MALE HORMONES IN THE MANAGEMENT OF LEPROUS GYNECOMASTIA

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Gynecomastia is recognized as a not uncommon complication of leprosy ([2, 5, 6, 10]), but as yet little is known of this condition, and it has not responded satisfactorily to medical therapy. In reviewing the literature of gynecomastia, the condition is found to be a concomitant of a large group of pathologic conditions, but its actual etiology remains obscure. However, there is one statement which can be made concerning its etiology, and that is that it is a condition caused by a hormonal imbalance due either to abnormal production or destruction and excretion of male and/or female hormone. And this, having been said, means very little.

There is considerable conflict in the literature as to the actual hormonal imbalances which can produce gynecomastia ([12]), and it is apparent that it can be caused by more than one hormonal abnormality. Some writers would attribute all gynecomastia to liver pathology ([7, 8]), which allows an increase of circulating estrogens through lack of conjugating ability—conjugating being necessary prior to excretion. Others ([11]) claim that there is no correlation between gynecomastia and circulating estrogens, but that gynecomastia may perhaps be initiated by a temporary excessive estrogenic stimulus, and when once established, may be maintained by smaller amounts of estrogen. Another suggestion, made by Kinnear and Davison ([6]), is that the disturbance in hormone balance is due to amyloid displacement of the adrenals with a decreased production of 17-ketosteroid precursors.

It has been found by Wheeler *et al.* ([15]) that unilateral gynecomastia can be produced in experimental animals by topical application to one breast of estrogens in the presence of normal pituitary secretion. Androgens and adrenocortical hormones will also produce gynecomastia by a similar application in the presence or absence of pituitary stimulus. Yet another investigator ([13]) states that any disease process that seriously affects the testes can lead to a hormonal imbalance sufficient to produce gynecomastia. Thus we have suggestions of implication of the liver, the adrenals, and the testes.

In summarizing the pathologic conditions in which gynecomastia

[1]This institution, operated by the Church of the Brethren Mission, is ordinarily known as the "Garkida Leprosarium." However, it is officially known as the Adamawa Provincial Leprosarium, there being one such institution in each of the 14 provinces of Northern Nigeria.

may occur Wheeler *et al.* list 47 disease entities—without mentioning leprosy as one of the etiologic factors.

Perhaps the most plausible statements on the hormonal relationships which may cause gynecomastia is that by Herrmann *et al.* [3] that:

> Steroid biosynthesis is a stepwise procedure and the secretory end-product is obtained by gradual enzymatic transformation of a precursor . . . . the suggested pathway being progesterone → 17-hydroxyprogesterone → androgen → estrogen. The morphologic concept of one particular type of cell being the source of production of one type of hormone is becoming rapidly obsolete.

Thus perhaps anywhere along this path malfunction may result in gynecomastia.

Although we were at the time in Nigeria in a place where a survey of the literature was not possible, we decided to determine the effect of the administration of male hormones on leprosy patients afflicted with gynecomastia. Since this study was done we have found that similar work had been done in nonleprous gynecomastia. Lloyd and Williams [8] discuss the association with hepatic cirrhosis. Treves [13] and Hoffman [4] give us good general summaries of the condition, and report the results of hormone therapy in idiopathic gynecomastia as being satisfactory. On the other hand McCullagh and Rossmiller [9] and Dexter [1] report instances where gynecomastia has been incited by the administration of male hormone in the form of methyl testosterone.

MATERIAL AND METHODS

A total of 19 patients were involved in this study. Originally there were 23 patients listed, but 4 were dropped as unsuitable because they probably did not have true glandular hypertrophy. The lot was originally listed by one of us (B.U.E.) and then assigned by the other (R.E.P.) to courses of treatment without reference to the degree of gynecomastia or the advancement of the leprosy, placing every fourth patient in any given group, because four courses of therapy were planned.[2] When these groups were set up they contained 6 cases each (except one, with 5 cases), but the size of the two groups was reduced when the cases that we concluded were not suitable were dropped.

Group 1, four patients, received intramusmular testosterone propionate, 20 mgm. daily for 2 weeks, after which because of side effects the dose was reduced to 10 mgm. for the further 5 weeks of the experimental period. Group 2, six patients, was given methyltestosterone orally in a dose of 20 mgm. per day. Group 3, also of six patients, was given methyltestosterone in the same dose combined with ethinyl estradiol 2 mgm. daily. Group 4, of three patients, was given methandriol (methylandrostenediol, a protein anabolic agent, chemically related to testosterone), 50 mgm. orally. These drugs and dosages are summarized in Table 1, in which the results are also given.

In evaluating the results of these courses of treatment, exact measurements were made of (1) the total palpable diameter of true glandular breast tissue, and (2) the distance of the nipple from the bony chest wall. The latter measurement, made with a rule held beneath the breast with the patient in the erect posture, was made weekly during the treatment period, monthly for three months thereafter, and finally 13 months after the completion of the treatment.

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[2]The hormones used in this study were provided by the Schering Corporation, Bloomfield, New Jersey.

RESULTS

The results of this trial can be summarized in four classes according to degree of response to the therapy as follows: (*a*) cure, (*b*) marked improvement, (*c*) slight improvement, and (*d*) no improvement. The figures are shown in the second part of Table 1.

TABLE 1.—*Hormones used in, and details of, treatment of gynecomastia cases, and improvement observed.*

Group	Hormone	No. cases	Treatment			Results; improvement			
			Route	Dose[a]	Time	Cure	Marked	Slight	None
1	Testosterone propionate	4	I.M.	20 mgm. / 10 mgm.	2 wks. / 5 wks.	2	1	1	0
2	Methyltestosterone	6	Oral	20 mgm.	7 wks.	0	3	1	2
3	Methyltestosterone / Ethinyl estradiol	6	Oral	20 mgm. / 2 mgm.	7 wks.	1	0	1	4
4	Methandriol	3	Oral	50 mgm.	7 wks.	0	1	1	1

[a]Dosage administered 6 times a week, not including Sundays.

In an attempt to analyze these results it appeared that certain conclusions could be reached correlating the patient's response to the treatment and his previous condition. Following is a discussion of these by the result classes.

(*a*) Cure: In all three of these cases the onset of leprosy had been fairly recent (2, 10 and 14 years), and they had been under treatment for 5 years or less. In all of them the gynecomastia was minimal at the beginning of treatment, and in 2 of them only one breast was involved. There was no evidence of recurrence of the gynecomastia up to 13 months after cessation of treatment.

(*b*) Marked improvement: All these 5 men regarded themselves as completely cured, but by measurement there was clinical evidence of residual gynecomastia. However, there was a reduction of induration and swelling. All of these cases had had leprosy for a long time, i.e., 15 years or more, and most of them had had prolonged treatment with Dapsone (DDS), and have responded satisfactorily.

(*c*) Slight improvement: The 4 patients in this group reported that there was a loss of the sense of fullness and tenderness in the breast, but that there was still hypertrophy. Clinically we could detect little or no evidence of change in the size of the breasts.

(*d*) No improvement: These 7 cases had all had leprosy for many years, and all had marked gynecomastia. It is perhaps especially significant that all of them have diffuse lepromatous leprosy which has not shown notable response to the usual therapy, and that the disease is consequently quite active.

DISCUSSION

There are several tentative conclusions which can be drawn from this study, although the group of patients treated is too small for the findings to be considered of great significance.

Not all cases of leprous gynecomastia will respond to male hormone replacement therapy, but some of the cases without marked hypertrophy, and responding well to the usual antileprosy drugs, will show a good response to testosterone given intramuscularly. Oral replacement does not seem to be as effective, probably because the drugs are poorly absorbed.

This study would seem to indicate that the hormonal abnormality which causes gynecomastia can be reversed fairly early in the disease, with resolution of the hypertrophy. In some cases this occurs with simply a satisfactory response to antileprosy therapy, which apparently causes a resolution of the testicular damage and restoration of hormonal function. But in certain cases it appears that an additional androgenic stimulation is required in order to reverse the imbalance and thus bringing about resolution.

In none of the cases showing a favorable response to treatment was there any relapse up to 13 months after it was discontinued.

Although there were some cases with good responses among those with significant hypertrophy, the generally poor response in such cases makes this type of therapy of little practical value.

After the conclusion of this trial, several of the cases which had not responded to this therapy were subjected to the Webster ([5, 14]) mammaplasty, with uniformly good results. This procedure is relatively simple, and can be done with a minimum of surgical facilities. This procedure is probably the one of choice in the management of gynecomastia in the majority of cases in the present state of our knowledge.

Although these results of hormone treatment are not spectacular, there is sufficient evidence of a definite response to indicate the need of further trials with parenteral androgenic hormones.

SUMMARY

1. Hormone therapy of leprous gynecomastia was attempted, using various drug preparations in a series of 19 patients. For the majority of cases the treatment was found to be of little value, although further investigations with parenteral testicular hormones is indicated.

2. Those cases with minimal breast involvement, and showing a good response to antileprosy therapy, usually responded well to testosterone replacement therapy.

3. The Webster mammaplasty is probably the surgical treatment of choice for the majority of cases of established gynecomastia at the present time.

RESUMEN

1. Se ensayó la hormonoterapia de la ginecomastia leprosa, usando varias preparaciones farmacéuticas en una serie de 19 enfermos. Para la mayoría de los casos, el tratamiento resultó ser de poco valor, aunque se hallan indicadas nuevas investigaciones con hormonas testiculares por vía parentérica.

2. Los casos de mínima invasión mamaria, y que revelaban buena respuesta a la terapéutica antileprosa, por lo general también respondieron bien a la opoterapia con testosterona.

3. La mamaplastia de Webster es probablement en la actualidad el tratamiento quirúrgico de elección para la mayoría de los casos de ginecomastia establecida.

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