HORMONE EXCRETION AND LIVER FUNCTION IN THE GYNECOMASTIA OF LEPROSY

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Gynecomastia occurs in 7 to 15 per 100,000 of otherwise apparently healthy white males (38, 40). It occurs commonly in the newborn, and some 40 per cent of boys show enlargement of the breasts during puberty.

The influence of estrogens on the growth of breast-duct tissue is well known, as is the gynecomastia induced by excess exposure to estrogens. Gynecomastia is often associated with liver disease (12, 22, 23). Inactivation of circulating estrogens probably takes place in the liver (9, 17).

The incidence of gynecomastia in leprosy has been reported by Baptista (3) as being 8.6 per cent, and by Grabstald and Swan (16) as 19 per cent. Our series showed an incidence of 6 per cent in 600 lepromatous cases examined. No tuberculoid case was found to have gynecomastia.

Lepromatous leprosy is a systemic disease, and primary and secondary lesions of the liver are a not uncommon finding (31). Coupled with this among our patients is the high carbohydrate, low protein diet of the Bantu, which might have a predisposing effect in the production of liver damage. For these reasons, and because the liver is probably linked with steroid metabolism, it was necessary in our study to establish liver function along with the hormone excretion values.

We report here the hormone excretion and liver function tests of 18 cases of lepromatous patients showing gynecomastia (Figs. 1 and 2). These findings are compared with results found in 20 lepromatous cases not showing that condition, with values derived from 20 tuberculoid cases, and with a further set of values derived from 20 normal Bantu males.

MATERIALS AND METHODS

HORMONE EXCRETION TESTS

Estrogens.—Twenty-four-hour specimens of urine were collected from the 18 lepromatous cases showing obvious bilateral gynecomastia. Urine specimens were also collected from the 20 lepromatous cases not showing gynecomastia, the 20 tuberculoid cases included in the study, and the 20 normal Bantu men who served as controls.

Estrogens in the urine were determined by the method of Brown (6), adopted for a hot climate and an altitude of 4,500 feet above sea level. The estrogens are expressed in micrograms per gram of creatinine.

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Gonadotrophins.—Gonadotrophins were adsorbed onto kaolin at pH 4 (36). Elution of the gonadotrophins was done by the method of Lorraine and Brown (24), and they were assayed in immature, intact female mice.

17-Ketosteroids.—These were estimated after the method recommended by the Medical Research Council Committee on Clinical Endocrinology (28).

LIVER FUNCTION TESTS

Electrophoresis of serum proteins.—A moving-boundary technique was used in a veronal-acetate-HCl buffer of pH 8.6 and $\mu = 0.1$. Interferometry was used for interpretation instead of the classical Schlieren diagrams. The current used was 6 volts per centimeter.

Thymol turbidity test.—Because of differences in sensitivity of different batches of thymol reagent prepared by different methods, confusion has arisen regarding normal limits (18, 19, 25, 27). The buffer used in this investigation was the standardized buffer of de la Huerga and Popper (18). The turbidity was read in an Evelyn colorimeter calibrated with copper sulphate (10). A standardized buffer of pH 7.72 was used, with 5 units the upper limit of normal.

Thymol flocculation test.—After the turbidity was read the solution was poured back into test tubes and left undisturbed overnight. Flocculation was graded 0 to 4+.

Serum colloidal gold.—The method of Maclagan (26) was followed.

Serum colloidal red.—The method of Ducci (11) was used.

Serum bilirubin.—The method of Powell (32) was used.

Bromsulphalein retention.—A dose of 5 mgm. per kilo was used with a 45-minute interval. Bromsulphalein in the serum was measured spectrophotometrically after the method of Gaebler (13).

Total cholesterol and cholesterol esters.—Total cholesterol was measured by the method of Abell *et al.* (1). Cholesterol esters were estimated by the method of Schoenheimer and Sperry as modified by Sobel and Mayer (37).

Pseudo-cholinesterase.—The electrometric method of Michel (29), as modified by Aldridge and Davies (2), was used.

RESULTS

The findings in these several examinations are shown in Table 1. The findings regarding the excretion of estrogens (estrone, estradiol and estriol) are shown graphically in Text-fig. 1.

Liver function.—Using the t test, a comparison of the liver function values of the normal controls with those of the tuberculoid group gave significant differences only for the thymol turbidity test ($t = 5.39$), the bromsulphalein retention test ($t = 2.4$), and serum gamma globulin ($t = 2.96$).

Comparison of values of the normals and the lepromatous cases without gynecomastia showed significant differences for all components tested except for serum bilirubin ($t = 1.47$), total cholesterol ($t = 1.9$) and cholesterol esters ($t = 0.9$). The lepromatous cases with gynecomastia gave similar findings.

The two groups of lepromatous cases, with and without gynecomastia, showed significant differences when the liver function values were compared with those of the tuberculoid group. Exceptions were total serum bilirubin, total serum cholesterol, and cholesterol esters.

TABLE 1. ***Biochemical values for normal Bantu control, tuberculoid leprosy patients and lepromatous leprosy patients with and without gynecomastia.***

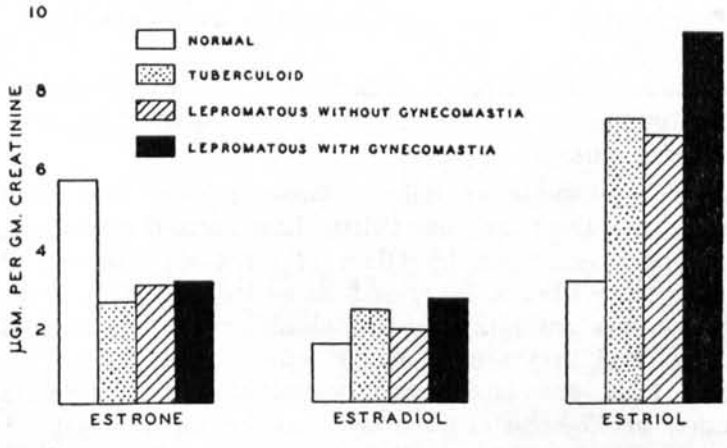
Biochemical values	Normal Bantu controls			Values for tuberculoid patients			Lepromatous patients without gynecomastia			Lepromatous patients with gynecomastia		
	Mean	S. D.	Range	Mean	S. D.	Range	Mean	S. D.	Range	Mean	S. D.	Range
Albumin, gm./100 cc.	3.33	0.28	2.87-3.64	3.15	0.51	2.9-4.1	2.74	0.46	1.78-3.29	2.60	0.39	1.86-3.4
α_1 Globulin, gm/100 cc.	0.49	0.043	0.42-0.54	0.62	0.21	0.42-0.81	0.54	0.14	0.37-0.75	0.43	0.16	0.33-0.9
α_2 Globulin, gm./100 cc.	0.67	0.13	0.47-0.79	0.63	0.17	0.51-0.90	0.72	0.13	0.49-0.97	0.84	0.16	0.60-1.0
β Globulin, gm./100 cc.	1.05	0.11	0.85-1.23	0.96	0.19	0.88-1.39	1.12	0.22	0.75-1.48	1.00	0.19	0.76-1.55
γ Globulin, gm./100 cc.	1.31	0.25	0.95-1.66	1.83	0.54	1.68-3.25	2.48	0.55	1.53-3.51	2.60	0.60	1.46-3.80
Thymol turbidity, Maclagan units	2.4	1.57	0-5	5	3.5	0-12	11	4.5	8-27	12	5	5-25
Thymol flocculation	0			±			3+			3+		
Serum colloidal gold	0			3			4			5		
Serum colloidal red	0			3			5			5		
Van den Bergh reaction	Neg.[a]			Neg.[a]			Neg.[a]			Neg.[a]		
Serum bilirubin, mgm./100 cc.	0.59	0.21	0.29-1	0.46	0.16	0.14-0.83	0.48	0.26	0.4-1.2	0.68	0.20	0.60-1.38
Bromsulphalein retention, %	4.3	1.5	0-6	7	2.6	0-11	12	3.6	7-22	12	2.10	8-26
Total cholesterol, mgm./100 cc.	184	38.9	123-288	165	38.9	118-256	160	46.1	124-235	150	38	138-210
Cholesterol esters, %	75			77			62			66		
Serum pseudo-cholinesterase, pH number	58	14.0	42-100	58	14	42-97	40	29	30-79	48	24	34-86
Estrone, µgm./gm. creatinine	5.7	2.3	3.4-8.2	2.6	1.1	1-4.3	3.0	1.7	0-5.9	3.1	1.4	1- 4.5
Estradiol, µgm./gm. creatinine	1.5	1.8	0.8-7.5	2.4	2.0	0-5.8	1.9	1.0	0-4.2	2.7	1.9	0- 8.6
Estriol, µgm./gm. creatinine	3.2	2.0	0.8-7.5	7.3	3.7	3-17.5	6.9	4.6	1-18.3	9.5	6.1	0-30.6
17-Ketosteroids, mgm./gm. creatinine	11.8	2.18	8.9-16	7.7	3.9	3.8-17	5.2	1.9	3-10	5	2.3	3.6-11.2

a Direct negative

17-Ketosteroids.—The excretion of neutral 17-ketosteroids, by the tuberculoid patients was significantly lower than that of the normal persons ($t = 4.04$). Both groups of lepromatous patients, with and without gynecomastia, excreted significantly less neutral steroid than normal persons ($t = 10.4$ and 11.0, respectively).

Gonadotrophins.—In view of the low steroid excretions and the testicular lesions, it was decided to examine the gonadotrophin excretion in lepromatous cases with gynecomastia and lepromatous cases not showing that condition. In 14 of the cases without gynecomastia, the gonadotrophin excretion varied from 0 (4 cases), 6.6 mouse units (7 cases), to 13.2 mouse units (3 cases). Cases with gynecomastia showed values varying from 0 (2 cases), 6.6 mouse units (8 cases), to 13.2 mouse units (4 cases); the remaining four cases showed 52.8, 52.8, 105.6, and 180 mouse units, respectively. These last four cases all showed marked atrophy of the testes.

Estrogens.—Text-fig. 1 shows the mean estrogen excretion for all of the leprosy groups and the normal controls. Significantly higher excretion of estrone was found in the normal group than in any of the leprous



TEXT-FIG. 1.—Showing the mean urine concentrations of the estrogens in the four groups of subjects involved in the investigation.

groups under study. Estradiol excretion showed no marked differences. Mean estriol excretion in all of the leprosy groups was significantly higher than normal. The patients with gynecomastia showed a significantly higher mean excretion than either the tuberculoid patients or the lepromatous patients without gynecomastia.

This difference is of doubtful significance, because the four gynecomastia cases showing elevated gonadotrophin titers also showed by far the highest levels of estriol in the urine (14.8, 20, 15, and 30.6 µgm., respectively). If these are omitted the mean excretion of estriol for the remaining 14 patients showing gynecomastia falls somewhat below that for the lepromatous cases without that condition.

DISCUSSION

Liver function.—Liver function tests have been done but scantily in leprosy. Isolated tests have been given undue importance, and many of the procedures used are today probably obsolescent. Reviews of the available literature are given by Sister Hilary Ross (34, 39).

From our results it would appear that tuberculoid cases differ from the normal only in an elevated thymol turbidity, an elevated serum gamma globulin, and a slightly abnormal retention of bromsulphalein. Tuberculoid leprosy is presumably a reactive form of the disease, and it is possible that the increased gamma globulin is due to antibody globulin. This increase in gamma globulin would have a positive effect on the abnormal thymol tests found in tuberculoid leprosy.

Lepromatous cases, both with and without gynecomastia, showed gross liver dysfunction. This is not surprising in view of the generalized nature of the disease, and the finding of lepromata and, frequently, secondary amyloid change in lepromatous leprosy (31).

A striking feature of the lepromatous groups was the normal esterification of cholesterol in spite of the gross liver dysfunction indicated by other tests. Zieve (42) and Reinhold (33) have also questioned the contribution that the determination of esterified cholesterol can make to the study of liver disease.

It would appear that minimal liver dysfunction exists in tuberculoid leprosy, while lepromatous leprosy is associated with gross liver dysfunction as indicated by the tests used.

17-Ketosteroids.—The adrenals contribute two-thirds of the total neutral 17-ketosteroids, and the testes one-third. Low steroid excretions in liver disease have been described by Glass *et al.* (15), Gilder and Hoagland (14), Lloyd and Williams (23), and Kinsell *et al.* (21). Both tuberculoid and lepromatous patients excreted significantly less steroid than the normal group, and in the case of the lepromatous groups the values were lower than those usually excreted by castrates. This suggests a decreased production of 17-ketosteroid precursors by the adrenal. A possible alternate explanation would be a disturbance of the intermediate metabolism of 17-ketosteroid intermediates in which the liver plays an important role. The role of the testes cannot be overlooked, because the testes seldom escape involvement in the lepromatous case.

Powell and Swan (31), studying autopsy material from the U. S. Federal Leprosarium at Carville, La., found amyloid change in 16 of 46 adrenals examined. That the adrenal is severely involved in lepromatous leprosy is shown by its unresponsiveness to intravenous ACTH as measured by the excretion of urinary 17-hydroxycorticosteroids hydrolysed with beta-glucoronidase, as found by one of us (20) in 1956.

In lepromatous cases the low 17-ketosteroid excretion would appear to be the resultant of changes in structure and function of the adrenals and

the testes in association with gross liver disease. No especially low values were found among the lepromatous cases showing gynecomastia.

Gonadotrophic hormones.—Because of the testicular lesions and the variable estrogen excretion, it was decided to examine the gonadotrophin excretion in the two groups of lepromatous cases. In 14 cases without gynecomastia, the gonadotrophin titers varied between 0 and 13.2 mouse units per 24 hours. The 18 cases with gynecomastia excreted gonadotrophins equivalent to 6.6 mouse units (6 cases), 13.2 units (8 cases), and—in the remaining 4 cases—52.8 units (2 cases), 105.6 units (1 case), and 180 units (1 case). These last four cases with elevated gonadotrophin titers all showed marked atrophy of the testes; but 6 lepromatous cases without gynecomastia showed equivalent degrees of atrophy. These 4 cases also showed significantly higher excretions of estrogen than was found in lepromatous leprosy without gynecomastia, or in the 14 other cases with it.

Rupp *et al.* (35) could find no correlation between liver disease and excretion of gonadotrophins. No correlation was demonstrated in this study. While the rise in titer of the 4 cases could be due to testicular failure, testicle atrophy was found in other lepromatous cases both with and without gynecomastia with no rise in gonadotrophin titer.

Estrogens and gynecomastia.—Working with estradiol-17 β-16-C^{14}, Beer and Gallagher (4, 5) showed that the urine was the principal way of excretion of radioactive metabolities. With small doses estriol was the principal metabolite on the first day after injection, and it was excreted in larger amounts than estrone in all the subjects studied. After a large dose the reverse held in that estrone was initially excreted in significantly higher amounts than estriol. As time progressed estriol became the major metabolite. This change was considered to be a function of the size of the dose administered, rather than of the other variables described. Brown (7) has shown that for pregnancy, with its known high estrogen levels, estriol was by far the most significant metabolite found in the urine.

While an enterohepatic circulation has been found for the dog (30), the fact that only a small portion of an intramuscular dose of tagged estradiol-17 β was found in the feces eliminates the bile and the intestine as major factors in the metabolism of estrogens in the human (4, 5). The liver, however, (1) probably conjugates the steroid, (2) breaks it down to compounds of lesser activity, and (3) degrades the molecule.

All of the leprous patients showed a significantly higher excretion of estriol than did the normal controls. In spite of minimal liver damage, tuberculoid cases excreted as much estriol as did lepromatous patients with or without gynecomastia. Yet gynecomastia has never been found in tuberculoid cases in this institution. Granted that lepromatous cases with testicular lesions and liver damage could account for a drop in androgens associated with poor inactivation of circulating estrogens, it is noteworthy that only 6 per cent of our lepromatous patients showed gynecomastia. Gynecomastia has been associated with a host of physi-

ological and pathological conditions, and its precise etiology is obscure (41). It is frequently associated with liver disease and to excess exposure to estrogens, but it is as frequently not found under similar circumstances. It would appear that tissue or target-organ sensitivity, as well as factors other than estrogens, may be involved. Also, the tests performed in this investigation may not have been done frequently enough to show up striking changes, or perhaps other estrogen metabolites would have been more informative. An indication that this may be so is the finding by Beer and Gallagher that significant residual radiation remained in urine after the usual metabolites estrone, estradiol and estriol, produced by injection of tagged estadiol, had been isolated.

Until about six years ago it was generally believed that stimulation of proliferation of the epithelium of the breast was a function of ovarian steroid hormones, while pituitary hormones were of importance only during lactation. Since then pituitary prolactin has come to be the key hormone in the development of the breast (8). It may be that this mammatrophic hormone is implicated in the gynecomastia of leprosy. Work on the isolation and assay of that hormone is in progress in our laboratory.

An interesting feature of the gynecomastia of leprosy was the Klinefelter-like syndromes shown by 4 of the cases with that condition. Perhaps, as indicated by Grabstald and Swan, leprosy is one of the disease entities of this group where the etiology is known.

SUMMARY

1. Hormone excretion and liver function were studied in 18 lepromatous cases with gynecomastia, 20 lepromatous cases without gynecomastia, 20 tuberculoid cases, and 20 normal Bantu controls.

2. The tuberculoid cases showed minimal liver dysfunction, while marked liver dysfunction was found in lepromatous cases whether they had gynecomastia or not.

3. Hormone excretion is discussed in relation to the disease process and liver function.

4. No correlation could be found between gynecomastia and liver dysfunction or estrogen excretion, or between liver dysfunction and estrogen excretion.

5. The finding of a Klinefelter-like syndrome in four cases is mentioned.

RESUMEN

1. La excreción de hornonas y la función hepática fueron estudiadas en 18 casos lepromatosos con ginecomastia, 20 casos lepromatosos sin ginecomastia, 20 casos tuberculoideos y 20 bantús normales como testigos.

2. Los casos tuberculoideos revelaron la mínima disfunción hepática, en tanto que se observó notable difunción del hígado en los casos lepromatosos, ya tuvierne o no ginecomastia.

3. Se discute la excreción de hormonas en relación con el proceso morboso y la función hepática.

4. No pudo descubrirse correlación entre la ginecomastia y la disfunción o la excreción de estrógeno, o entre la disfunción hepática y la excreción de estrógeno.

5. Menciónase el hallazgo de un síndrome parecido al de Klinefelter en cuatro casos.

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DESCRIPTION OF PLATE

PLATE 5

FIG. 1 and 2. Two examples of gynecomastia in lepromatous leprosy.

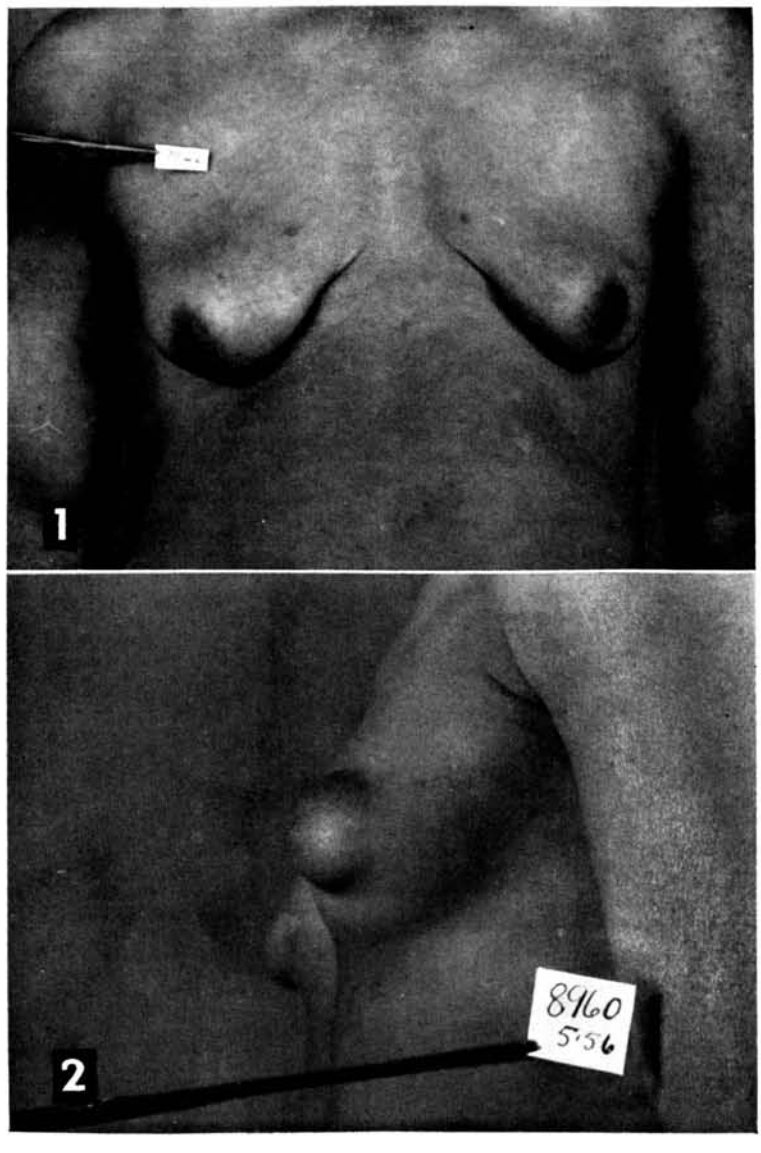

PLATE 5