The Journal of
CLINICAL
ENDOCRINOLOGY

VOLUME 2 NOVEMBER, 1942 NUMBER 11

Syndrome Characterized by Gynecomastia, Aspermatogenesis without A-Leydigism, and Increased Excretion of Follicle-Stimulating Hormone[1]

[Gynecomastia]

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THE SYNDROME under discussion begins during adolescence and is characterized by gynecomastia and a very specific type of hypogonadism. This latter is almost entirely in respect to the function of the tubular tissue (germinal epithelium and Sertoli cells) while the function of the Leydig cells (growth of phallus and prostate and of sexual hair) remains relatively normal. Thus one finds bilateral gynecomastia, small testes, aspermatogenesis, evidence of normal to moderately reduced function of the Leydig cells, increased excretion of follicle-stimulating hormone (FSH), and usually a reduced excretion of 17-ketosteroids. During the last 4 years, 7 cases have been observed in the clinics of the Massachusetts General Hospital; studies on these patients and two additional private patients form the subject of this report.

Received for publication August 5, 1942.

[1] The expense of these studies was partly defrayed by the Committee for Research in the Problems of Sex of the National Research Council and the Macy Foundation.

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Read before the Twenty-sixth Annual Meeting of the Association for the Study of Internal Secretions, Atlantic City, N. J., June 9, 1942.

REVIEW OF LITERATURE

Although these cases are not uncommon, few reports are found in the literature, and to our knowledge, no author has grouped them together as a definite clinical entity. Bedor in 1812, according to a later writer (1), described two brothers, 21 and 24 years old, with bilateral gynecomastia and small testes. Around 1840, several English authors (2–5) independently described a soldier, previously normal, who at the age of 53, developed small testes and gynecomastia a few months after trauma to the testes. The reports of this case vary in their details but the sequence of events seems to have been as stated. The development of gynecomastia in a previously normal 22-year-old patient a few months after mumps orchitis was reported in 1877 (1). During the last 20 years, there have been several reports (5–9) of cases which possibly fit into this syndrome. Bronstein (10) in 1939 reported the only case, however, in which those hormone studies necessary for the diagnosis were carried out. This concerned a 17-year-old negro with gynecomastia of 5 years' duration. The testes were very small and there was azo-

öspermia. The phallus was normal, while the other accessory sex organs were small; the amount and distribution of the pubic and axillary hair were normal; the span was 10.5 cm. greater than the height. Estrin excretion was not increased while that of gonadotropin was. The adrenals were normal as shown by roentgenograms after perirenal air injection; the sella turcica was not enlarged. The author did not believe that the gynecomastia was due to hyperestrinism and suggested a pituitary origin.

Other Causes of Gynecomastia

During puberty, nearly all boys have some breast enlargement (11). Usually slight and often unnoticed, it recedes rapidly as a rule but may become so great as to require excision. Strangely enough, the enlargement may increase on one side and regress on the other, often without apparent cause, although trauma is thought to be an important factor.

Gynecomastia is frequently found in association with testicular tumors. Gilbert (12) has recently subdivided these cases into 'choriogenic' and 'physiologic' types. In the former, which occurs with chorionepitheliomata, the breasts may secrete; the areolae are enlarged and pigmented; the estrin and gonadotropin titers of the urine are very high. The gynecomastia is presumably caused by the estrin secreted by the tumor. 'Physiologic' gynecomastia, on the other hand, occurs with other testicular tumors, such as seminomata, teratomata and interstitial cell tumors. In this type, the breasts do not secrete, the areolae are not enlarged or pigmented, and the gonadotropin titer of the urine is only moderately increased. This form of gynecomastia is presumably secondary to atrophy of the remaining testis, as it frequently occurs after roentgen ray treatment has been given post-operatively (13, 14). It is probably related to the syndrome under discussion (*vide infra*).

Adrenal cortical tumors of the so-called 'feminizing type' cause gynecomastia (15). With the breast enlargment, there is loss of libido, decrease in secondary sex characteristics, and testicular atrophy. In one case, large quantities of estrin were found in the urine (16); it is quite possible that hyperestrinism is the cause of the gynecomastia in this condition.

Gynecomastia not infrequently occurs with cirrhosis of the liver. Glass, Edmondson, and Soll (17) found atrophic testes in all of their cases and an increased partition of free estrin as opposed to conjugated estrin in the urine. They believe that the cause of the gynecomastia is hyperestrinism, secondary to failure of the liver to properly metabolize estrin. No testicular biopsies were made in their cases.

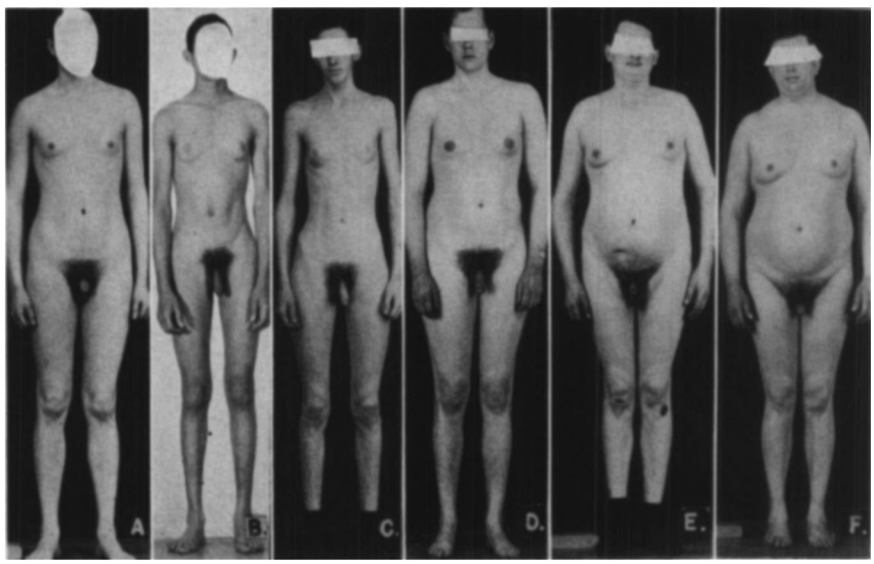

Fig. 1. MASCULINE BODY CONFIGURATIONS and relatively normal development of the accessory sexual organs, except for the breasts. *A, case 1; B, case 2; C, case 3; D, case 6; E, case 8; F, case 9.*

Gynecomastia rarely occurs with pituitary tumors (18, 19), hyperthyroidism (20) and after prostatectomy (21).

Clinical Findings

The 9 cases here reported whose histories are outlined in the appendix varied in age from 17 to 38 years; all were white except one negro. Three had an asthenic habitus; 4 were somewhat obese; 2 had a normal build. All of the patients were strong and had good muscular development (fig. 1).

Early development was normal in every case. None of the patients had undescended testes. There was no history of orchitis, although most of the patients had had mumps. Puberty started between the ages of 12 and 14 in each case.

The gynecomastia was bilateral in every case; (fig. 2 and 3); it was first noticed by the patients from

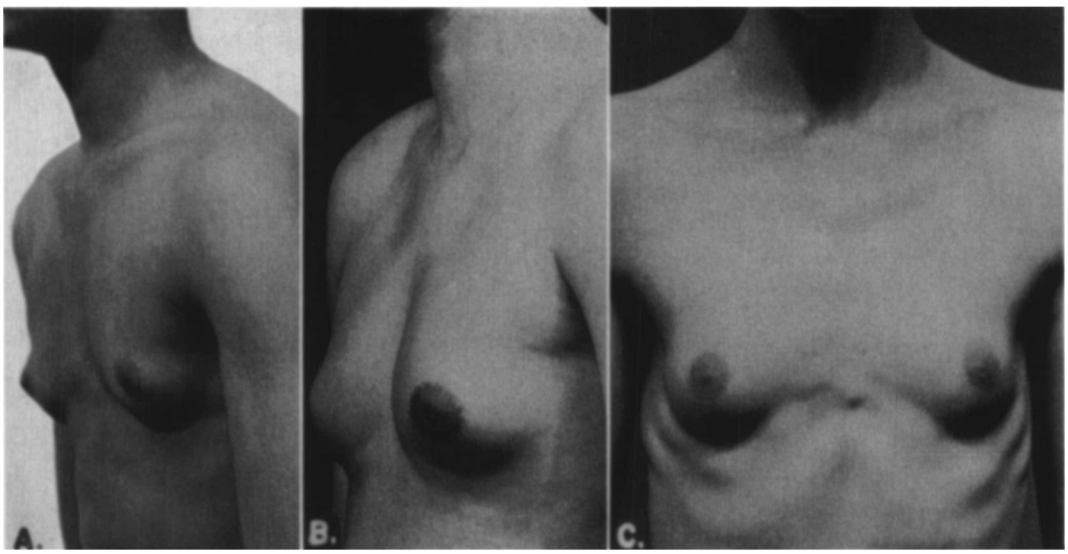

Fig. 2. A, *case 2;* B, *case 6;* C, *case 3.*

1 to 6 years after puberty began. Those patients who observed breast enlargement during the first few years after the onset of puberty stated that the breasts slowly increased in size over a period of several years and then remained stationary; those who did not notice the enlargement until 4 to 6 years after the onset of puberty, on the other hand, said that there was no further change during the subsequent years. The gynecomastia was marked in 7 cases and moderate in 2. The breasts resembled those of the adolescent female, with some areolar enlargement and very little increase in pigmentation. No secretion was expressed in any case, and in only two cases was tenderness present. This was unilateral and started after manual stimulation in one case.

The testes were very small, measuring about 1.5 × 1.0 × 0.5 cm. There was no difference between the two sides and there was very little variation among cases. The testes were normal as to firmness and sensitivity to pressure. Those patients who had observed the size of their testes stated that they had always been small.

Three of the patients had no semen, i.e., aspermia while the remaining 6 had ejaculations. Semen examination showed azoöspermia in the 4 cases in which this test was made. Sterility was the chief complaint of 3 patients.

Eight of the 9 cases had well developed accessory sexual organs, and clinically all 8 patients had relatively good Leydig function, although the younger patients appeared immature for their age. Only *case 5* had obviously diminished Leydig function. He, at the age of 28, had a high-pitched voice, a small larynx, sparse beard, small phallus and small prostate. He had

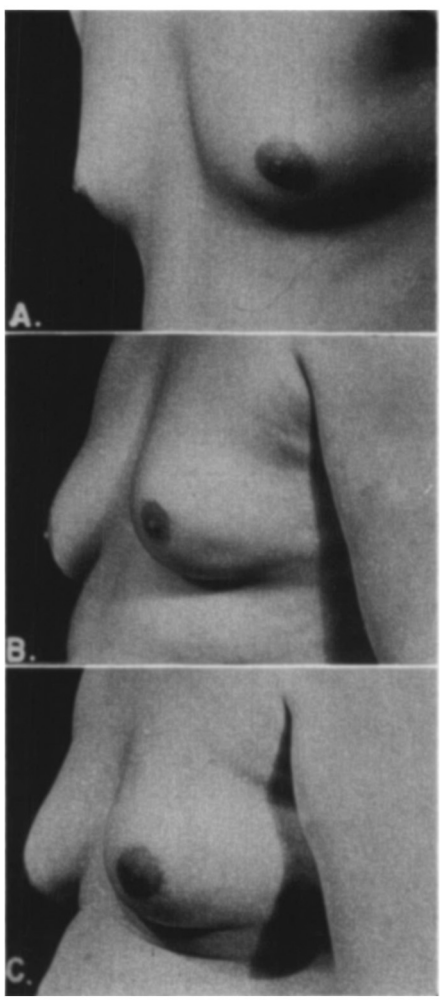

Fig. 3. A, *case 1;* B, *case 8;* C, *case 9.*

erections but no ejaculations and never attempted intercourse, although he was attracted to the opposite sex.

Axillary, pubic and perianal hair growth were essentially normal in these patients, and several of the older ones had definite recession of the hair above the temples, an indication of good Leydig function (22). The 5 younger patients, aged 17, 18, 22, 24, and 28, respectively, did not shave. Two of the 4 older ones had scanty beards localized to the chin and upper lip which required shaving only once or twice a week. In one patient, however, this was a familial characteristic. Body hair was scanty in all of the 7 patients with abnormal beards while the 2 with heavy beards had abundant body hair.

Bone age (table 1) was determined in all of the younger patients and was definitely delayed in only one patient, *case 5*. At the age of 21 the epiphyses of the radius and ulna were open, indicating a delay of 3 years in bone age; however, at the age of 28, without treatment, these epiphyses were closed. The span exceeded the height in every case, however; where this discrepancy was marked, circa 4 to 5 cm., there probably had been some delayed epiphyseal union.

There was questionable serological evidence of syphilis in only one patient, *case 2*; the Hinton test was negative in the others. Roentgenograms of the sella turcica were uniformly normal. Perirenal air injections were performed on 2 patients and the findings were normal. Glucose tolerance tests were made on 3 patients and revealed nothing remarkable. Basal metabolic rates were obtained on 6 patients and showed no consistent deviation from normal. There was no clinical evidence of liver disease in any of the patients; in *cases 2* and *5*, the bromsulphalein test, the cephalin flocculation test, the serum Van den Bergh reaction, the serum proteins, and the A/G ratios were normal.

Hormonal Findings

Follicle-stimulating hormone. All of the patients excreted excessive amounts of the pituitary follicle-stimulating hormone (FSH) in the urine. By our assay method (23), which is a modification of the alcohol precipitation method of Zondek, a normal male rarely excretes 10 mouse units of FSH per 100 cc. of concentrated first morning urine. These patients uniformly excreted more than 30 M.U. per 100 cc., and 5 of the 8 have excreted more than 50 M.U. per 100 cc. (table 1). In the table, FSH excretion levels in some cases are also recorded in M.U. per 24 hr. Calculated on this basis, the excretion levels were also much above normal. Such data required very accurate collections of urine which were not obtainable in all cases. These high levels of FSH excretion are comparable to the levels found in castrates and their significance will be discussed later.

17-Ketosteroids. The urinary excretion of 17-ketosteroids varied from relatively normal to definitely subnormal levels. Thus, in a small series of normal males between the ages of 20 and 40, values from 8.1 to 22.6 with an average of 13.8 mg. per 24 hours were obtained in this laboratory (24). As can be seen from the table, the range in this series of 9 patients was from 3.9 to 13.5 with an average of 8.3 mg. per

TABLE 1. CLINICAL DATA ON PATIENTS WITH GYNECOMASTIA

Case no.	Age, yr.	Onset of Puberty, yr.	Gynecomastia First Noted, age,	Bone Age, yr.	Height, cm.	Span, cm.	Highest FSH Determinations				17-Ketosteroids, mg./24 hr.			Remarks
							Mouse Units/100 cc.		Mouse Units/24 hr.					
							Greater than	Less than	Greater than	Less than	Low	High	Ave.	
1	17	13	13	Normal	181.1	185.0	30	50	235	350	5.6	8.7	7.2	
2	18	14	14	Normal	170.7	180.2	100	150	640	840			*	Negro
3	22	14	17	Normal	175.4	178.0	50	80	150	248	6.0	9.0	7.2	
4	24	14	18	Normal	182.2	183.5	80	100			1 Assay		4.8	Hysteria
5	28	14	18	Delayed	177.0	181.5	50	100			3.9	5.2	4.6	Definite hypoleydigism
6	30	13	14	Normal	183.5	184.2	50	80	200	320	12.6	13.5	13.1	Narcolepsy. Renal lithiasis
7	33	13	16		182.2	184.2	30	50	270	450	7.2	13.2	9.6	
8	35	14	16	Normal	177.5	178.0	30	50	330	455	9.6	11.2	10.3	
9	38	12	18		171.6	175.5	50	80			7.9	10.5	9.2	Chronic cystic disease of right lung

* The pre-treatment assays of 1.2 and 2.4 mg. averaging 1.8 mg. per 24 hr. are thought to be due to faulty technique, and are not included. Later assays, after 4 to 6 weeks without treatment, ranged from 4.3 to 9.0 mg., with an average of 5.7 mg. per 24 hr.

24 hr. By and large, there was a parallelism between the degree of hypoleydigism, as judged clinically, and the lowering of the 17-ketosteroid excretion.

Estrin assays. Estrin assays were made on *case 2* by Drs. C. V. and O. W. Smith in the Fearing Research Laboratory of the Free Hospital for Women. They found no evidence of increased excretion of either estrin or estrin-breakdown products, the levels being about the same as those found in menopausal women and in the only normal male they had studied. Estrin assay on *case 8* made in our laboratory in 1938 was negative for 10 R.U. per 24 hr.

Histological Findings

Testis. Testicular biopsies were obtained from 7 patients and showed varying degrees of the same lesion. This involved the tubules and in its most advanced state consisted of hyalinization of all the tubular elements (fig. 4, 5). This hyaline tissue stained pink with eosin and like collagen with phosphotungstic acid and aniline blue. Stains for amyloid were negative. In many of the biopsy tissues, fine granules were seen in the hyaline tissue; these granules did not stain like collagen, however, and their nature is obscure; they seem to be part of the atrophic or degenerative process. This lesion of the tubules is not the 'peritubular fibrosis' described by Charny and Meranze (25), and there was no evidence of an inflammatory process in any of the biopsies. The less advanced lesions showed partial hyalinization with impaired spermatogenesis (fig. 4, B); in no instance was normal spermatogenesis present.

The interstitial cells were numerous in all of the biopsies and in most cases the Leydig cells seemed, at first, more numerous than could be accounted for by the atrophy and shrinkage of the seminiferous tubules. Indeed, the diagnosis 'hyperplasia of the interstitial cells' was considered by the pathologist. When one calculates the size of these small testes, however, it seems probable that simple shrinkage can account for the apparent increase in the number of interstitial cells. A testis measuring 1.5×1.0×0.5 cm. equals approximately 0.75 cc. of tissue, while a normal testis measuring 5.0×3.0×2.0 cm. equals approximately 30 cc. of tissue. In other words, one would expect the interstitial cells to be 40 times as numerous as in the normal testis.

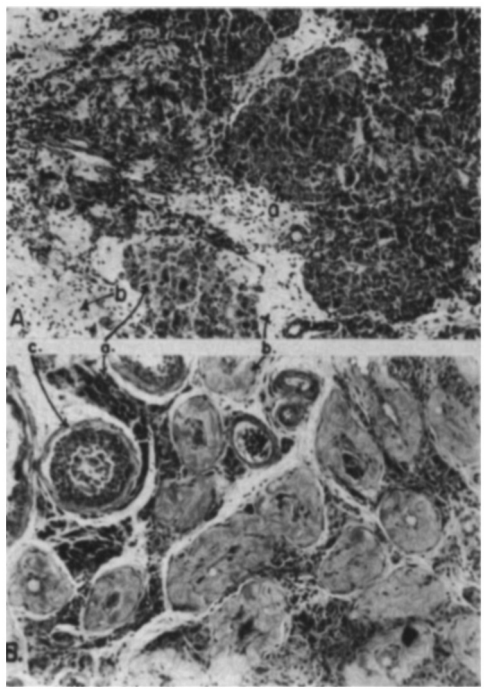

Fig. 4. TESTICULAR BIOPSY TISSUE. A, *case 6;* B, *case 7. a,* Leydig cells; *b,* completely hyalinized tubules; *c,* partially hyalinized tubule. Note that the Leydig cells in A almost suggest adenoma formation.

Breast. The breast tissue was examined microscopically in 4 patients and showed some hyperplasia of the duct epithelium and marked proliferation of the periductal connective tissue (fig. 6, A and B.). These findings are definitely different from the effects produced by estrin therapy in an elderly male (fig. 6, C); there the ratio of ductal to periductal hyperplasia was greater.

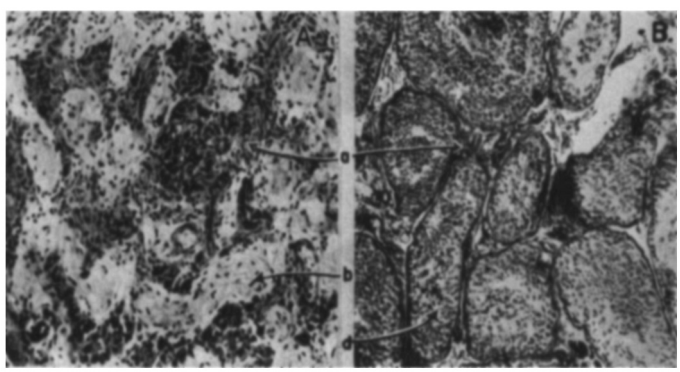

Fig. 5. TESTICULAR BIOPSY TISSUE. A, *case 1;* B, normal. *a,* Leydig cells; *b,* completely hyalinized tubule; *d,* normal tubule.

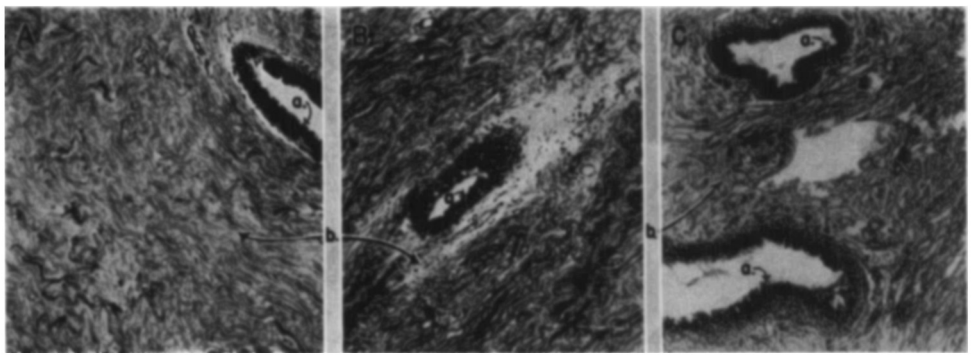

Fig. 6. BREAST TISSUE. *A, case 2; B, case 6; C, M. G. H. 334479*, a 78-year-old male with estrin-induced gynecomastia. In *A* and *B* there is only moderate ductal hyperplasia (*a*), with marked proliferation of the periductal connective tissue (*b*); in *C*, the ductal hyperplasia (*a*) is more marked and the periductal connective tissue (*b*) is less dense.

Pathological Physiology

Significance of increased FSH excretion. Since the significance of an increased FSH excretion has been more thoroughly studied in the female, it may be well for purposes of orientation to consider first the hormonal patterns in the normal and in the gonadectomized female. In figure 7, A the part of the anterior pituitary under consideration is divided into 2 compartments, one for FSH and one for the luteinizing hormone (LH). In this and subsequent diagrams, stimulating influences are indicated by arrows with solid heads while inhibiting influences are indicated by arrows with open heads. It will be noted that FSH stimulates the ovary to produce estrin (E); that estrin in turn inhibits FSH production and stimulates LH production. The evidence for these statements is discussed in a previous paper (26). To be absolutely accurate it is still a question whether estrin stimulates LH or luteotropin or both; this uncertainty is indicated by the question mark after LH in the second compartment. For the present argument this is immaterial. The important fact is that estrin stimulates some hormone of the pituitary which in turn stimulates the ovary to produce more progestin (P). Finally, it will be noted that progestin inhibits LH production (27).

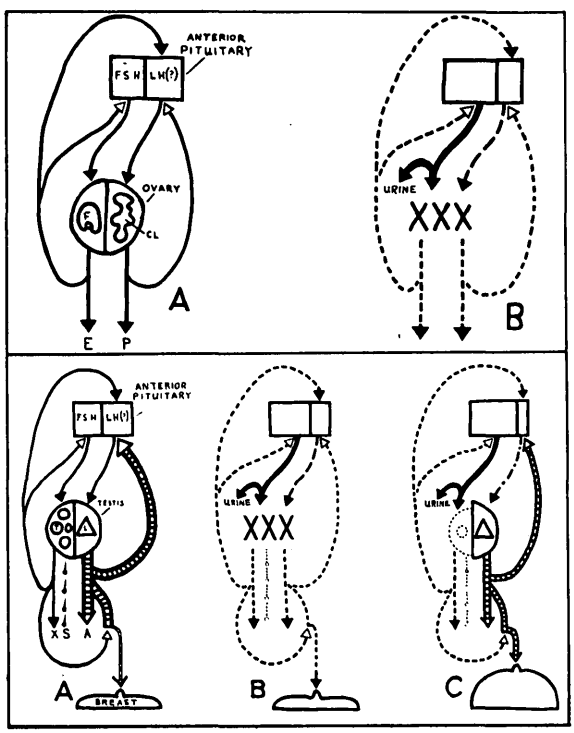

Fig. 7. SCHEMATIC DRAWING REPRESENTING HORMONAL PATTERNS in normal female (A) and gonadectomized female (B). Finely dotted line indicates absence of hormone; broken line indicates decreased production of hormone. For discussion, see text.

Fig. 8. SCHEMATIC DRAWING REPRESENTING HORMONAL PATTERNS in normal male (A), gonadectomized male (B), and syndrome under discussion (C). Finely dotted line indicates absence of hormone; dot-dash line indicates markedly decreased production of hormone; broken line indicates decreased production of hormone. For discussion, see text.

Figure 7, B is constructed in a similar manner to show the changes in the hormonal pattern resulting from castration. Estrin is absent and consequently there is no inhibition of FSH production. There results an overproduction of FSH and large quantities are excreted in the urine. It will be noted that LH production is depicted as decreased. Whether this is true in the gonadectomized female probably depends on whether the loss of the stimulating effect of estrin on LH overbalances the loss of the inhibiting effect of progestin on LH.

Before describing the hormonal pattern in the syndrome under discussion (fig. 8, C) it will be helpful to outline these patterns in the normal and in the gonadectomized male (fig. 8, A and B). These diagrams follow the same general scheme as those in figure 7. It will be noted that FSH stimulates the tubules (T) to produce spermatozoa (S) (28) and an 'X-hormone.' The arguments for the existence of this X-hormone and for its actions will be enumerated

below. It will be noted further that the X-hormone is analogous to estrin in that it inhibits FSH production and stimulates LH production. LH stimulates the Leydig cells (L) to produce androgen (A) (28); androgen, like progestin, inhibits LH production. The discussion of the effect of these various hormones on the breast is reserved for a later section.

In figure 8, B it should be emphasized that it is primarily lack of the inhibiting effect of the X-hormone on FSH, and not lack of androgen, that leads to overproduction of FSH. The situation, therefore, is depicted as exactly analogous to that in a gonadectomized female; the arguments for this rendering will be discussed below.

Turning to the hormonal pattern of the syndrome under discussion (fig. 8, C) one notes first that the tubular part of the testis is non-functioning while the part which has to do with Leydig cells is relatively normal (cf. biopsies, fig. 4, 5). The increased FSH production is the result of lack of X-hormone with its inhibiting effect. LH production is less than normal because of lack of stimulation by the X-hormone; it is even less than that in the male castrate (fig. 8, B) because the inhibiting effect of androgen is partially retained. Androgen production, while less than normal, is still present.

The description of the hormonal pattern has been expressed in rather dogmatic terms. The argument will now be taken up point by point.

Evidence for a second or X-hormone (inhibin) of the testis. The first and weakest argument for the presence of a second testicular hormone is by analogy with the female. There FSH facilitates production not only of the germ cells but of a hormone, estrin, as well; it would seem, therefore, in the male that FSH might be concerned with the production of a hormone in addition to the germ cells.

The literature, furthermore, contains considerable evidence in favor of the existence of such a hormone. Mottram and Cramer (29) in 1923 found castration cells in the pituitaries of adult male rats that had received roentgen ray treatment to the testes. This treatment resulted in atrophy of the seminiferous tubules but preservation of the interstitial cells and accessory sex organs. Witschi, Levine and Hill (30) in 1932 found that female rats in parabiosis with such male rats develop continuous estrus. This finding is good evidence for increased FSH production. Martins and Rocha (31) in 1931 reported on parabiotic union of castrated males with infantile normal females. When the males were untreated, precocious puberty resulted in the females; however, when the males were treated with testicular extracts or implants, precocious puberty did not occur in the females, in spite of the fact that the extracts did not contain androgen as judged by the accessory sex organs of the treated males. McCullagh and Walsh (32) confirmed this work and coined the word 'inhibin' for the water-soluble, non-androgenic hormone of the testis. They showed furthermore that inhibin caused regression of the prostate and seminal vesicles in normal rats. This finding was confirmed by Vidgoff, Hill, Vehrs, and Kubin (33) in 1939 and brings to mind Huggins' studies (34) on the effect of estrin (a hormone closely related to inhibin) on the prostates of dogs. Nelson (35) in 1934 studied rats made cryptorchid by operation and found castration cells in the pituitaries after 75 days, while 240 days were required for atrophy of the seminal vesicles and 400 days for the prostate. Since the tubules in cryptorchid males degenerate long before the interstitial cells, these time relationships suggest that the occurrence of castration cells is correlated with the tubules while the atrophy of the seminal vesicles and prostate is correlated with the interstitial cells. Indeed, the atrophy of the interstitial cells may very well be due to lack of stimulation of LH by inhibin (fig. 8, A). There are, of course, other interpretations (*vide infra*).

The clinical findings in certain cases of arrhenoblastoma of the ovary suggest that these tumors produce some hormone other than androgen. Thus, in one (*M.G.H. 176118*) of the 4 cases studied in this clinic there were no masculinizing effects, merely amenorrhea. The amenorrhea in this case disappeared shortly after removal of the tumor. Although complete hormonal studies are lacking, it would seem in retrospect that the finding could best be explained on the supposition that the tumor in this case primarily produced inhibin. Indeed, in the 2 cases with definitely masculinizing symptoms, (*M.G.H. 174195* and *245129*) the 17-ketosteroid excretion levels were not elevated which suggests that even in these cases the amenorrhea might have resulted from excessive production of inhibin.

The authors believe that the findings in the syndrome here described offer strong evidence in favor of the dual hormonal theory of testis physiology. Here nature has apparently produced destruction of one part of the testis while sparing the other. In the face of only slight if any hypoleydigism, one encounters FSH excretion of the order of magnitude of that found in castrates. Thus *case 6*, with perfectly normal development of the accessory sexual organs, aside from the gynecomastia, and with a relatively normal 17-ketosteroid output, excreted more than 200 M.U. of FSH per 24 hours. Furthermore, the very fact that gynecomastia occurs in this syndrome while it does not occur after castration is further evidence that some hormone other than androgen is involved.

Evidence against a second or X-hormone of the testis. The fact that testosterone inhibits FSH pro-

duction has led to an alternate theory, the monohormonal theory. Thus, Nelson (35) points out that the sequellae of experimental cryptorchidism in rats discussed above disappear under testosterone therapy in the reverse order in which they occur, and thinks that everything can be explained on the basis of dosages. If this interpretation were extended to the syndrome here presented, the argument would be that the patients were suffering from a mild degree of hypoleydigism, not sufficient to affect the genital organs but sufficient to cause increased FSH production. A point perhaps against this argument is that *case 2* with the highest FSH excretion did not have the greatest degree of hypoleydigism.

In rebuttal, the authors point out that the histological picture of hyalinized tubules in the presence of normal or hypertrophic interstitial cells make it difficult to believe that one is dealing primarily with an underfunction of the androgen-producing elements. Moreover, the fact that so much more testosterone is required to prevent development of castration cells than to affect seminal vesicles and prostate suggest to the authors that inhibition of formation of castration cells is not a physiological function of testosterone. It seems not impossible to the authors, furthermore, that the inhibitory effect of testosterone on FSH production may very well be connected with the observation that if testosterone is administered to eunuchoids and castrated females, the excretion of estrin is increased (36–39). It is very possible that testosterone is converted into estrin which inhibits FSH.

Cause of the decreased 17-ketosteroid excretion. The 17-ketosteroids in the male are produced in two places, the adrenal cortex and the cells of Leydig (24). In the syndrome here described the values vary from apparently normal to definitely subnormal. Since the 17-ketosteroid excretion level varies considerably among normal individuals it can not be said that any one of the patients here reported had an excretion level as high as it would have been without the disease. The authors suggest, as an explanation for this lowering, a lack of X-hormone to stimulate both the Leydig cells and possibly those cells of the adrenal cortex which produce 17-ketosteroids. The above chain is thoroughly discussed in the paper previously referred to (26).

Cause of the gynecomastia. The most puzzling part of the whole syndrome is the gynecomastia. One first considers the possibility of too much estrin. Against this possibility are *a*), the presence of high FSH excretion, *b*), the fact that the histological changes in the breast are more periductal than ductal hyperplasia, and *c*), the fact that no increased estrin excretion was found in *case 2* by Drs. G. V. and O. W. Smith or in *case 8* in our laboratory.

One might consider the uncommon causes of gynecomastia such as adrenal hyperfunction, pituitary tumors and testicular tumors. No evidence in favor of these has been found. Progesterone was administered to *cases 1* and *2* with the thought that this would be followed by lactation if excess of prolactin had anything to do with the etiology. Lactation did not occur.

Could the gynecomastia be due to testosterone? It has been shown that testosterone stimulates breast tissue in normal and castrated female and male rats (40). Gynecomastia is not uncommon in eunuchoid patients treated with testosterone (41); it became so marked in one of our patients as to require excision. The excised breasts in this particular case showed the same histological picture seen in this syndrome. But testosterone can not be the only factor, since if this were so, normal males would have gynecomastia.

After all, the pathology indicates isoleydigism accompanied by hypoinhibinism. The authors bring up for discussion the hypothesis that for the production of this type of gynecomastia, two conditions must be fulfilled. *a*), presence of androgen, *b*), absence of inhibin. One is reminded of Huggins' observations on the prostate of dogs in which he found that testosterone causes growth and estrin prevents such growth (34). Could it not be that in the male breast testosterone causes growth and inhibin prevents this growth? If such were the case the castrate would not develop gynecomastia because of the lack of testosterone (fig. 8, B), the normal would not because of the presence of inhibin (fig. 8, A), while the patients with this syndrome would, since they have testosterone but no inhibin (fig. 8, C). To be sure, Hamilton (42) has found that testosterone therapy does not always cause gynecomastia in male castrates. Since these cases were all adults, it may very well be that a third condition need be fulfilled, namely that the patient be growing at the time of the hormonal imbalance.

To recapitulate, the selective lesion of the seminiferous tubules results not only in aspermatogenesis but also in lack of X-hormone (inhibin); lack of X-hormone leads not only to increased FSH production but to decreased LH production as well; consequently the intact Leydig cells produce somewhat less androgen than normally; the androgen produced acts on the breast during puberty in the absence of X-hormone to cause gynecomastia.

Etiology

Nothing has been found in these patients to explain the testicular lesion. There is no evidence of any inflammatory disease clinically or histologically. An obstructive lesion of the vas deferens seems most

unlikely since histological studies of the testes in cases of known obstruction do not resemble at all the histological picture seen here (43). Furthermore an epididymal biopsy from *case 6* contained normal tissue. The changes, moreover, are not those seen with lack of gonadotropic hormones, as in pituitary dwarfs in which one finds rudimentary tubules with aspermatogenesis but no hyalinization. One is left with the conclusion that the lesion is a degenerative one of unknown etiology, starting early in life.

Treatment

It is very improbable that the gynceomastia is reversible. Testosterone propionate and progesterone have been tried without success; estradiol dipropionate caused further enlargement. Surgical removal of the breast is recommended for cosmetic reasons, and if carefully done is an exceedingly satisfactory procedure.

From the histological findings, it seems unlikely that anything can be done to correct the aspermatogenesis. The high FSH titers in the urine demonstrate that these patients are over-producing FSH in an effort to stimulate spermatogenesis. Therefore, therapy with gonadotropins is probably illogical.

For those patients in this group who are suffering from hypoleydigism, testosterone therapy is probably indicated. Chorionic gonadotropin therapy by stimulating the interstitial cells might conceivably be used to produce the same results as testosterone; it has not been tried by the authors in the series of cases here reported.

SUMMARY OF FACTS

1. Nine cases are presented of a syndrome characterized by gynecomastia, and small testes with aspermatogenesis but without a-leydigism.
2. The follicle-stimulating hormone (FSH) excretion in the urine is increased to a degree comparable to that found in castrates.
3. Estrin excretion was studied in two cases and found not to be increased.
4. The 17-ketosteroid excretion level and the development of the accessory sexual organs vary from apparently normal to definitely subnormal.
5. Testicular biopsies were obtained on 7 patients and showed hyalinization of the seminiferous tubules and normal appearing interstitial cells.
6. Breast tissue was examined on 4 patients and showed some ductal hyperplasia with marked proliferation of the periductal connective tissue.

Interpretations

1. These studies support the point of view that the testis produces two hormones; *a*), androgen from the Leydig cells, and *b*), X-hormone (inhibin) from the tubules.
2. Inhibin is analogous and probably very similar to estrin.
3. The increased FSH excretion which is found in certain types of hypogonadism depends primarily upon lack of inhibin and only to a lesser degree upon lack of androgen; indeed the action of testosterone in inhibiting FSH may depend upon its conversion into estrin.
4. The gynecomastia is not due to hyperestrinism; it is not due to androgen alone; it may be due to the combination of androgen and lack of inhibin.

The authors wish to thank Dr. Fred A. Simmons for making the testicular biopsies; Drs. Howard I. Suby and Jack O. W. Rash for permission to publish their cases; and Drs. C. V. and O. W. Smith for estrin assays on *case 2*. The authors are indebted to Dr. Erwin Schwenk, Schering Corp., Bloomfield, N. J., for the testosterone propionate (Oreton), progesterone (Proluton), estradiol dipropionate (Progynon DP) and pregnenolone.

CASE HISTORIES

In the following case abstracts, the data for the FSH tests and the 17-ketosteroid excretion levels are omitted, as they are recorded in table 1.

Case 1 (fig. 1, A), R.R. (*M.G.H. 344755*), a 17-year-old white schoolboy, was seen in March, 1942, complaining that he had been rejected by the Navy because of small testes. His general health was excellent. He had mumps at 2 years of age without orchitis. At 10 or 11, he suffered from trauma of the scrotum, but there was no swelling or pain. Since that time, he noticed that the testes were small. Puberty began at 13 and progressed normally. He had normal erections, masturbated occasionally, but had no ejaculations or nocturnal emissions. He never shaved, but his voice had changed. Shortly after the onset of puberty, he noted enlargement of the breasts which slowly increased for a few years (fig. 3, A). The enlargement was never enough to cause him embarrassment.

Examination showed a well developed, muscular boy with mild acne, with somewhat narrow shoulders and rather wide hips. The span was 4.0 cm. greater than the height. Axillary and facial hair were scanty, but pubic hair was normal. The voice was deep and the larynx showed normal masculine enlargement. The breasts were moderately and equally enlarged, non-tender, and no secretion could be expressed. The phallus and scrotum were well developed; the prostate was slightly small. The testes were very small, equal in size, firm and normally sensitive.

Hinton test for syphilis was negative. Roentgenograms showed a normal bone age. Biopsy of the right testis showed complete hyalinization of the tubules and apparently normal interstitial cells (fig. 5, A). Estradiol dipropionate, 5 mg. intramuscularly every 5 days, caused tenderness and further enlargement of both breasts after 4 injections.

Case 2 (fig. 1, B), *G.B.* (*M.G.H. 147829*), an 18-year-old negro, was admitted in September, 1941, complaining of gynecomastia. His general health was always good; early development was normal. He had measles, chicken

pox, scarlet fever and pneumonia in childhood, but not mumps. At the age of 10, he was seen in another hospital because of a coarse tremor of both hands. Wassermann reaction and Kolmer tests were positive, while the Kahn test was negative. He received no antisyphilitic treatment, and the tremor ceased after a few weeks. Five and 7 years later, Hinton tests were negative; there was never any clinical evidence of syphilis. He had never had orchitis or testicular trauma, and had never noticed the size of the testes. Puberty began at 14 and progressed fairly normally. He masturbated occasionally with pleasurable sensation, but without ejaculations; he had erections but no nocturnal emissions. Within a year of the onset of puberty, he noticed enlargement of the breasts and this increased slowly during the next few years (fig. 2, A).

Examination showed a well developed, thin boy who appeared younger than his stated age. The span was 9.5 cm. greater than the height. Axillary, pubic and perianal hair were normal; he had no beard. The voice was deep and the larynx was normal in size. The breasts were quite large, resembling those of a pubertal girl, non-tender and no secretion could be expressed. The phallus was quite large; the scrotum was well developed; the prostate about normal in size. The testes were extremely small and equal in size. There was a small hydrocele on the right.

Hinton test was negative on three occasions and doubtful on one. Estrin essays: 15 R.U./24 hr. (equivalent to 7.5 micrograms of estrone/24 hr.) before zinc hydrolysis; 42 R.U./24 hr. after zinc hydrolysis (Drs. G. V. and O. W. Smith). The bromsulphalein, cephalin flocculation and Van den Bergh tests were all normal, as was the serum protein content of the blood. Glucose and insulin tolerance tests were entirely normal. Roentgen-ray examination showed a normal sella turcica, normal bone age, and normal adrenals after air injection. Biopsy of the right testis showed marked impairment of spermatogenesis with hyalinization of many seminiferous tubules while the interstitial cells were well preserved.

This patient was treated with large doses of testosterone propionate, progesterone, and pregnenolone without grossly altering the breasts or testes. In June, 1942, both breasts were excised and showed proliferation of the ductal epithelium with marked proliferation of the periductal connective tissue (fig. 6, A). Hinton test was again negative.

Case 3 (fig. 1, C), *F.S.* (*M.G.H.* 119837), a 22-year-old single white laborer, was seen in March, 1940, complaining of gynecomastia. His general health was always fairly good, but he had always been thin. He had mumps without orchitis. There was no history of any previous disease of the testes; the patient thought they were 'always small.' At 13, he had an operation on the left eye for strabismus. For many years he had had severe dental caries and pyorrhea. Puberty began at 14 and progressed normally. At 17 he first noticed enlargement of the breasts and this increased slowly for several years (fig. 2, C). There was no further enlargement during the 2 years that he was under observation. He had satisfactory erections, intercourse and ejaculations.

Examination showed a tall, thin man with large hands and feet who appeared younger than the stated age. The span was 2.5 cm. greater than the height. Axillary and pubic hair was normal, but the beard was scanty. The voice was a little high-pitched, but the larynx was of normal size. The breasts were markedly enlarged, resembling those of an adolescent girl; they were not tender and no secretion could be expressed. The phallus, prostate, and scrotum were normally developed. The testes were extremely small, but the epididymes were well developed.

Hinton test was negative. Biopsy of the left testis showed complete hyalinization of the seminiferous tubules and normal looking interstitial cells. This patient was treated for several months with large doses of testosterone propionate without any effect on the breasts or testes.

Case 4, *B.C.*, (private patient of Dr. J. O. W. Rash), a 24-year-old unmarried white laborer, complained of gynecomastia and small testes. He was always robust and was somewhat obese from the age of 10 to 15 years. He had measles at 9 and influenza 3 or 4 times in childhood. There was no history of mumps orchitis, or trauma to the testes. From 8 to 12, he had frequent attacks of syncope, with loss of memory, lasting 30 to 45 minutes, without epileptiform symptoms. Puberty began at 12 and progressed fairly normally, except that the voice never changed and he had never shaved. Intercourse was unsatisfactory; he had ejaculations, but no nocturnal emissions. Glasses were prescribed at 10 because of poor vision in the right eye; at 17 he complained of increased loss of vision with blurring and was admitted to the Johns Hopkins Hospital. It was noted then that he had gynecomastia and small testes. Ventriculograms revealed no abnormality; visual fields showed a binasal hemianopsia, which was thought to be functional in origin. The gynecomastia was first noticed by the patient at the age of 18 and has not progressed since that time.

Examination showed a rather obese, unintelligent, timid, self-conscious man with wide hips and slightly narrow shoulders. The span was not significantly greater than the height. The axillary and perianal hair were scanty; the pubic hair was normal; the beard was scanty. The voice was high-pitched. There was complete loss of vision in the right nasal quadrants; the optic fundi were normal. The breasts were greatly enlarged. The phallus was normal in size, with a slight degree of hypospadias; the prostate was somewhat small. The testes were very small, equal in size and normal in consistency. Roentgenograms showed a normal bone age. No semen specimen or testicular biopsy could be obtained.

Case 5, *W.J.* (*M.G.H.* 296608), a 28-year-old feeble-minded white houseboy was admitted in April, 1934, at the age of 21 because of gynecomastia. He was an inmate of a State Institution and during the few months before admission manual manipulaton resulted in swelling and pain of the right breast. His general health was fairly good. He had had influenza on two occasions, but did not remember having mumps. He never had orchitis or trauma to the testes, and thought the testes were 'always small.' Puberty began at 15, but the voice did not change, and he never had nocturnal emissions. He had erections but never attempted intercourse and masturbated only a few times, with no ejaculations. At about 18, he first noticed

breast enlargement and this continued for the next few years. The breasts were never painful or tender until the months before admission (*vide supra*).

Examination showed a tall immature boy with narrow sloping shoulders and wide hips. The height was 2.0 cm. greater than the span. Axillary and pubic hair were normal; the voice was high-pitched. Both breasts were markedly enlarged, the right more than the left; the right breast was slightly tender to palpation. The phallus and scrotum were fairly well developed while the prostate was small. The testes were very small.

The FSH test was positive for at least 8 M.U. per 100 cc. The glucose tolerance test was not remarkable. Roentgenograms showed a normal sella turcica; the epiphyses of the radius and ulna were open, indicating a 3-year delay in bone age. Basal metabolic determinations were −4, −5 and +9. Both breasts were amputated and showed hyperplasia of the ductal epithelium and proliferation of the periductal connective tissue.

The patient was again seen in November, 1941, at the age of 28. The voice had not changed and he had not shaved. He had only occasional erections, no ejaculations and had not attempted intercourse.

Examination showed a tall, immature boy who was quite thin. The span was 5.0 cm. greater than the height. Axillary and pubic hair were normal; facial hair was sparse. The voice was high-pitched and the larynx did not show normal masculine development. No breast tissue could be felt under the scars of the amputations. The phallus and scrotum were still only fairly well developed and the prostate was small. The testes were extremely small. There was a hydrocele on the left.

Hinton test was negative. Roentgenograms showed that the epiphyses of the radius and ulna had closed. The bromsulphalein, cephalin flocculation, and Van den Bergh tests were normal, as were the serum proteins. Biopsy of the right testis showed marked impairment of spermatogenesis with hyalinization of most of the tubules and normal appearing interstitial cells.

Case 6 (fig. 1, D), *L.B.* (*M.G.H. 141135*), a 30-year-old unmarried mechanic, was seen in May, 1942, complaining of small testes and gynecomastia. His general health was always good. He had never had mumps and there was no history of orchitis. The testes were 'always small.' At 11 and again at 30, he had pneumonia without complications. Puberty began at 13 and progressed normally. At 14, he first noticed lumps in both breasts which were slightly tender. The breasts slowly increased in size, and he could not remember when they ceased enlarging, but they had remained stationary for at least 6 years (fig. 2, B). At 28, he received testosterone propionate, 25 mg. intramuscularly 3 times weekly because of soreness of the left breast; this caused no change in the size of the breasts but the soreness was perhaps improved. There was never any secretion.

He first noticed pubic hair at 14 and began to have nocturnal emissions the same year. Intercourse was always satisfactory. The voice remained high-pitched until he took thyroid at 26 at which time the voice became deeper; he could still voluntarily pitch his voice high, and was occasionally mistaken for a girl over the telephone. He started to shave at 21, and now shaves every day. Recession of the hair above the temples was first noticed at 21 and has slowly progressed (see fig. 1, D).

For 5 years he has had mild narcolepsy characterized by uncontrollable attacks of sleeping and cataplexy. Four years ago, he had left renal colic when a small stone lodged at the uretero-vesical junction. He was admitted to the hospital and finally passed the stone. On analysis it contained phosphates and oxalates. He had always been a heavy milk drinker. Serum calcium was 11.5 mg. per cent; serum phosphorus was 3.2 mg. per cent. During the next 4 years, he had a few mild attacks of colicky pain on the left side, during which he passed small stones.

Examination showed a tall, well developed swarthy male. The span was not significantly greater than the height. Axillary, pubic and perianal hair were normal; beard and body hair were heavy. There was marked recession of the hair above the temples. The voice was somewhat high-pitched but definitely masculine and the larynx was normal in size. The breasts were greatly enlarged; the nipples were enlarged and pigmented. The left breast was slightly tender, without masses, and the left nipple was retracted somewhat. No secretion could be expressed. The phallus, scrotum, and prostate were well developed. The testes were quite small, measuring about 2.0 cm. in length. They were firm, normally sensitive and about equal in size. The epididymes were well developed.

Hinton test was negative. Roentgenograms showed a normal sella turcica, normal bone age, and normal kidney outlines without evidence of stones. Intravenous pyelogram showed normal urinary passages. B.M.R. was −12. The urine was of high specific gravity (1.028) and contained large amounts of calcium, many oxalate crystals, a few leukocytes, but no albumin. Cultures showed a light growth of *staph. albus*. Serum calcium was 10.3 mg. per cent; serum phosphorus was 2.8 mg. per cent. Semen examination showed azoöspermia. Biopsy of both testes showed complete hyalinization of the seminiferous tubules and normal appearing interstitial cells (fig. 4, A). Biopsy of the left epididymis revealed entirely normal tissue.

Bilateral subcutaneous mastectomy was performed in July, 1942; the breast tissue showed ductal hyperplasia and proliferation of the periductal connective tissue (fig. 6, B).

Case 7, *S.C.* (private patient of Dr. H. I. Suby), a 32-year-old married Jewish school teacher, complained of sterility. He had been married for 4.5 years. He had mumps at 10, without orchitis, and had never had any trauma to the testes. At 27 he had a urethral discharge which cleared promptly with methenamine treatment; there were no complications with this infection and no recurrences. He was always obese. Puberty began at 13 and progressed normally; intercourse was satisfactory, and he had ejaculations. Hair and beard growth were normal. At 16 he first noticed prominence of the breasts, which have increased in size very little since that time.

Examination showed an obese, well developed male with normal axillary, pubic and facial hair. The span was not significantly greater than the height. The voice was low-pitched. The breasts were moderately enlarged, not tender, and no secretion was expressed. The phallus,

scrotum, and prostate were fairly well developed and within normal limits. The testes were small.

Semen examinations repeatedly showed azoöspermia. Biopsies of the right testicle showed impaired spermatogenesis with hyalinization of the seminiferous tubules and normal appearing interstitial cells. The patient was treated with chorionic gonadotropin, 750 to 1,000 U intramuscularly 3 times weekly for 3 months without any change in the size of the testis or breasts and without improvement in the appearance of the testis biopsy (fig. 4, B). He continued to have azoöspermia. He was then treated with testosterone propionate, 25 mg. intramuscularly 3 times weekly with no noticeable effect.

Case 8 (fig. 1, E), C.G. (*M.G.H. 12047*), a 35-year-old married Jewish porter, was admitted at the age of 31 complaining of sterility and gynecomastia. His general health was always good. He had mumps at 8 without orchitis; he had never suffered any injury to the testes and said they were 'always small.' At 19 an appendectomy was performed; it was noted then that the testes were small and the breasts were enlarged. Puberty began at 14 and progressed normally. At 16 he noticed enlargement of the breasts which progressed for about 3 years and has since remained stationary (fig. 3, B); the breasts were never painful or tender and no secretion was present. He married at 25 and had satisfactory intercourse with ejaculations but no pregnancies resulted. He had slowly gained weight during the last 10 years.

Examination showed an obese, well developed man with smooth skin. There were telangiectases of the cheeks. Axillary, pubic and perianal hair were normal; head hair was heavy and there was a slight recession of the hair above the temples. There was a myopia and a few lenticular opacities; the visual fields were normal. The voice was deep and the larynx was of normal size. The breasts were greatly enlarged and resembled those of an adolescent female; they were not tender and no secretion was expressed. The phallus, scrotum, and prostate were well developed. Both testes were very small.

The FSH was positive for at least 10 M.U. per 100 cc. of urine. Estrin assay was negative for 10 R.U. per liter of urine. The glucose tolerance test was not remarkable. Roentgenograms showed a normal sella turcica, a normal right adrenal after perirenal air injection, and union of the epiphyses of the radius and ulna. Basal metabolic determinations were −20 and −26. Serum cholesterol was 138 mg. per cent. Semen examination showed azoöspermia. Biopsy of the left testis showed almost complete hyalinization of the seminiferous tubules and normal interstitial cells. Biopsy of the right breast showed hyperplasia of the ductal epithelium and proliferation of the periductal connective tissue.

The patient was seen in 1942 with the same complaints. He married again at 32 and his second wife had not become pregnant. The breasts were not changed. During the last year, libido had decreased but he still had erections, intercourse and ejaculations. He shaved only once a week and the beard was limited to the chin and upper lip. It is interesting that his father who had 11 children had the same type of beard.

Examination revealed essentially the same findings as before. The span was not significantly greater than the height. The epididymes as well as the phallus, scrotum and prostate were well developed. The testes were very small, about 1.5 cm. in length, and equal in size. Hinton test was negative.

Case 9 (fig. 1, F), A.C. (*M.G.H. 249898*), a 38-year-old married Jewish merchant, was admitted in May, 1940, complaining of sterility. He had married 3.5 years before and his wife had not conceived although no contraceptives were used. After pneumonia at the age of 6 he had infrequent hemoptyses.

Examination revealed bilateral gynecomastia, very small testes and signs of cavitation in the right upper lobe. Roentgenograms showed chronic cystic disease of the right lung; the sella turcica was normal. The visual fields were normal. Semen examination revealed azoöspermia.

In 1942 he was seen again, still complaining of sterility. There was no history of mumps or orchitis. The testes were 'always small.' Puberty began at 12 and progressed normally. He had satisfactory intercourse with ejaculations. He shaved twice a week. Breast enlargement was first noted at 18 when he was thin. During the next few years he slowly gained weight and the breasts increased in size. The breasts were never painful or tender and had not changed in size for the last 10 years (fig. 3, C).

Examination showed a well developed muscular man. The span was 4.5 cm. greater than the height. Axillary, pubic and perianal hair were abundant; head hair was heavy and there was recession of the hair line above the temples. The beard was limited to the chin and upper lip, but was quite heavy. The voice was deep and the larynx normal in size. The breasts were greatly enlarged, but not tender and no secretion was expressed. There were signs of cavitation over the right upper lobe. The phallus, scrotum, and prostate were normal. The testes were extremely small, equal in size and firm. Hinton test was negative. The patient refused to have a testicular biopsy performed.

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