GYNECOMASTIA AND LEPROUS ORCHITIS
A PRELIMINARY STUDY

C. K. Job, B.Sc., M.D.

Schieffelin Leprosy Research Sanatorium
Karigiri, North Arcot District
South India

Gynecomastia is an enlargement of the mammary glands in males due to proliferation and increase in the glandular component of the organ ([11]). Occasionally, enlargement due to deposition of fat is difficult to distinguish from this condition. Enlargement of the nipple in males has been considered part of gynecomastia, and it has to be differentiated from lepromatous infiltration of the nipple without actual hypertrophy. There may be also widening and hyperpigmentation of the areola.

Although gynecomastia is a well-known complication in leprosy ([5, 27, 30]), there is no general agreement regarding its etiology in this disease. Atrophy of the testis, liver disease, hormonal disturbances, nutritional deficiencies have all been suggested ([8, 10, 17, 19, 31]).

This paper describes the findings in 21 cases of leprosy with gynecomastia, with special reference to testicular biopsies.

MATERIAL AND METHODS

Selection of cases.—Leprosy patients undergoing treatment in this institution are classified according to the recommendations of the Madrid Congress into two types, lepromatous and tuberculoid, and two groups, indeterminate and borderline. Among those attending as outpatients, a number of cases of gynecomastia were detected, from among whom 21 who were willing to submit to hospitalization and further investigations were selected during the period 1958 to 1960. The clinical history of each was recorded on a especially prepared form, and each was subjected to a thorough clinical examination. A general impression of the size of the genital organs was recorded, and the testes were measured with a centimeter scale. This measurement was inexact, but it helped to substantiate our impression about the size. Grossly, 4.5 cm. x 3.0 cm. x 2.5 cm. was taken as normal dimensions.

The breast enlargement was classified by size into three grades, according to Hall ([11]). "Enlargement of the breasts which is quite obvious on clinical examination which is scarcely evident in an oblique view of the chest is described being of grade I severity." Breast enlargement to the size of adolescent female breast or larger was classified in grade III. Grade II includes those which were obviously enlarged but not as much as grade III. (See Figs. 1 to 4.)

Control cases without gynecomastia were selected from among inpatients who were willing to undergo testicular biopsy. They were matched as far as possible with the study sample, as regards age and duration of the disease.

GYNECOMASTIA

Clinical pathology.—In all cases, the bacteriologic index (B.I.), an indication of the severity of the infection, was estimated from the find-

ings in 8 routine skin smears from different parts of the body ([6]). Estimation of 17-ketosteroids was done in 6 cases according to the method described by Robinson and Warren ([29]).

Tissue pathology.—Biopsy of one of the testes was done in every case. A wedge of the testicular tissue was removed, fixed in 10% formalin, and embedded in paraffin wax. Sections 5-7 μ were cut and stained with hematoxylin and eosin and for acid-fast bacilli according to Fite's method ([7]). In the case of patients who underwent surgical treatment, the tissue removed from both breasts was also submitted to examination.

Classification.—Of the 21 gynecomastia cases studied, 20 were classified as lepromatous and 1 as borderline. In the control group there were 14 patients, 8 lepromatous and 6 borderline.

Age.—The average age of the 21 patients was 26.7 years, the youngest being 16 and the oldest 51. All but 2 cases were between 15 and 35 years of age. (See Text-fig. 1A.) In the control group (14 patients) the average age was 31.3 years, the lowest 15 and the highest 45.

Duration of gynecomastia.—The data on duration were as in the following tabulation.

Duration	*Cases*
<6 months	2
6 mo.-1 yr.	2
1-2 years	10
2-3 years	2
3-4 years	3
4-5 years	2

The borderline case is included in the 1-2-years group.

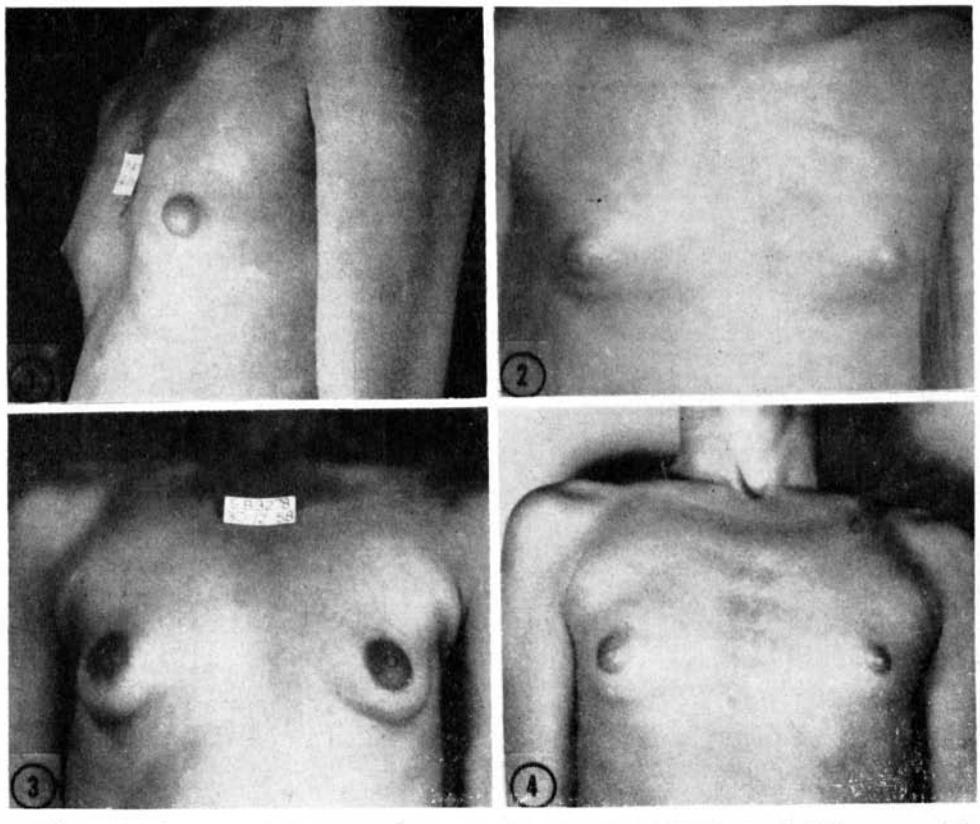
Breast affected.—Both breasts were affected in all cases. In 3 cases one side was larger than the other, causing an asymmetric appearance. In two the right side was the larger.

Grading of the breast.—The sizes of the breasts are indicated by the grading, as described.

Symmetrical cases		*Asymmetrical cases*	
Grade	*Cases*	*Grade*	*Cases*
I	4	I & 0	0
II	6	I & II	2
III	8	II & III	1

Symptoms.—Of 19 patients whose histories were available, 12 had complained of pain in the breast. In some cases the pain was pricking in nature and was present during the process of breast enlargement; in 5 cases it was noticed during periods of lepra reaction. No patient complained of secretion from the nipple, nor could any fluid be expressed by manipulation. Hypertrophy of the nipple was present in 10 cases.

Leprosy history.—Temporary regression of gynecomastia in leprosy is not infrequently seen, especially in cases in which the enlargement



FIGS. 1-4. Degrees of gynecomastia: 1, Grade I; 2, Grade II; 3, Grade III; asymmetric.

is not marked. In my series 5 cases told of intermittent enlargement during lepra reaction, followed by partial regression. Complete remission was seen in 2 other cases. It was observed that once the gynecomastia was well developed, it persisted. Surgical treatment was given at the request of the patients for cosmetic reasons in 6 cases, all grade III.

Duration and bacteriologic index.—Data on these features of the cases, including the controls, are given in Table 1.

Sixteen of the 21 study cases had high bacteriologic indices (more than 2.0), they obviously being advanced lepromatous cases. In 5 patients the B.I. was below 2.0; one of them was borderline and the other 4 were resolving lepromatous cases who had come for surgical treatment.

GENITAL ORGANS

In the study sample, a history of pain and swelling of the testes was elicited from 11 patients, while 8 of them could not remember any abnormal swelling or pain in the testis. In the 2 other cases the history was not recorded.

TABLE 1.—*Duration of the disease and the bacteriologic index of the cases studied.*

	Type of cases			
	Lepromatous		Borderline	
	Study cases (No.)	Control cases (No.)	Study cases (No.)	Control cases (No.)
Duration (years)				
0 - 4	—	—	1	6
5 - 9	4	1	—	—
10+	16	7	—	—
Bacteriologic index				
0 - 2.0	4	—	1	5
2.1 - 4.0	12	4	—	1
>4.0	4	4	—	—

Among the control cases a history of pain and swelling was obtained in 6 out of 8 lepromatous cases, and in 2 out of the 6 belonging to the borderline group.

The size of the penis in all cases was that of a normal adult male of a comparable age. The appearance of the testes is tabulated in Table 2.

TABLE 2.—*Appearance of the testis, study cases and control cases.*

Description of testis	Lepromatous		Borderline	
	Study cases (No.)	Control cases (No.)	Study cases (No.)	Control cases (No.)
Small and atrophic, both sides	9	4	1	2
Small and atrophic, one side; minimal hydrocele on the other side	3	2	—	—
Small and atrophic, one side, absent on the other	1	—	—	—
Size within normal limits, both sides	5	2	—	—
Large hydrocele on both sides	1	—	—	—
Findings not recorded	1	—	—	1

SECONDARY SEXUAL CHARACTERISTICS

Hair.—Study cases: (*a*) Head: Temporal recession of the hair line was seen in only 1 case; in 18 cases the hair was normal; in 2 cases it was not recorded.

(*b*) Pubic hair: Distribution was that of the male in 14 cases; in 6 cases it was that of the female; in one case it was not recorded. The amount of hair in the pubic region was scanty in 10 cases, normal in 10 cases, not recorded in 1 case.

(*c*) Axillary hair: Scanty in 13 cases, normal in 4 cases, not recorded in 4 cases.

Control cases: The 6 borderline-group cases were all normal with respect to the features of the hair enumerated above. In the 8 lepromatous cases there was no evidence of receding hair line. The quantity of axillary and pubic hair was normal in 4, sparse in 2, and extremely scanty in another 2 cases. In 6, the distribution of hair was that of the normal male, while in the other 2 the hair was too scanty for a pattern of distribution to be defined.

Voice.—The voice was that of an adult male in all cases.

Measure of sexual function and fertility.—In 15 cases erection and emission was present, in one case erection only, and in 2 cases no erection or emission. In 3 cases the history was inadequate.

Thirteen patients were not married. Of 4 who were known to be married only one had a child, and that was before he contracted leprosy. In 4 cases the marital status was not recorded.

Control cases: All 6 borderline patients had erection and emission. Five were married and had more than one child; in 1 the history was inadequate. Among the 8 lepromatous patients erection was not present in 1 case, and there was no emission in another case. Seven of these patients were not married; the one who was married had 3 children, but all were born before he developed the disease.

Excretion of 17-ketosteroids.—Twenty-four-hour excretion of 17-ketosteroid in the urine was estimated in 4 cases with gynecomastia and in 2 controls. Findings in the study cases: (1) 6.0 mgm., (2) 3.3 mgm., (3) 5.7 mgm., (4) 2.8 mgm. In the control cases: (1) 3.3 mgm., (2) 3.6 mgm. In our laboratory the normal values range from 7 to 10 mgm.

PATHOLOGIC CHANGES IN THE TESTES OF STUDY CASES

(*See Figs. 5-12*)

The tunica vaginalis was markedly thickened in all of the study cases. The tissue was abnormal in consistence. In no case could normal seminiferous tubules be picked up with forceps.

On microscopic examination, definite pathologic changes of varying degrees were present in all cases. The inflammatory process could be differentiated into three stages: invasion, acute inflammatory reaction, and resolution with atrophy. These stages merged into each other, and different stages were found in different parts of the same testis. Evidently the inflammatory process could become arrested at any stage, and the tubules and interstitial cells could undergo regeneration if total atrophy had not taken place.

(1) *Stage of invasion.*—Testicular tissue may be invaded by lepra bacilli in two ways, by direct invasion from the surrounding tissue into the interstitial tissue of the testis, or via the lymphatics and blood stream. The latter is much more common, and it may often take place during lepra reaction.

In cases where there is direct invasion from the periphery, cells of

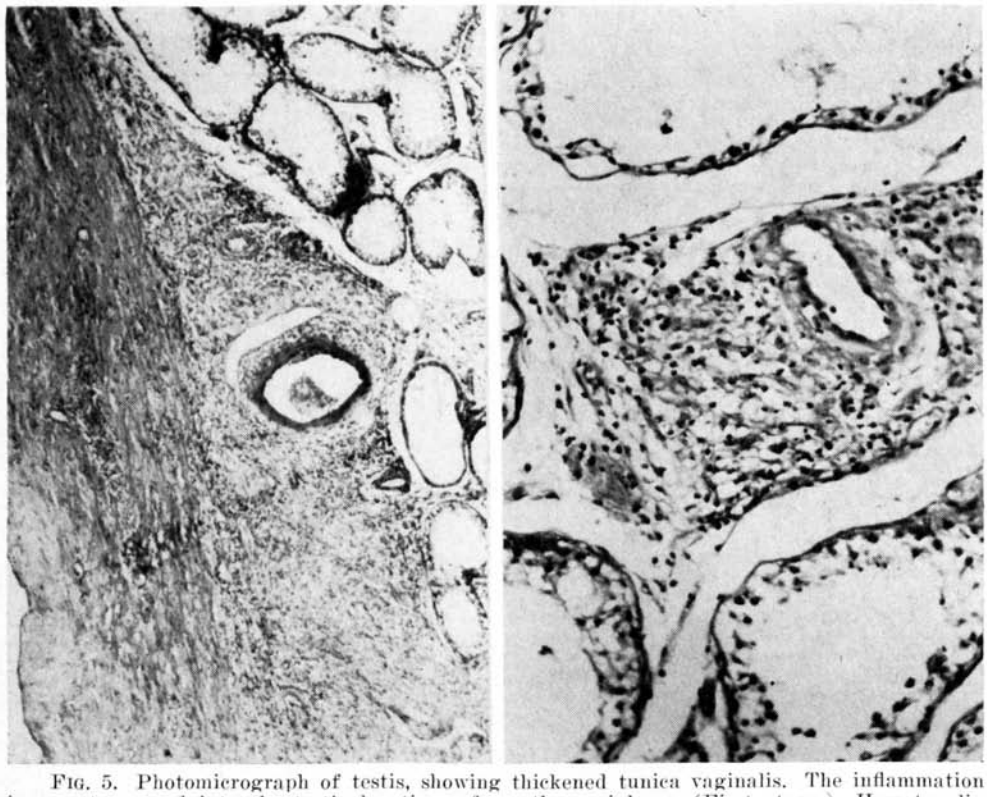


FIG. 5. Photomicrograph of testis, showing thickened tunica vaginalis. The inflammation is seen to spread into the testicular tissue from the periphery. (First stage.) Hematoxylin and eosin, 50X.

FIG. 6. Focal collection of inflammatory cells is seen around a blood vessel in the testis. From such foci the infection spreads centrifugally to surrounding areas. (First stage.) Hematoxylin and eosin, 160X.

inflammation, consisting of lymphocytes, plasma cells and macrophages, are found in large numbers below the tunica vaginalis, which shows marked fibrous thickening. There is extension of the inflammatory infiltrate toward the deeply-situated seminiferous tubules along the interstitial tissue. Acid-fast staining shows bacilli inside macrophages and lying free in tissue spaces. In cases where the infection is apparently carried through the lymphatics or the blood stream, focal areas of inflammation are scattered through the testis. These consist of collections of lymphocytes, plasma cells and macrophages, around lymphatics and blood vessels, which show some thickening and proliferation of endothelium. Inflammatory infiltrate spreads centrifugally into the surrounding tissue from these foci.

During this stage, in many areas there is commencing thickening of the basement membrane of the seminiferous tubules with early signs of atrophy. In these the development of sperms stops at the stage of spermatogonia and there is no active spermatogenesis. In other areas where there is no evidence of inflammatory-cell reaction the seminiferous tubules appear normal and there is active spermatogenesis. The

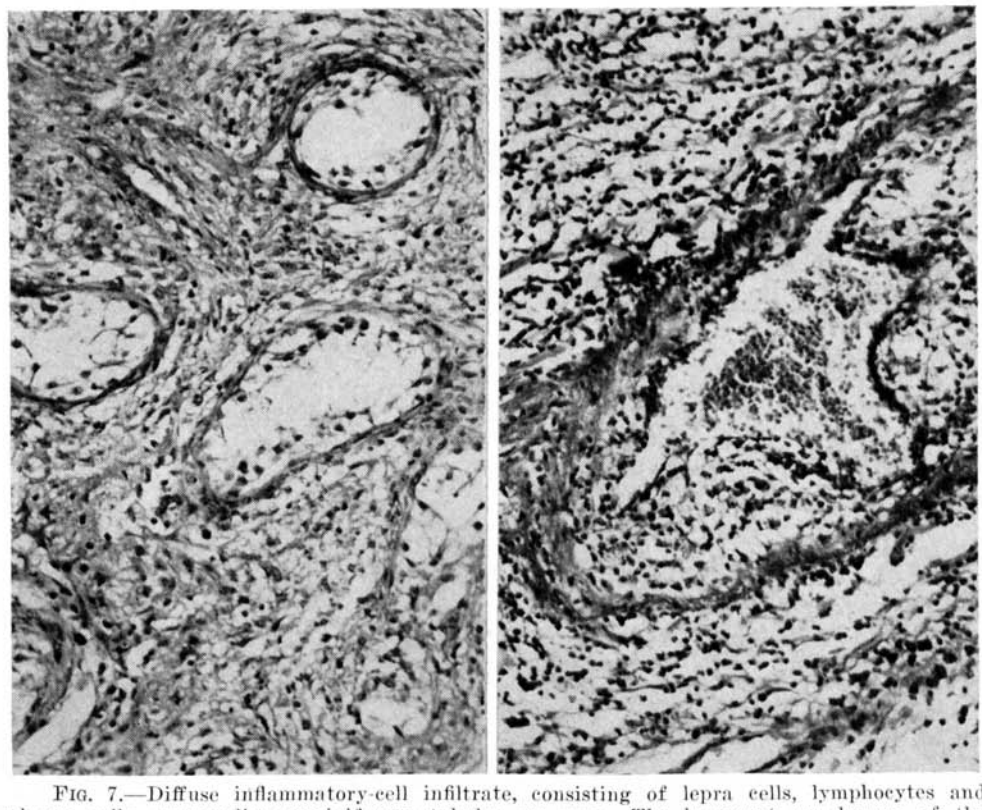


FIG. 7.—Diffuse inflammatory-cell infiltrate, consisting of lepra cells, lymphocytes and plasma cells, surrounding seminiferous tubules are seen. The basement membranes of the tubules are thickened, and there are only a few Sertoli cells remaining. (Second stage.) Hematoxylin and eosin, 160X.

FIG. 8.—Blood vessel showing infiltration of its entire wall with lymphocytes, plasma cells and lepra cells. There is edema of the vessel wall, and narrowing of the lumen by irregular thickening of the intima. Hematoxylin and eosin, 160X.

Leydig cells are seen in clumps. Acid-fast staining shows in all cases bacilli inside macrophages and also lying free in the interstitial tissue.

(2) *Stage of acute inflammatory reaction.*—The inflammatory reaction involves the entire testis, having spread in the interstitial tissue and surrounded the seminiferous tubules. The inflammatory cells consist of macrophages, lymphocytes and plasma cells. The cell of reaction at this stage is the macrophage, or the "lepra cell." The lepra cells appear in various forms. They may be large, with pink granular cytoplasm and vesicular central nuclei, or they may have a foamy and vacuolated cytoplasm with the nuclei displaced to the periphery, or they may resemble young fibroblasts. Quite often invasion of the seminiferous tubules by bacillus-laden macrophages is seen. Degeneration of the seminiferous tubules is always extensive. Diffuse marked thickening of the basement membrane and hyalinization of the tubules are invariably present. There is complete arrest of spermatogenesis. In some cases spermatogonia are still seen, but in most cases all of the germ cells are destroyed, leaving only Sertoli cells or completely

hyalinized tubules. Clumps of Leydig cells may be present in the interstitial tissue.

The vessels show marked perivascular inflammation and marked thickening and hyalinization of the media, and there is also intimal proliferation. This picture is typical of an obliterative endarteritis and periarteritis.

Acid-fast bacilli are inside lepra cells in the interstitial tissue and inside seminiferous tubules. Bacilli are also found in the spermatogonia, and in the walls of blood vessels and lymphatics. Clumps of bacilli are also seen lying free. In some cases the invasion by bacillus-laden macrophages is so massive that in the section stained for acid-fast bacilli these cells obscure all other cells.

(3) *Stage of resolution and atrophy.*—At this stage there is only scanty inflammatory-cell reaction. Scattered plasma cells and lymphocytes are present, with very few if any lepra cells. The plasma cells are more numerous than in the previous stages. The cytoplasm of the lepra cells is markedly foamy and the nuclei are pale. One is repeatedly struck by the paucity of the inflammatory-cell reaction. Also by the extent and completeness of the degeneration of the seminiferous tubules,

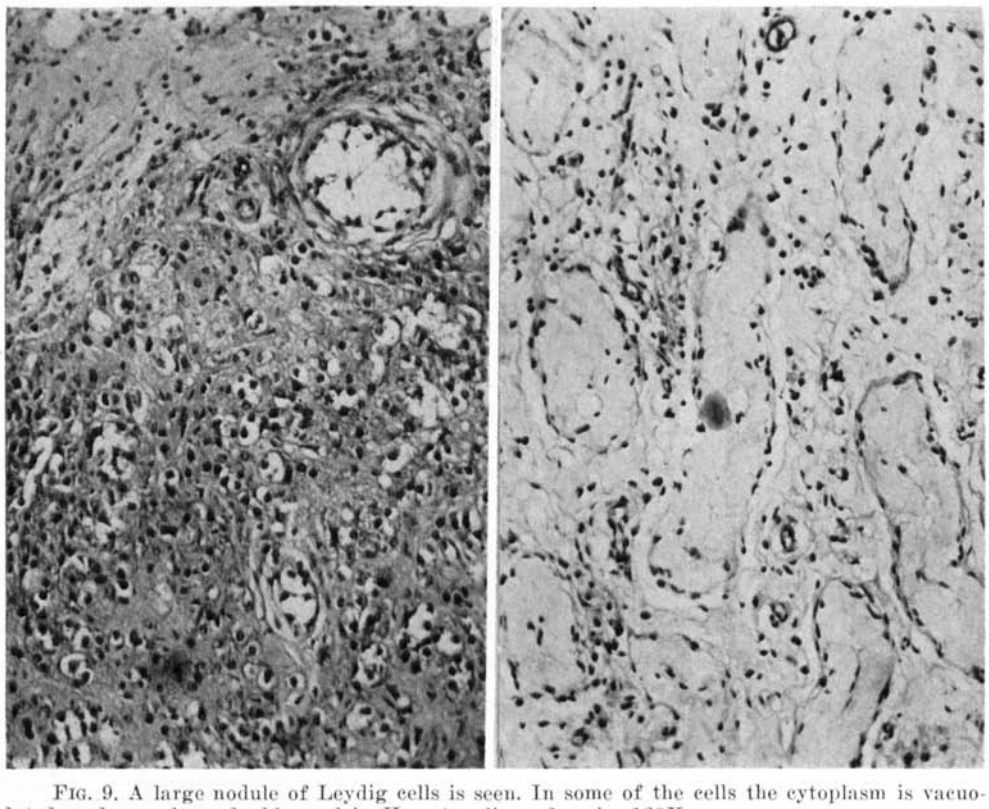


FIG. 9. A large nodule of Leydig cells is seen. In some of the cells the cytoplasm is vacuolated, and some have double nuclei. Hematoxylin and eosin, 160X.

FIG. 10. Complete hyalinization of seminiferous tubules. There are a few scattered lymphocytes, plasma cells and foamy macrophages. (Third stage.) Hematoxylin and eosin, 160X.

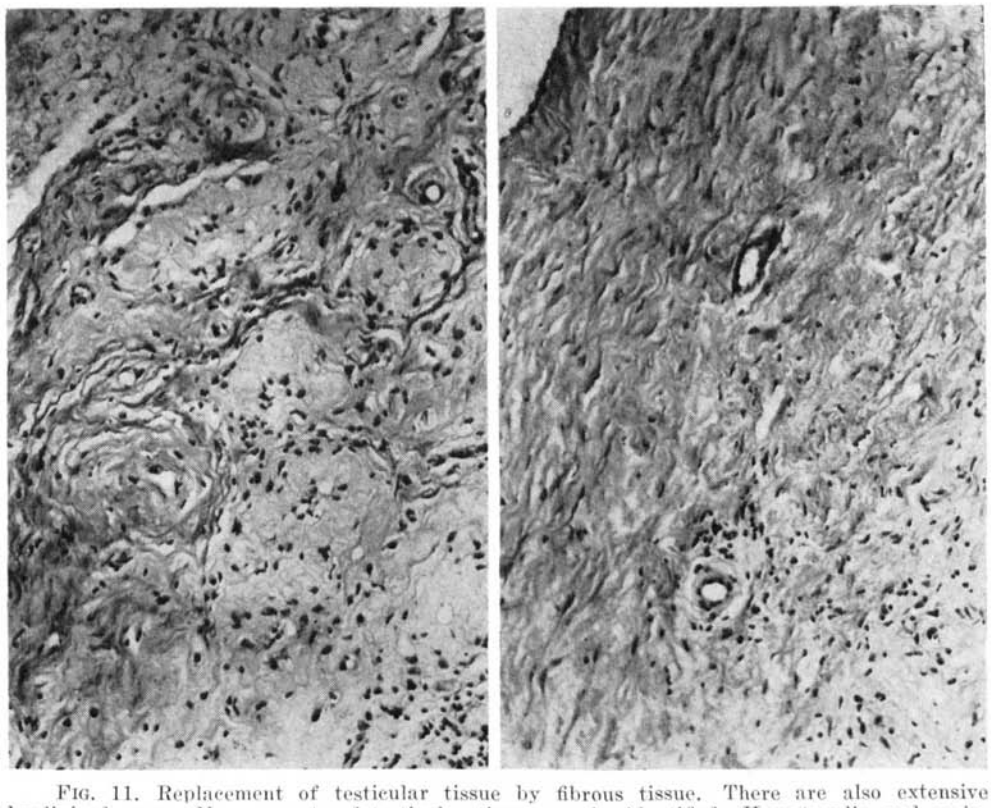


FIG. 11. Replacement of testicular tissue by fibrous tissue. There are also extensive hyalinized areas. No remnants of testicular tissue can be identified. Hematoxylin and eosin, 160X.

FIG. 12. Complete fibrosis of testis. The thickened tunica vaginalis (left and above) is seen to merge with the fibrosed testicular tissue. Hematoxylin and eosin, 160X.

which is out of all proportion to the degree of lepromatous infiltration. The tubules are small, atrophic, well-hyalinized and fibrosed. In some cases only the outlines of the tubules may be made out; in others they are completely replaced by fibrous tissue, giving rise to a peculiar laminated onion-peel appearance.

In general, the degree of atrophy of the tubules is proportional to the clumping and apparent increase in number of the Leydig cells. The medium-sized and small vessels show marked hyalinization of the entire walls, with much narrowing of the lumen. Leydig cells are apparently increased in number and hypertrophied, and are seen in clumps. The tunica vaginalis is very much thickened and tends to merge with the fibrosed seminiferous tubules. In most cases acid-fast staining reveals no bacilli at this stage.

In the borderline case there are large collections of lymphocytes, epithelioid cells and giant cells. A few scattered macrophages are also seen. The seminiferous tubules show only Sertoli cells. The basement membrane is thickened. Some of the tubules show hyalinization and replacement fibrosis. Acid-fast staining reveals no bacilli.

Out of the 21 study cases, 2 were in the stage of invasion, 5 in the stage of acute inflammation, and 14 in the stage of resolution and atrophy. Active spermatogenesis was seen in 4 cases. In 1 case there was evidence of spermatogenesis side by side with tubules showing complete atrophy and hyalinization. Acid-fast bacilli were present in all cases in the stages of invasion and acute inflammation, and in 5 cases in the stage of resolution and atrophy. Acid-fast bacilli were absent, even though skin smears were positive, in 8 of the 14 cases in the atrophic stage.

Leydig cells.—The striking feature in all the 21 cases was the presence and appearance of the Leydig cells. The collections of these cells varied from small clumps to large groups of about 2 mm. diameter. They were collected between the atrophic tubules, and in some areas surrounded them completely. In a few cases the Leydig cell collections were found immediately below the thickened tunica vaginalis. The larger collections completely occupied the interstitial spaces between the tubules.

The Leydig cells were larger than normal, with abundant cytoplasm. The cytoplasm contained mostly eosinophilic granular material. In some cells there was marked vacuolation of the cytoplasm, which appeared pale. The nuclei were large and are of various sizes, sometimes dense but often vesicular. Few cells were binucleated, but some had two nucleoli. No definite mitotic activity was observed.

The Leydig cells were present in apparently increased numbers in a majority of the cases. Their presence was very evident in all cases and in most cases their appearance in the midst of a more or less completely hyalinized tissue was striking.

THE TESTES IN THE CONTROL CASES

1. *Borderline cases.*—Two of the biopsy specimens from the borderline cases showed no significant lesion. In the other 4 there was thickening of the tunica vaginalis, and the inflammatory reaction was in the stage of invasion. Focal collections of epithelioid cells, poorly-formed giant cells, lymphocytes and plasma cells were present. The testicular tissue showed patchy areas of atrophy, with thickened basement membrane and hyalinization of the tubules. In all 6 cases there were also normal-looking areas showing active spermatogenesis.

A few scattered Leydig cells like those seen in the normal adult testis were present in the interstitial tissue in 4 cases. In two cases the Leydig cells in focal areas were infiltrated and gradually destroyed.

Acid-fast staining showed a few scattered bacilli in one case.

2. *Lepromatous cases.*—Of the biopsy specimens of the testis from the 8 lepromatous cases, 2 were at the stage of invasion, 4 at the stage of acute inflammatory reaction, and 2 at the stage of resolution and atrophy. In one there was evidence of active spermatogenesis.

Acid-fast staining showed bacilli in all cases. In 6 cases, belonging

to the first two stages, bacilli were abundant inside macrophages and inside germ cells.

The striking feature is the complete absence of Leydig cells in 6 cases belonging to the last two stages of the inflammatory reaction. In 2 cases with early infiltration the Leydig cells were infiltrated by inflammatory cells and were being destroyed. Only a few remnants of them could be made out among the inflammatory cells.

PATHOLOGY OF BREAST TISSUE

The gross appearance of the surgical specimens was of hemispherical pieces of fibro-fatty tissue, firm in consistence.

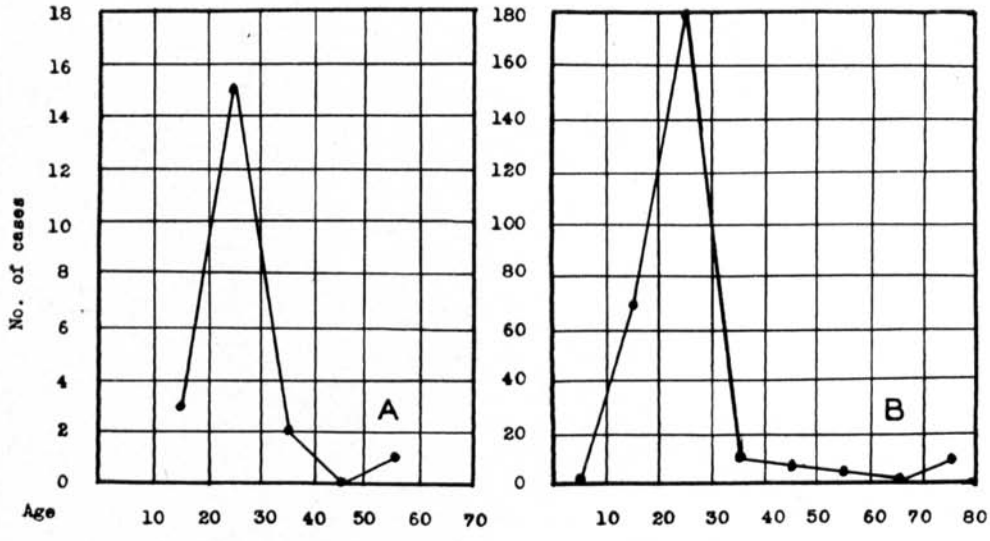
Microscopy revealed a typical picture of breast in gynecomastia, with proliferation of duct epithelium. No secretion was seen in the lumens of the ducts. There was marked proliferation of connective tissue around these ducts. In a few cases adipose tissue was also present, but the amount of connective tissue was far more than was that of fatty tissue. No alveoli as found in the female breast were present. There were scattered lymphocytes and plasma cells in the stroma. Acid-fast staining showed no bacilli. Both the breasts examined microscopically appeared exactly similar, and were not different from specimens obtained from cases of essential gynecomastia.

DISCUSSION

Incidence.—Baptista, writing from Brazil ([1]), reported gynecomastia in 72 out of 842 patients of all ages (8.6%). Of a series of 600 lepromatous cases studied in South Africa, 6 per cent had gynecomastia ([19]). The incidence in South India has been reported as being 11.8 per cent, in a study of 488 lepromatous patients ([13]). No tuberculoid case was found to have gynecomastia ([19]). In my series gynecomastia was observed only in cases of the lepromatous type and the borderline group, and not in patients belonging to the tuberculoid type or the indeterminate group.

Age distribution.—In the present study the largest incidence was between the ages of 20 and 30 years, as shown in Text-fig. 1A, very similar to the incidence of essential gynecomastia in healthy and well-nourished persons ([18]) in whom the maximum incidence was likewise in the third decade, (see Text-fig. 1B). Cochrane ([5]) states that the great majority of those acquiring leprosy are infected and show manifestations of the disease before the age of 15 years. It is only to be expected that the onset of gynecomastia in leprosy will be after a period of 5 to 10 years, long enough for this slowly progressive disease to cause pathologic changes in various internal organs and to produce gynecomastia. Therefore, in general the age of onset of gynecomastia in leprosy is found to be sometime in the third decade, although it can occur at any age after puberty.

Breast affected.—Some authors have described a high percentage of



TEXT-FIG. 1. Age distribution of gynecomastia cases. A. Age distribution of the 21 cases of the series reported. B. Age distribution of Karsner's cases of essential gynecomastia.

unilateral involvement in essential gynecomastia, with no appreciable difference of incidence with respect to left or right ([23, 26]). In the present study of leprosy cases all the cases were bilateral, only 3 of them asymmetric.

Duration of the complaint.—The duration of gynecomastia in the cases studied varied from 6 months to 5 years. There was no significant correlation between the duration of the complaint and the size of the breast. There were 2 cases in which the condition had existed for 4 and 5 years, but the breasts were only grade I, while on the other hand there was 1 patient who had noticed the enlargement only 6 months before, but it had already attained the grade II size.

Hypertrophy of the nipple was not an infrequent feature (Fig. 1). The nipple was biopsied in 4 cases, and hyperplasia and hypertrophy of smooth muscle and proliferation of ducts were seen in all of the specimens.

It is said that once gynecomastia has developed it is permanent ([35]). Among 34 patients with essential gynecomastia seen at Guy's Hospital, only 2 showed spontaneous remission ([11]). They were of grade I severity. It is felt that in essential gynecomastia, spontaneous remission is extremely rare and cannot be anticipated. Of my cases, 2 showed complete regression. Both belonged to grade I. In 5 cases there was enlargement during a period of lepra reaction, followed by partial regression. It may be said that once gynecomastia has developed to grade II, it tends to be well-established and permanent.

Sexual characteristics and function.—Out of 25 patients in one series, 5 had only scanty hair in the axilla, and hair on the trunk was

sparse ([10]). In my series axillary hair was scanty in 13, and the pubic hair was female in distribution in 6 lepromatous cases. In any case of advanced lepromatous leprosy, with or without gynecomastia, the skin appendages undergo extensive destruction and atrophy. The distribution of hair on the trunk and other parts of the body cannot, therefore, be used for evaluating secondary sexual characteristics. However, the axillary hair was scanty in a larger proportion of cases with gynecomastia than of controls, and may therefore be useful.

The voice was that of an adult male in all cases, with and without gynecomastia.

Erection and emission were present in 15 out of 18 cases in the study sample. This was not significantly different from the lepromatous patients studied in the control group. None of the lepromatous patients belonging to either group had children after they contracted leprosy. No examination of the semen was made in these cases, but the biopsy specimens indicated that among the study cases there were normal sperms in 3 cases of early testicular involvement and in one case in the stage of resolution and regeneration.

17-ketosteroid.—The 17-ketosteroid in urine was estimated in 4 cases with and 2 cases without gynecomastia, and the values were found to be low in all. This finding is consistent with those of other authors, who have found 17-ketosteroid excretion normal or below normal ([10, 19]).

Pathology of testes.—In cases with gynecomastia the following features are seen: (1) gross atrophy of testis (in 17 out of 20 cases examined); (2) marked thickening of tunica vaginalis; (3) thickening with hyalinization of the basement membrane, to total replacement of the seminiferous tubules by hyalinized fibrous tissue; and (4) hypertrophy of Leydig cells, with clumping in all and apparent increase in number in the majority of cases.

The chief difference seen in the control cases was in regard to the Leydig cells. They were either totally absent or undergoing degeneration, or they appeared normal. The difference was so obvious that it was possible to say in every case, from the microscopic appearance of the testis, whether or not gynecomastia was present.

Sections from all of the 35 cases included in this study were examined independently by two other pathologists,[2] who were not given any information regarding the clinical histories. They were able to pick out all of the cases with gynecomastia, except one.

Lepromatous leprosy is a systemic disease, involving chiefly the skin, the nerves and the reticuloendothelial system. The lymph nodes are sometimes extensively affected. Invariably during a period of lepra reaction there is bacteremia. The lepra bacilli are carried to the testis either through lymphatics or blood vessels. Invasion may also occur directly from the surrounding skin. The testis is the only internal

[2] Dr. E. W. Gault and Dr. Irwin Samuel.

organ which may be completely destroyed by leprosy. Clearly there is no inherent physiologic factor in the gonads responsible for their vulnerability, because the ovaries in lepromatous cases are not found to be affected [10]. It is observed that in leprosy superficial nerves and large nerve trunks lying subcutaneously are affected causing destructive changes, in contrast to those deeply situated. That lowered temperature is an important factor in augmenting the pathogenicity of lepra bacilli [4] is an interesting speculation.

When there is an invasion of the testis by lepra cells and inflammation of the blood vessels of the testis, the parenchyma begins to atrophy. It is said in general that spermatogenic cells are most sensitive while the Sertoli and Leydig cells are least sensitive to the various injurious agents which cause testicular atrophy [33]. This is found to be true in leprosy. In early cases and in mild or moderate infections there is atrophy of the seminiferous tubules, but the Sertoli cells and Leydig cells are preserved. Later on the Sertoli cells may also be replaced by hyalinized fibrous tissue. In cases of massive and severe infection, all testicular tissue, including Leydig cells, is destroyed and gradually replaced by hyalinized fibrous tissue.

A number of authors have described atrophy of seminiferous tubules coexisting with Leydig cell proliferation, and it was believed that Leydig cell hyperplasia was largely or entirely secondary to tubular degeneration [16, 22, 34]. In the present study some correlation was seen between the extent of the atrophy of the tubules and the degree of Leydig cell hyperplasia. There were, however, instances with marked interstitial cell hyperplasia with moderate tubular degeneration, and others with small interstitial cell collections with marked tubular degeneration and atrophy. In the control group there were cases with total atrophy of the seminiferous tubules as well as the Leydig cells. It is difficult to accept the suggestion [16] that the tubular atrophy causes a lowering of pressure on the interstitial cells, which is responsible for the Leydig cell proliferation. It is reasonable to assume that tubular atrophy initiates a chain of hormonal changes which stimulate hypertrophy and proliferation of interstitial cells if they or their precursors are not already destroyed by the injurious agent. It may be that the destruction or absence of germinal epithelium causes the release of, or production of, abnormal quantities of interstitial-cell-stimulating hormone from the pituitary [11].

Klinefelter syndrome.—Klinefelter *et al.* [21] described a syndrome consisting of hyalinization of seminiferous tubules in a small testis, aspermatogenesis, gynecomastia, clumping of Leydig cells, normal or decreased urinary 17-ketosteroids, and increase in urinary gonadotrophin. Heller and Nelson [12] modified this concept and said that there are 4 basic and consistent factors, namely, small testis, hyalinization of seminiferous tubules, azoospermia and high urinary gonadotrophin, and a number of other variable features. It is suggested that

testicular atrophy in leprosy may be an acquired Klinefelter-like syndrome ([10, 11, 19]).

From my own observations it may be said that in leprous orchitis the only constant feature is the thickening of the basement membrane and hyalinization of seminiferous tubules, which may be focal or diffuse. Depending on the severity and duration of the infection and other factors such as antileprosy treatment, there is a wide variety of manifestations which may include one or more features described under the Klinefelter syndrome.

Pathogenesis of gynecomastia in leprosy.—Gonadotrophin may be markedly elevated in cases of testicular atrophy in leprosy, with or without gynecomastia ([10, 19]). This is attributed to atrophy of the seminiferous tubules. It has been suggested that the tubules produce a hormone, "inhibin," which inhibits the gonadotrophic hormone and also inhibits the mammogenic activity of testosterone ([3]). Absence of "inhibin" may result in increased gonadotrophin. This theory is entirely hypothetical, however, and the existence of "inhibin" is not confirmed.

Most cases of chorionic epithelioma are associated with gynecomastia, usually bilateral, and in these cases there is excess of chorionic gonadotrophin ([9]). Chorionic produces hyperplasia of Leydig cells, gynecomastia and an increase in urinary estrogens ([25]). It is reasonable to assume that in these cases chorionic epithelioma secretes gonadotrophin which produces hyperplasia of Leydig cells, which in turn produce estrogens. Estrogens are known to cause gynecomastia ([23]).

In leprosy, depending on the severity and duration of infection of the testis, the Leydig cells or their precursors may be spared or destroyed. All our cases with gynecomastia showed clumping and hypertrophy of the Leydig cells, and in a large majority of cases there was apparent hyperplasia as compared with the control cases without gynecomastia, in which the Leydig cells were normal or totally destroyed or undergoing degeneration. So it can quite conceivably be that the increase of gonadotrophin due to atrophic tubules stimulated the cells of Leydig which hypertrophied, multiplied, and produced estrogens in excess, which in turn caused the development of gynecomastia.

It is well known that degeneration of seminiferous tubules and hypertrophy and clumping of Leydig cells do not always result in gynecomastia ([14, 16]). There may be other accessory factors in leprosy which contribute to the development of gynecomastia. One of the most important of these factors is liver disease. Testicular atrophy and gynecomastia are reported in cirrhosis of the liver, infective hepatitis, and carcinoma of the liver ([20, 24, 32]). In lepromatous leprosy, lesions in the liver are not uncommon ([2, 28]). Liver function tests have showed that lepromatous cases with and without gynecomastia have gross liver dysfunction ([19]).

I have seen hepatomegaly in cases of lepra reaction, during which the liver was painful and tender. Liver biopsies performed in two such cases in lepra reaction showed periportal lepromatous infiltration, consisting of large collections of lepra cells, plasma cells and lymphocytes. The lepra cells and also the Kupffer cells were distended with bacilli. In this connection it should also be noted that in some cases the breasts enlarge during the course of a lepra reaction. It is well known that circulating estrogens are inactivated in the liver ([15]). In lepromatous leprosy, especially during reaction, it may well be that there is liver disease interfering with the inactivation of estrogens released in large quantities by the proliferating Leydig cells. Consequently there is increase in circulating estrogens, resulting in gynecomastia. This seems a reasonable hypothesis, but no conclusion can be drawn before interstitial-cell-stimulating hormone and estrogen levels are measured in these cases in blood, urine and testicular tissue during the period of development of gynecomastia.

SUMMARY

1. Twenty-one cases of leprosy with gynecomastia, and a control group of 14 cases, were studied with special reference to testicular biopsies. Of the 21 cases, 20 were lepromatous and 1 was borderline. No tuberculoid or indeterminate case was found to have gynecomastia.

2. In all cases with gynecomastia, atrophy of seminiferous tubules and hypertrophy and clumping of Leydig cells were present. In the control group the important difference was that the Leydig cells were either totally destroyed or undergoing degeneration, or were normal. The suggestion that leprous atrophy of the testes is one of Klinefelter syndrome has been considered. It is felt that in leprous orchitis there is invariably atrophy of tubules, but that the presence of other features of the Klinefelter syndrome is variable and depends on the severity and duration of the infection in the testes.

3. The pathogenesis of gynecomastia in leprosy is discussed. It is shown that in the testes of cases with gynecomastia there is hypertrophy and hyperplasia of the Leydig cells. It may be that excess of estrogens produced by these interstitial cells was not effectively inactivated by the liver already impaired by leprosy, and that they stimulated the breast to produce gynecomastia.

4. It is suggested that interstitial-cell-stimulating hormone and estrogens in these cases must be measured, especially during the development of gynecomastia, before a definite conclusion can be arrived at.

RESUMEN

1. Veintiún casos de lepra con ginecomastia, y un grupo de 11 testigos, fueron estudiados con referencia particular a las biopsias testiculares. De los 21 casos, 20 eran lepromatosos y 1 era limítrofe. No se observó ningún caso tuberculoideo o indeterminado que tuviera ginecomastia.

2. En todos los casos de ginecomastia, había atrofia de los conductos seminíferos e

hipertrofia y conglutinación de las células de Leydig. En el grupo testigo, la diferencia importante consistió en que las células de Leydig se hallaban bien totalmente destruídas o experimentando degeneración, o eran normales. Se ha considerado la indicación de que la atrofia leprosa de los testículos es un síndrome de Klinefelter. Opínase que, en la orquitis leprosa, existe invariablemente atrofia de los conductos, pero que es variable la presencia de otras características del síndrome de Klinefelter, basándose en la gravedad y duración de la infección de los testículos.

3. Se discute la patogenia de la ginecomastia en la lepra. Se demuestra que, en los testículos de los sujetos con ginecomastia, existen hipertrofia e hiperplasia de las células de Leydig. Tal vez el exceso de estrógenos producido por estes células intersticiales no fuera inactivado eficazmente por el hígado, ya afectado por la lepra, y excitaran la mama a producir ginecomastia.

4. Se sugiere que hay que medir en estos casos la hormona y los estrógenos que excitan las células intersticiales, sobre todo durante la formación de la ginecomastia, antes de poder formular una conclusión bien definida.

SOMMAIRE

1. Vingt-et-un cas de lèpre avec gynécomastie, et 14 malades témoins, ont été étudiés par des biopsies testiculaires. Parmi les 21 cas, 20 étaient lépromateux, 1 borderline. Aucun malade tuberculoïde ou indeterminé n'a été reconnu atteint de gynécomastie.

2. Une atrophie des canalicules séminipares, ainsi qu'une hypertrophie et une aggrégation des cellules de Leydig, ont été notée, dans tous les cas avec gynécomastie. La difference importante à noter dans le groupe témoin fut que les cellules de Leydig y étaient soit totalement détruites ou en voie d'involution, soit normales. La suggestion que l'atrophie lépreuse des testicules relève du syndrome de Klinefelter a été examinée. On a le sentiment qu'alors que dans l'orchite lépreuse il y a invariablement atrophie des canalicules, la présence des autres composantes du syndrome de Klinefelter est variable et dépend de la séverité et de la durée de l'infection au niveau des testicules.

3. La pathogénie de la gynécomastie dans la lépre est discutée. On note de l'hypertrophie et de l'hyperplasie des cellules de Leydig dans les testícules des malades atteints de gynécomastie. Il se peut que les oestrogènes produits de manière excessive par ces cellules interstitielles ne soient pas efficacement inactivés par le foie déjà altéré par la lèpre, et qu'ils stimulent le tissu mammaire, entraînant la gynécomastie.

4. Avant qu'une conclusion précise puisse être tirée, il serait souhaitable que l'I.C.S.H. (hormone de stimulation des cellules interstitielles) et les oestrogènes soient dosés dans ces cas, particulièrement pendant l'établissement de la gynécomastie.

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