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Alcohol and Sexual Function[1]

D. H. VAN THIEL,*[2] J. S. GAVALER,* P. K. EAGON,* Y.-B. CHIAO,* C. F. COBB† AND R. LESTER‡

Department of Medicine and the Department of Surgery†*
University of Pittsburgh School of Medicine, Pittsburgh, PA 15261
and
Department of Medicine,‡ University of Texas at Houston, Houston, TX 77025

VAN THIEL, D. H., J. S. GAVALER, P. K. EAGON, Y.-B. CHIAO, C. F. COBB AND R. LESTER. *Alcohol and sexual function.* PHARMAC. BIOCHEM. BEHAV. 13: Suppl. 1, 125–129, 1980.—The pathophysiologic factors which either document or which have been shown to be responsible for not only the hypogonadism and feminization of chronic alcoholic men but also the loss of gonadal function with resultant defeminization of chronic alcoholic women are reviewed. Evidence is presented which suggests that alcohol abuse is associated with the production of a primary form of hypogonadism characterized by loss of endocrine and reproductive function of the gonads. Moreover, evidence is presented which suggests that alcohol abuse is associated with the production of an associated hypothalamic-pituitary defect in gonadotropin secretion which prevents appropriate enhancement of gonadotropin secretion in response to the primary gonadal injury. Finally, the factors which have been found to partially explain the feminization often seen in chronic alcoholic men with advanced liver disease are discussed individually and a composite mechanism incorporating each is presented.

Alcohol Ethanol Hypogonadism Feminization Gonadal atrophy
Hypothalamic-pituitary-gonadal failure

DURING the past decade there has been an increasing appreciation of the fact that ethanol is a pan-tissue toxin which adversely effects multiple organ systems including the endocrine system [2, 37, 48]. In particular, it has been recognized that ethanol impairs the normal functioning of the hypothalamic-pituitary-gonadal axis. Thus, in both sexes, hypogonadism is a common consequence of chronic alcohol abuse [33, 37, 42]. Moreover, such hypogonadism has been shown to occur independently of the presence of liver disease, nutritional inadequacies or other evidence of alcohol-associated disease [16, 35, 42, 45, 47].

The adverse effects of ethyl alcohol upon sexual functioning can be shown to occur at several different levels. First, ethanol is a central nervous system depressant [29]. As such, ethanol can have several adverse effects. It can remove inhibitions that normally regulate interpersonal sexual behavior and thereby enhance libidinous drives. It also can inhibit neurosensory function such that impotence, failure to ejaculate, failure to lubricate or achieve orgasm occur, and other similar responses are either delayed or prevented, thereby adversely affecting sexual performance [10, 15, 21].

In addition to acting centrally, ethanol adversely effects gonadal function *per se*. Thus, as a result of prolonged ethanol abuse, gonadal injury or hypogonadism occurs, as characterized by reproductive failure and endocrine failure of the gonad. In males who abuse alcohol, reproductive failure is well established [33, 35, 45]. This is principally because of the ease with which reproductive function can be assessed clinically in the male. For example, gross testicular atrophy has been found in 70–80% of chronic alcoholic men [33]. Because the seminiferous tubules comprise approximately 85 to 90% of the total testicular volume, any testicular atrophy seen in alcoholic men must of necessity involve the reproductive compartment of the testes. Such injury is demonstrated readily by the high prevalence of oligoazospermia that is present in alcoholic men and by the magnitude of the histologic changes noted when testicular tissue is examined microscopically (Fig. 1) [14–16]. In one study it was reported that only five of forty chronic alcoholic men (12.5%) studied could obtain an ejaculate [4]. Of these five, two were consistently azospermic while the remaining three were oligospermic (having <40 million spermatozoa/mm^3) at each examination. In all of the reported studies in which testicular tissue has been obtained and examined from chronic alcoholics, a consistent microscopic picture has been found [25, 27, 28]. In each case, the seminiferous tubular diameter has been reduced and the number of germ cells contained within the tubules has been markedly reduced with the loss being most prominent at the level of the more mature germ cells (Fig. 1). In addition, peritubular fibrosis

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[2]Send reprint requests to: David H. Van Thiel, M.D., 1000 J Scaife Hall, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261.

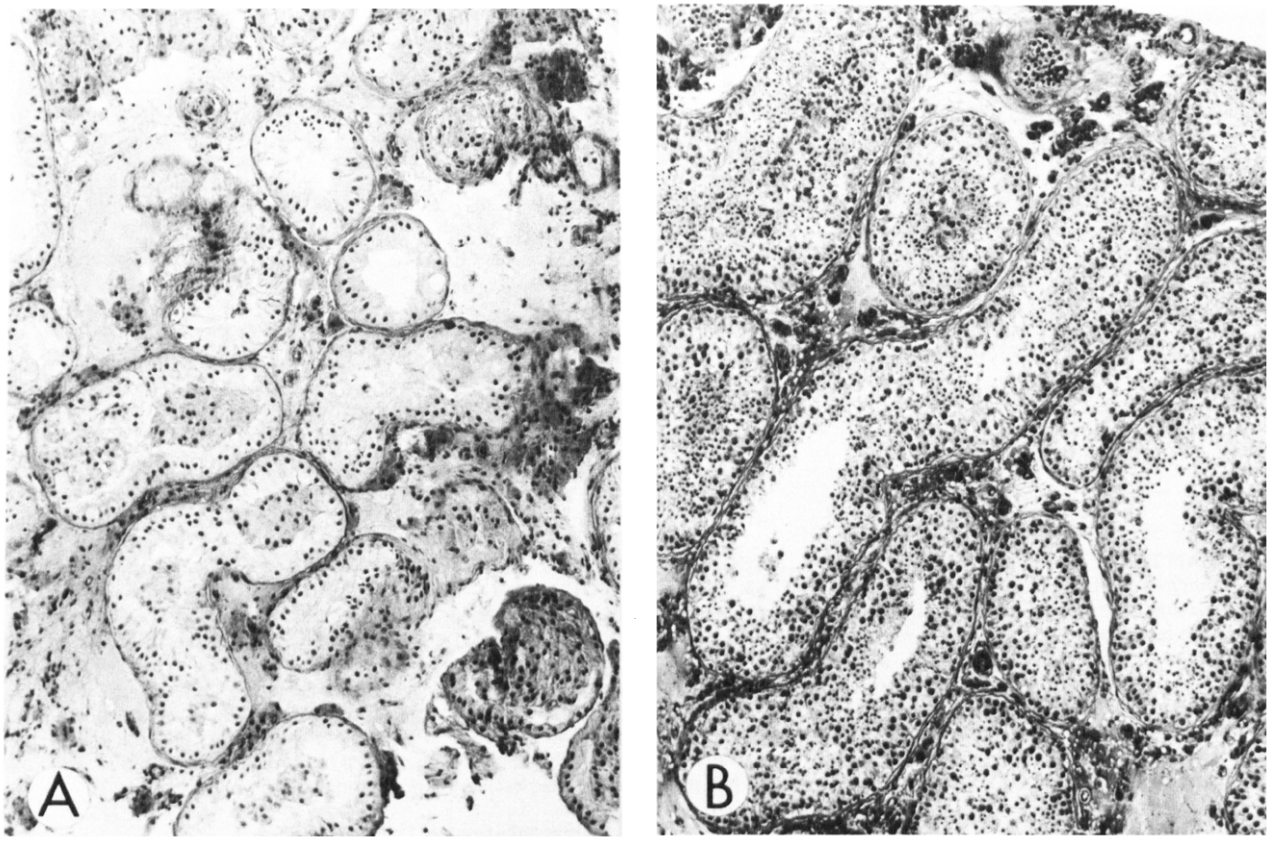

FIG. 1. Testicular histology of an alcoholic male (a) and a normal control (b). Note absence of germ cells within seminiferous tubules of the alcoholic. (H and E×125).

and collapse of residual interstitial cells (Leydig cells) around such atrophic tubules has been a consistent finding.

Reproductive failure in the female chronic alcohol abuser is less well established but, nonetheless, does appear to occur [23,28]. Thus, there is a high prevalence of oligo-amenorehea in such women [28]. Moreover, when the ovaries of chronic alcoholic women who have died during their reproductive years have been examined at necropsy, a paucity of corpora lutea has been found, consistent with ovulatory failure [23].

As noted earlier, endocrine failure of the gonads is also evident in chronic alcoholics either when the secondary sex organs and other sex steroid-dependent tissues are examined or when the plasma levels of sex steroids are assayed in such individuals. Thus, prostatic atrophy, loss of scrotal wrinkling, absence of sexual hair and a reduced seminal plasma volume are common findings. Moreover, plasma testosterone levels are reduced, being either overtly outside and below the normal range or in the lower half of the normal range in most individuals studied [33]. Similarly, chronic alcoholic women demonstrate breast, uterine and vaginal wall atrophy. In addition, they consistently have low estradiol levels such as are usually seen in the early follicular phase of the menstrual cycle, and they rarely have progesterone levels as high as those normally seen in the luteal phase (unpublished data).

Not unexpectedly, the mechanisms responsible for the overt gonadal failure present in chronic alcoholics are less clear than is the evidence of their hypogonadism [32,38]. Acute ethanol ingestion by normal nonalcoholic men has been shown to be followed by a decline in plasma testosterone levels [18,41]. Moreover, ethanol administration to male mice has been shown to produce a dose dependent reduction in plasma testosterone levels [1]. Similarly, chronic feeding of ethanol to male rats has been shown to produce severe testicular atrophy and marked reductions in plasma testosterone levels [35,45]. It should be noted that such injury can be produced in male rats whether the alcohol administration has been begun after or before puberty. Moreover, such gonadal injury does not occur in pair-fed animals given the identical diet with the exception that the ethanol has been isocalorically replaced by carbohydrate. It should also be noted that such gonadal injury occurs in these animals in the absence of significant biochemical or histologic evidence of alcohol-induced liver disease.

As was the case with the reproductive injury produced by ethanol in male rats, female rats also can be shown to develop severe endocrine failure as a result of alcohol administration [16,42]. Such failure is characterized by reduced estradiol and progesterone levels as well as by atrophy of the ovaries and secondary sex steroid-dependent tissues.

Several different biochemical mechanisms have been proposed as the specific toxic reaction responsible for such alcohol-induced gonadal injury. These include gonadal oxidation of ethanol in preference to retin*ol*, thereby limiting gonadal retin*al* generation and altering the gonadal redox state [34]. Because retin*al* is essential for spermatogenesis, limitation of retin*al* generation may indeed contribute to the

germinal injury present in chronic alcoholic males. Whether such is also the case in the female, however, remains to be determined. NADH generation as a result of either ethanol or acetaldehyde oxidation by the gonads may limit gonadal steroidogenesis also. Because the conversion of pregnenolone to progesterone by 3β hydroxysteroid dehydrogenase/Δ 4–5 isomerase is NAD-dependent, the utilization of NAD to oxidize ethanol or acetaldehyde may reduce the effective activity of this enzyme within the gonads.

Experimental evidence exists for such a hypothesis [7]. It has been shown that ethanol and acetaldehyde acutely inhibit the activity of steroid 17,20-lyase, an enzyme which is required for the removal of the side chain from 17α hydroxyprogesterone or 17α hydroxypregnenolone in the production of sex steroids [22]. Moreover, it has been shown that chronic ethanol feeding of male rats is followed by a reduction in the activity of 3β hydroxysteroid dehydrogenase/Δ 4–5 isomerase activity, whether expressed as specific activity (activity/mg protein) or total activity per testis [7]. As this enzyme is the rate limiting step in gonadal steroidogenesis responsible for the conversion of pregnenolone to progesterone, alcohol-induced reduction in its activity may be of considerable importance. In addition, because this enzyme complex requires NAD, the reduction in testicular NAD that occurs with gonadal ethanol and/or acetaldehyde oxidation may act to compound the defect in steroidogenesis produced by alcohol-induced reduction in 3β hydroxysteroid dehydrogenase/Δ 4–5 isomerase activity.

Support for such a conclusion can be found in the isolated perfused rat testes model where it has been shown that both alcohol (Fig. 2) and acetaldehyde inhibit human chronic gonadotropin (hCG)-stimulated testosterone synthesis and secretion [8,9]. Moreover, 4-methyl pyrazole (an inhibitor of alcohol dehydrogenase) partially corrects the testicular steroid production abnormality which occurs in the presence of alcohol or acetaldehyde perfusion (unpublished data). It should be noted that in this system, acetaldehyde is at least 100 times more potent on a molar basis than is ethanol in inhibiting testosterone production and secretion.

Other factors might also contribute to the reduced steroidogenic response of the gonads after alcohol exposure. Thus, it has been shown that luteinizing hormone (LH) binds less well to gonadal receptors in the presence of ethanol [4,5]. In addition, an alcohol-associated reduction in gonadotropin secretion has been reported both in normal volunteers fed alcohol for short periods under metabolic ward conditions as well as in chronic alcoholics [41]. Such alcohol-associated inadequate gonadotropin secretion can be shown to persist in men and laboratory animals despite prolonged stimulation with either clomiphene or luteinizing hormone releasing factor (LRF) [33,41]. Thus, inadequate gonadal function in alcohol-abusing individuals occurs not only as a consequence of primary gonadal injury but also as a result of a hypothalamic-pituitary defect in gonadotropin secretion and peripheral action.

Considerable evidence exists also for alcohol-induced or associated defects in regulation of other pituitary hormones as well. Thus, following alcohol exposure, prolactin and growth hormone secretion and possibly TSH secretion have been shown to be abnormal under basal conditions and to respond atypically to various standard stimuli [26, 31, 40, 43, 44]. Relevant to the present discussion, it should be considered that the hyperprolactinemia seen in chronic alcohol abusers may contribute to the hypogonadism seen in such individuals. Such may be the case whether the hyperprolactinemia occurs as a primary result of the alcohol abuse *per se* or as a secondary effect due either to the alcohol-induced liver disease seen in such individuals or possibly to the presence of prolactin secreting microadenoma. In the absence of alcoholism, hyperprolactinemia *per se* is an established cause of hypogonadism in both males and females [6,14].

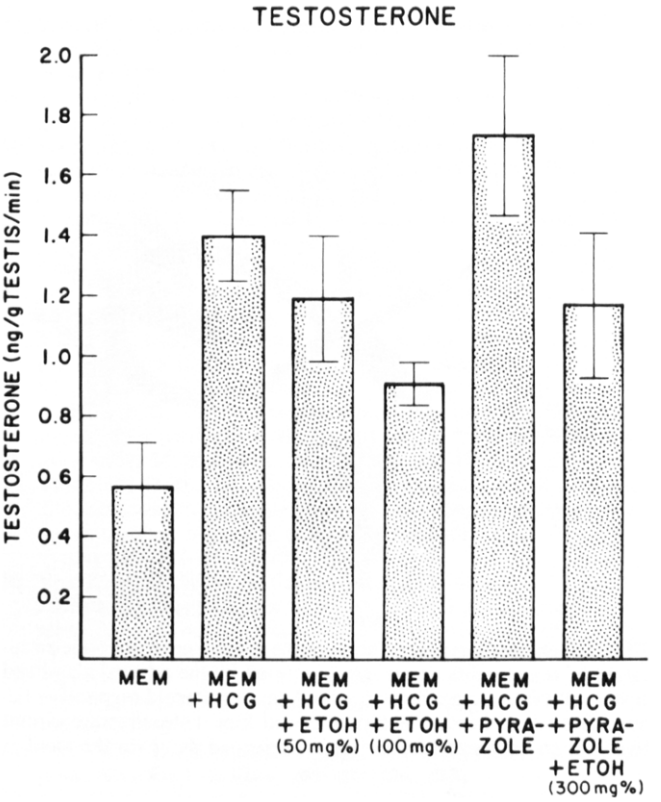

FIG. 2. Testosterone secretion rate of the isolated rat testes perfused with minimum essential medium (MEM) alone or with various additives. The ordinate shows the secretory rate in terms of ng testosterone secreted per gram testes per minute. Along the abscissa are shown the various perfusate mixtures. HCG=human chorionic gonadotropin (1.0 IU/ml) and ETOH=ethanol at the indicated concentrations. Each bar is the mean value for 10 individual perfusion studies. The brackets represent SEM.

At this point it should be noted that, in addition to being hypogonadal, chronic alcoholic men, particularly those with advanced alcoholic liver disease, often are feminized [36,37]. It should also be noted that hypogonadism in the male does not imply feminization. What then makes chronic alcoholic men feminized? Several potential mechanisms have been proposed and experimental evidence exists for each. Thus, the pathogenesis probably consists of a variable combination of these individual mechanisms occurring together in a given alcoholic individual. For example, considerable evidence has been accumulated documenting an increased nonglandular, nonhepatic conversion of weak adrenal androgens to estrogens in alcoholic men with advanced histologic liver disease [13, 17, 30]. Moreover, evidence has accumulated to suggest that this increased conversion of androgens to estrogens is probably due to two interacting forces: first, an increase in aromatase activity which occurs as a consequence of alcohol-induced enhancement of hepatic microsomal enzyme activity [19], and second, portal-systemic shunting

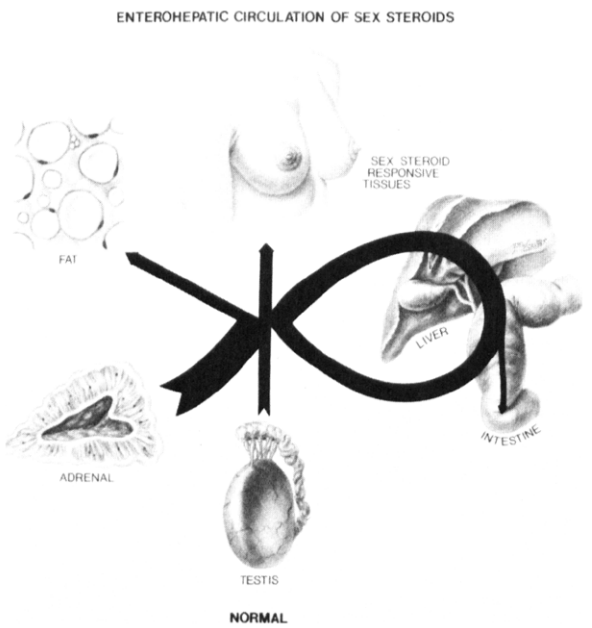

FIG. 3. Schematic representation of the normal enterohepatic circulation of sex steroids. Androgens secreted by the adrenal gland and testes circulate; some fraction stimulates sex steroid responsive tissues and some fraction enters a closed loop enterohepatic circuit from which only small losses are experienced daily via the stool.

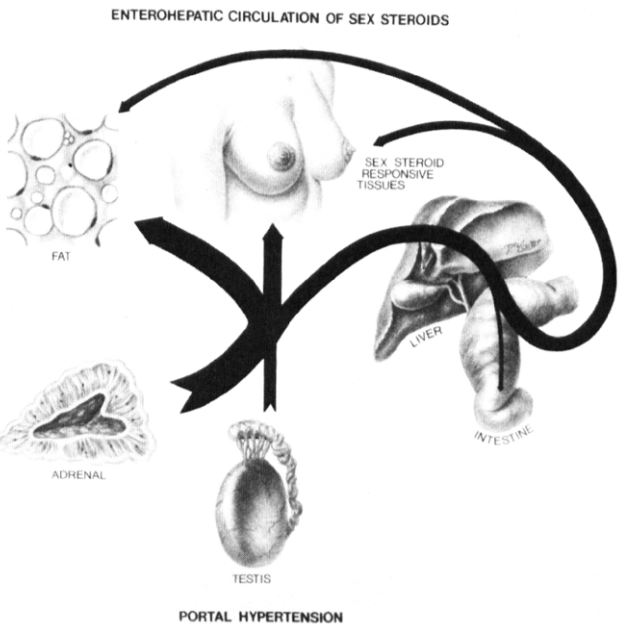

FIG. 4. Enterohepatic circulation of sex steroids in portal hypertension. Androgens secreted by the adrenal gland and testes circulate; some fraction directly stimulates sex steroid responsive tissues and some fraction is removed by the liver, secreted into bile and upon being reabsorbed, escapes the enterohepatic circuit because of portal systemic shunts and is made available for peripheral conversion to estrogens.

which occurs as a consequence of alcohol-induced liver disease [46]. Such shunts allow weak adrenal androgens to escape the enterohepatic circuit and thereby become available for peripheral nonhepatic aromatization (Figs. 3 and 4).

Finally, a reduction in the hepatocyte content of a unique male specific estrogen-binding protein has been suggested as being of pathogenic importance in the genesis of feminization [11, 12, 24]. The loss of such a protein in the alcoholic genetic male may explain why alcoholic men become both hypogonadal and feminized while alcoholic females in contrast become progressively defeminized. Moreover, the combination of (1) increased nonglandular conversion of androgen to estrogen occurring as a result of alcohol-induced increased hepatic (and possibly other sites as well) aromatase activity and (2) an interrupted enterohepatic circulation combined with (3) reduced estrogen binding by a non-receptor estrogen-binding cytosolic protein in alcoholic males would be expected to act synergistically and enhance feminization [20].

As must be evident from the above discussion, the combination of hypogonadism and feminization that occurs in alcoholic men has a multifactorial origin. In part it is due to alcohol-induced gonadal and hypothalamic-pituitary injury that limits testicular androgen production. It is also due, in part, to alcohol-induced liver disease and the associated portal-systemic shunting that occurs with such liver disease. It is due in part also to a loss of a unique male specific cytosolic estrogen-binding protein within hepatocytes and presumably other cells which allows feminization to occur even in the absence of excess circulating estrogen levels. Finally, it may also be due in part to enhanced 5β reductase and aromatase activity which enhance androgen catabolism and estrogen formation, respectively. The situation in the female alcoholic is less clear but chronic alcoholic women would appear to become progressively hypogonadal and as a result, increasingly less feminized.

Clearly, much has been learned about the adverse effects of alcohol abuse upon sexual functioning during the last several decades. Despite such advances our knowledge of the pathophysiologic basis responsible for such phenomena is only beginning to be established. Much yet remains to be learned. Only with a true understanding of the pathophysiology responsible for not only alcohol-induced hypogonadism both in men and in women but also for feminization in chronic alcoholic men with advanced liver disease, will physicians be able to attempt to therapeutically reverse such unwanted phenomena in abstinent alcoholics.

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