long Duration vs. Short Duration of Alcohol Dependence) on Regional Brain Volumes in Alcoholic Women and Alcoholic Men for the First Examination at Week 1

Because we carried out two examinations (week 1 and week 6) only for alcoholics, we performed ANOVA and analysis of covariance of sex and time effects on regional brain volumes with duration of alcohol dependence as covariate. Individual intracranial volume, representing a constant factor, did not show a significant time effect between week 1 and week 6 ($F = 0.0$, $p = 0.97$; Table 6). Absolute intracranial volumes showed hardly any difference between the two scans for both genders (Table 3), which minimizes the likelihood of an offset effect and supports good measurements reliability. Besides the intracranial volume, all regional brain volumes showed significant time effects. Comparing week 1 and week 6, alcoholics developed an increase in brain volume, an increase of the global atrophy index (ratio of brain volume over intracranial volume), and a decrease of all CSF volumes with abstinence. Looking at the single group comparison, differences from week 1 and week 6 were more significant in alcoholic women. With duration of alcohol dependence as covariate, time effects reached significance only for ventricle volume. The remaining volumes showed only a trend for a time effect in regard to the covariate (Table 6).

Table 6. ANOVA and Covariance (Duration of Alcohol Dependence) of Sex Effects (Female vs. Male), Time Effects (Week 1 vs. Week 6) and Single Group Comparison on Regional Brain Volumes in Alcoholic Women and Alcoholic Men

---

Differences Between Alcohol-Dependent Women and Men

The anatomical differences between women and men in intracranial volume and brain volume were confirmed. Alcoholic men and women did not differ significantly in the degree of brain volume abnormalities measured relative to their sex-matched controls. In particular, alcoholic men and women did not differ in the global atrophy index (ratio of brain volume over intracranial volume) at initial or follow-up scanning (Tables 4 and 6). At the end of the 6-week treatment program with complete sobriety, a significant increase in brain volume was found for both male and female patients. Changes of brain volume and global atrophy were found in alcoholic women and alcoholic men. However compared with men, women developed brain atrophy after a significantly shorter period of alcohol dependence (Tables 1 and 2). Decrease in brain volume was partly reversible, but brain volumes in alcoholics did not reach the level in the control groups for both genders.

DISCUSSION

Alcohol dependence seems to develop faster in women than in men. This telescoping effect has been shown in a number of studies where different "milestones" in the developmental course toward dependence occurred more rapidly in women (Piazza et al., 1989; Schuckit et al., 1995, 1998; Randall et al., 1999). We were able to confirm the telescoping effect in two independent samples (Mann et al., 1992, 1996). In our earlier study, we found indications that the development of alcoholic brain atrophy is accelerated in women as well. The current study was designed to test this hypothesis in a larger sample of alcohol-dependent women and men compared with a matched group of healthy men and women. Because the telescoping effect in the developmental events in the course of alcoholism seems to be established, we concentrated on a valid and reliable measurement of brain atrophy in relation to the duration of alcohol dependence in both men and women.

Our study confirmed alcoholic brain atrophy in alcoholic women and men compared with healthy controls and the reversibility of brain atrophy with abstinence. Women had equal alcohol consumption in relation to body weight in the last year and developed equal brain volume reductions as men after a significantly shorter period of alcohol dependence. We determined the global atrophy index (ratio of brain volume over intracranial volume) as an indicator of relative atrophy. This global atrophy index showed the same relative brain volume reduction in female alcoholics compared with female controls as in male alcoholics compared with male controls. These results complete our earlier report demonstrating equivalent atrophy in both sexes despite a lower total lifetime dose of ethanol consumption in women (Mann et al., 1992). They are in line with other studies (Schuckit et al., 1995, 1998) that demonstrated a significantly faster progression in the course and consequences of alcohol dependence in female compared with male alcoholics and with more recent studies indicating gender

differences using methods with higher spatial resolution (Hommer et al., 2001; Agartz et al., 1999). Assuming a gradual development of consequential brain tissue damage over time, our finding of a comparable degree of brain atrophy despite a shorter period of alcohol dependence could be explained by a more pronounced vulnerability in women. At the end of the 6-week treatment program with complete sobriety, we found an increase in brain volume in both genders, but significance of this reversibility of brain atrophy was higher in women than in men.

Besides the sex effects on regional brain volumes, there is some evidence for an impact of the duration of alcohol dependence on regional brain volumes. We found significant duration of alcohol dependence effects on total and sulcal CSF volumes. In addition, significance of the time effect referring to regional brain volume changes between week 1 and week 6 was influenced by duration of alcohol dependence as covariate.

Our results of equivalent brain atrophy despite a shorter duration of alcohol dependence in female alcoholics corroborate previous studies referring to other gender-related consequences of alcohol. Women with alcohol abuse showed cognitive deficits earlier than men did (Acker, 1986). Alcoholic cardiomyopathy and myopathy of skeletal muscle were shown to be as common in female alcoholics as in male alcoholics, despite a significantly shorter exposure to alcohol in women (Urbano-Marquez et al., 1989, 1995; Fernandez-Sola et al., 1997). The same seems to be true for alcoholic liver disease, which may be even more severe in women after consumption of less alcohol than in men (Pequignot et al., 1974; Loft et al., 1987).

Although we have known for more than 25 years that equal doses of alcohol lead to higher peak alcohol concentrations in women than in men (Jones and Jones, 1976), the neurobiological substrate of a higher physiological vulnerability among women is still not clear. One possible explanation is gender difference in first-pass metabolism due to lower concentrations of alcohol-metabolizing enzymes in women's gastrointestinal tracts (Frezza et al., 1990). Another reason could be the lower content in body water compared with men of similar body weight, leading to higher blood alcohol concentrations (Taylor et al., 1996). However, gender differences of the gastric alcohol dehydrogenase activity are still controversial. They may be age-related. The gastric alcohol dehydrogenase activity appeared higher in young men than in young women but was higher in middle-aged women than in middle-aged men (Parlesak et al., 2002). In a study regarding the bioavailability of alcohol, no gender effect was found for the first-pass metabolism (Oneta et al., 2001). In addition to gender differences in metabolism, a higher vulnerability to alcohol effects could possibly be caused by gender-related differences in innate hormone profiles and genetic risk factors (Prescott et al., 1999).

Even though the pathophysiology of the higher vulnerability to alcohol's effects in women has not yet been clarified, evidence is accumulating that women are exposed to a comparatively higher health risk through alcohol consumption than are men.

ACKNOWLEDGMENTS

The authors thank D. Petersen, M. Gut, and P. Wakat for CT scanning, and V.M. Hesselbrock for providing helpful comments in manuscript preparation.

REFERENCES

Acker C (1986) Neuropsychological deficits in alcoholics. The relative contributions of gender and drinking history. Br J Addict 81:395-403. LEARN link Bibliographic Links

Agartz I, Momenan R, Rawlings RR, Kerich MJ, Hommer DW (1999) Hippocampal volume
in patients with alcohol dependence. Arch Gen Psychiatry 56:356-363. LEARN link Bibliographic Links

Asendorpf J, Wallbott HG (1979) Ma[beta]e der Ubereinstimmung. Z Sozialpsychol 10:243-252.

Ashley MJ, Olin JS, le Riche WH, Kornaczewski A, Schmidt W, Rankin JG (1977) Morbidity in alcoholics: Evidence for accelerated development of physical disease in women. Arch Intern Med 137:883-887. LEARN link Bibliographic Links

Beck AT, Beamesderfer A (1974) Assessment of depression: the depression inventory. Mod Probl Pharmacopsychiatry 7:151-169. LEARN link Bibliographic Links

Fernandez-Sola J, Estruch R, Nicolas JM, Pare JC, Sacanella E, Antunez E, Urbano-Marquez A (1997) Comparison of alcoholic cardiomyopathy in women versus
men. Am J Cardiol 80:481-485. LEARN link Bibliographic Links

Frezza M, Di Padova C, Pozzato G (1990) High blood alcohol levels in women, the role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. N Engl J Med 322:95-99. LEARN link Bibliographic Links

Hesselbrock MN, Meyer RE, Keener J (1985) Psychopathology in hospitalized alcoholics. Arch Gen Psychiatry 42:1050-1055. LEARN link Bibliographic Links

Hommer D, Momenan R, Kaiser E. Rawlings R (2001) Evidence for a gender-related effect of alcoholism on brain volumes. Am J Psychiatry 158:198-204.

Jacobson R (1986) Female alcoholics: A controlled CT brain scan and clinical study. Br J Addict 81:661-669. LEARN link Bibliographic Links

Jernigan TL, Butters N, DiTraglia G, Schafer K, Smith T, Irwin M, Grant I, Schuckit M, Cermak L (1991) Reduced cerebral gray matter observed in alcoholics using magnetic resonance imaging. Alcohol Clin Exp Res 15:418-427. LEARN link Bibliographic Links

Jones BM, Jones MK (1976) Women and alcohol: Intoxication, metabolism, and the menstrual cycle, in Alcoholism Problems in Women and Children (Greenblatt M, Schuckit MA eds), pp 103-136. Grune and Stratton, New York.

Kessler RC, McGonagle KA, Zhao S (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Arch Gen Psychiatry 51:8-19. LEARN link Bibliographic Links

Lehrl S (1989) Mehrfachwahl-Wortschatz-Intelligenztest MWT-B. Perimed, Erlangen.

Loft S, Olesen KL, Dossing M (1987) Increased susceptibility to liver disease in relation to alcohol consumption in women. Scand J Gastroenterol 22:1251-1256.

Mann K, Ackermann K, Gunther A, Jung M, Morlock P, Mundle G (1996) Long-term course and relapse prevention in alcohol dependent women and men. Final report, BMBF project, University of Tuebingen.

Mann K, Batra A, Gunthner A, Schroth G (1992) Do women develop alcoholic brain damage more readily than men? Alcohol Clin and Exp Res 16:1052-1056.

Mann K, Kapp B, Kuhnel P, Federle E (1995) Good estimates for reliability and validity in alcoholics' self reports. Alcohol Alcohol 30:545.

Oneta CM, Pedrosa M, Ruttimann S, Russell RM, Seitz HK (2001) Age and bioavailability
of alcohol. Z Gastroenterol 39:783-788.

Parlesak A, Billinger MH, Bode C, Bode JC (2002) Gastric alcohol dehydrogenase activity in men: Influence of gender, age, alcohol consumption and smoking in a Caucasian population. Alcohol Alcohol 37:388-393. LEARN link Bibliographic Links

Pequignot G, Chabert C, Eydoux H, Courcol MA (1974) Augmentation du risque de cirrhose en fonction de la ration d'alcool. Rev l'Alcoolisme 20:191-202.

Pfefferbaum A, Lim KO, Zipursky RB, Mathalon DH, Lane B, Ha CN, Rosenbloom MJ,
Sullivan EV (1992) Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: A quantitative MRI study. Alcohol Clin Exp Res 16:1078-1089. LEARN link Bibliographic Links

Pfefferbaum A, Rosenbloom M, Deshmukh A, Sullivan E (2001) Sex differences in the effects of alcohol on brain structure. Am J Psychiatry 158:188-197. LEARN link Bibliographic Links

Pfefferbaum A, Sullivan EV, Mathalon DH, Lim KO (1997) Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics, Alcohol Clin Exp Res 21:521-529. LEARN link Bibliographic Links

Piazza N, Vrbka JL, Yeager RD (1989) Telescoping of alcoholism in women alcoholics. Int J Addict 24:19-28. LEARN link Bibliographic Links

Prescott CA, Aggen SH, Kendler KS (1999) Sex differences in the sources of genetic liability to alcohol abuse and dependence in a population-based sample of U.S. twins. Alcohol Clin Exp Res 23:1136-1144. LEARN link Bibliographic Links

Randall CL, Roberts JS, Del Boca FK, Caroll KM, Conners GJ, Mattson ME (1999) Telescoping of landmark events associated with drinking: A gender comparison. J Stud Alcohol 60:252-260.

Schuckit MA, Athenelli RM, Buchholz KK, Hesselbrock VM, Tipp J (1995) The time course of development of alcohol-related problems in men and women. J Stud Alcohol 56:218-225. LEARN link Bibliographic Links

Schuckit MA, Daeppen JB, Tipp JE, Hesselbrock M, Buchholz KK (1998) The clinical
course of alcohol-related problems in alcohol dependent and nonalcohol dependent drinking women and men. J Stud Alcohol 59:581-590. LEARN link Bibliographic Links

Taylor JL, Dolhert N, Friedman L (1996) Alcohol elimination and simulator performance of male and female aviators. Aviat Space Environ Med 67:407-413. LEARN link Bibliographic Links

Urbano-Marquez A, Estruch R, Fernandez-Sola J, Nicolas JM, Pare JC, Rubin E (1995) The greater risk of alcoholic cardiomyopathy and myopathy in women compared with men. JAMA 274:149-154. LEARN link Bibliographic Links

Urbano-Marquez A, Estruch R, Navarro-Lopez F, Grau JM, Mont L, Rubin E (1989) The effects of alcoholism on skeletal and cardiac muscle. N Engl J Med 320:409-411. LEARN link Bibliographic Links

Key Words: Alcohol Dependence; Brain Atrophy; Computed Tomography Scans; Gender
Differences; Telescoping Effect

Accession Number: 00000374-200505000-00025