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Gynecomastia Associated with Cirrhosis of the Liver.*

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(Introduced by E. M. Hall.)

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The occurrence of gynecomastia associated with cirrhosis of the liver was first noted by Silvestrini,[1] and more fully described in 1923 and in 1926. Corda[2] added the observation that testicular atrophy accompanied the condition. More recent Italian writers refer to the phenomenon as the "Silvestrini-Corda syndrome."

Some 65 cases have been recorded in the foreign literature, but none has been found in English. Silvestrini believed the enlargement of the breast to be due to some substance or substances carried in the collateral circulation, while Corda considered it to be of endocrine origin.

We have observed 8 cases since 1935, 5 of whom came to autopsy. Three of the group had sex hormone studies. The essential anatomic findings were similar in all, *viz.*, atrophic cirrhosis, ascites, testicular atrophy and gynecomastia. All of our patients were chronic alcoholics and mammary enlargement occurred in each instance after the onset of ascites.

Studies of androgen and estrogen values in the urine were undertaken, 6-day specimens having been collected. The first specimens were allowed to stand at room temperature with toluene added as a preservative. Later (in C.F., M.C., G.A., and A.S.) the samples were kept on ice.

Estrogen was determined by a modification of the Allen-Doisy method with counter-current ether extraction after 2-hour hydrolysis of the sample acidified with 5% H_2SO_4. The smallest amount producing estrus in spayed rats of uniform weight was compared with the effect of crystalline estrone. Results of determinations were computed as gammas for 24-hour specimens.

Androgen extraction was done by a modification of Koch's method with 15-minute hydrolysis of the sample acidified with 5% H_2SO_4 and extraction with ether instead of benzene. Results of comb growth were compared with those obtained by the use of crystalline

* Aided by a gift from Ethel Mossman Jacobs.

1 Silvestrini, R., *Riforma Med.*, 1926, **42**, 701.

2 Corda, L., *Minerva Med.*, 1925, **5**, 1067.

TABLE I.

	Age	Estrogens (gamma) Free	Estrogens (gamma) Total after hydrol.	Androgens (I.U.) Free	Androgens (I.U.) Total after hydrol.
Normal Sex Hormone Values in Male Urine.*					
11-13, Dorfman[3]			1-5		1.1-15
20 adults, age 22-30 (our data)			10-12		20-82
Sex Hormones in Gynecomastics.*					
J.M.	12		9		32
F.R.	52		60		36
C.F.	55	10.5	10.5	0	
Controls.					
M.C.	26	4.5	12	20	32
G.A.	58	0	3	0	8
A.S.	48	0	1.2	0	8
M.	66		15	14	85

[3] Dorfman, R. I., Greulich, W. W., and Solomon, C. I., *Endo.*, 1937, **21**, 741.

* All data computed for 24-hour specimens.

androsterone and computed as international units for 24-hour specimens.

Later in the work, as noted in the tables, the free fraction was determined by the same procedure except that hydrolysis was omitted. The amount obtained by hydrolysis was called the total, which included the free and combined form.

Controls used were one individual with acute hepatic necrosis (M.C.), 2 with atrophic cirrhosis and ascites without gynecomastia (G.A. and A.S.), one with unilateral gynecomastia (M.), and a group of normal men, age 22 to 30 years.

The results are significant in 2 respects. First, 2 of the gynecomastics had increased estrogen (J.M. and F.R.), and second, the last (C.F.), and the individual with acute liver damage (M.C.) had 4.5 to 10.5 gamma estrogenic substance in the free form.

The only available data (Peterson[4]) indicate that negligible amounts of the free form, *i. e.*, without hydrolysis, are found in the urine of healthy men.

The rôle of the liver in inactivating estrogen is shown by Israel, *et al.*,[5] who found that estrone in the perfusion fluid in a heart-lung-liver preparation disappeared in 15 minutes. With the liver removed from the preparation all the estrone was recovered by bioassay. Golden and Sevringhaus[6] found that if the ovaries of rats

[4] Peterson, D. H., Gallagher, T. F., and Koch, F., *J. Biol. Chem.*, 1937, **119**, 185.

[5] Israel, S. L., Meranze, D. R., and Johnston, C. G., *Am. J. Med. Sc.*, 1937, **194**, 835.

[6] Golden, J. B., and Sevringhaus, F. L., PROC. SOC. EXP. BIOL. AND MED., 1938, **39**, 361.

were transplanted to the mesentery, estrus failed to occur, but if the same ovaries were retransplanted into the axilla then estrus occurred normally.

Summary and Conclusions. 1. We have studied 8 patients with hepatic cirrhosis in whom gynecomastia occurred late in the disease, confirming the findings of Silvestrini, Corda and others. 2. In all of these cases bilateral gynecomastia was preceded by the development of ascites. 3. The histological changes in these hyperplastic mammae are similar to the changes seen in experimental estrone stimulation (growth of ducts). 4. Sevringhaus, Israel, *et al.*, have shown experimentally that the liver normally plays a rôle in the inactivation or destruction of estrogen. Accordingly, it is reasonable to suspect that organic liver disease may result in abnormalities in estrogen metabolism. The increased urinary excretion of total estrogen in 2 cases and of free estrogen in 2 cases tends to justify this assumption. 5. An explanation of the absence of gynecomastia in acute hepatic necrosis and in the majority of cases of cirrhosis is not as yet apparent. The effect of testicular atrophy upon androgen excretion also is not clear.

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Changes in the Parenchymatous Organs Produced by Artificially Induced Fever.

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The purpose of this experimental study has not been to investigate the pathological changes which could be produced by lethal doses of artificially induced fever, as has been done previously by Hartman, Jacobsen and Hosoi, Baldwin and Nelson, and a few others,[1] but to make a quantitative comparison between the organ changes occurring in fatal and non-fatal doses of fever, and to investigate the fate of these changes after recovery of the animal. In our series of experiments male adult rabbits of a healthy standard breed were used. Nine animals died after a rapid high rise of temperature induced by the diatherm or radiotherm in a short period of 30 minutes (Group

[1] Hartman, F. W., and Major, R. C., *Am. J. Clin. Path.*, 1935, **5**, 392; Jacobsen, v. G., and Hosoi, K., *Arch. Path.*, 1931, **11**, 744; Baldwin, W. M., and Nelson, W. C., PROC. SOC. EXP. BIOL. AND MED., 1928, **26**, 588.