THE ETIOLOGY OF BENIGN PROSTATIC HYPERTROPHY*

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THROUGHOUT every one of the branches of medicine there runs an identical methodology in scientific development which is so similar that it must be considered as a basic pattern of human thought which man is conditioned to use as he investigates the unknown. The evolutionary stages are historically as well as in order of increasing importance, Speculation, Observation and Experimentation. In considering a subject it is well at times to reflect on which stage one finds himself and how important that phase may be with reference to the others.

Consideration of the etiology of disease entered medicine as a late and sophisticated development. Early man, no doubt attempted by preference to cure his pain and malaise through mystical means and when these therapeutic agents often proved to be erratic and capricious he reluctantly turned to more earthy methods. I presume that the first attempts at treatment were considerably later superceded by primitive diagnosis since some sort of a classification seemed to be helpful if not prerequisite to therapeutics. The classification of illness naturally led to thought about the causation of disease.

What is the etiology of benign prostatic hypertrophy? There was much early speculation about it and many theories have invoked such diverse factors as venereal disease of the several sorts, inflammation, arterio-sclerosis and various human sexual habits as well as celibacy. The causation of disease is not nearly so simple as it seems at first glance. In a few fields one can give succinct although sometimes superficial statements of etiology. For example, it is easy to state that a waxy bacillus is the cause of tuberculosis and that a green streptococcus is the inciting agent in sub-acute bacterial endocarditis but even here such

* Read March 19, 1947, before the Section on Genito-Urinary Surgery of the Academy. Original research reported in this paper was done under grants from Mr. Ben May, the Albert and Mary Lasker Foundation, Inc., the Sidney and Frances Brody Foundation and the Committee for Research in Problems of Sex, The National Research Council.

things as resistance of the host complicate the problem in certain individuals and species.

The etiology of prostatic hypertrophy seems to be particularly difficult to investigate since many of the characteristics of the disease are peculiar to man. Since experiment thereby is greatly limited we are largely thrown back on observation so that concerning the cause of the enlarged prostate only an approximation can be given at this time. I wish now to consider how far contemporary morphologic and functional knowledge can provide a limiting frame in which the etiology should fall.

Benign prostatic hypertrophy so far as is known occurs only in man and dog and it has not yet been successfully induced in the laboratory. Probably any attempts at experimental production should involve the dog as the experimental animal; it is a fundamental dogma of the laboratory that any disease which occurs spontaneously can be experimentally reproduced but unnatural disease may be something else again. The disease differs in man and dog. Canine prostatic hyperplasia in essence is a cystic hyperplasia of epithelium. The cause of the cysts is not ductal obstruction since plugging the ducts with a graft of striated muscle[1] although producing cystic change does not result in hyperplasia. Also the injection of India ink into the dilated cysts of spontaneous cystic hyperplasia reveals that the ducts are patent. Always tall columnar epithelium is present but its functional capacity is damaged. The prostatic secretion in canine prostatic hyperplasia is identical with that of young adult normal dogs but the volume is greatly reduced. A fist sized canine prostatic hyperplasia (100 grams) secretes much smaller volumes (2-5 cc.) than does the 10 gram gland of a normal young adult (30-50 cc); but each prostate produces the same type of fluid.

Canine prostatic hyperplasia is under androgenic control. The disease does not occur in castrates. Testicular excision causes prompt atrophy[2] and differing from the hypertrophy of man, where the effect is slower, profound involution of the tumor occurs promptly after estrogen. Dogs feminized by estrogen produced by Sertoli cell tumors of the testis[3] have been extensively investigated; they never have canine prostatic hyperplasia. The disease only occurs in old age. Nearly all ancient dogs (objective evidence—worn teeth and cataracts) with functioning testis[2] have this disturbance. Age itself does not confer on prostate gland the necessity for epithelial proliferation. We have injected androgen,

testosterone propionate, 10 mg. daily for 3 months, in 3 dogs known to be older than 16 years and castrate in early life; in each case a normal prostatic gland with no signs of cystic hyperplasia resulted.

We deduce from all this that androgen and senility are important factors in the hyperplasia of dogs and that the senility factor is not a matter of chronology alone. The time component is the expression of continued stimulation by androgen over long years. The evidence for cystic hyperplasia being a neoplasm is presumptive but not clear cut in the dog.

It is well now to consider the following facts and their interpretation concerning the prostatic hypertrophy of man.

1. *The lesion is composed of spheroidal neoplastic nodules.* It is not an hypertrophy at all; however smooth the lesion may appear in the gross, spheroidal masses are invariably found on dissection. The nodules are always multiple. At times the right and the left sides of the prostate are asymmetrically involved, a larger nodule being present in one portion than the other; however nodules are always found in each side of the gland and a single spheroid in the prostate must be a rarity.

The spheroids usually are composed of 3 elements, epithelium, smooth muscle and fibroblasts; less often epithelium may fail to be present. Strictly, multiplicity of nodules in pathology indicates only that there are multiple centers of origin of the lesion. Since pure myomas and fibromas occur in addition to the characteristic epithelial containing growth it may be deduced that the spheroidal nodules of the prostate are benign neoplasms. Further benign prostatic hypertrophy[4] has an appreciable aerobic glycolysis (Q_LO_2 2.21) and possession of this metabolic pathway is one of the characteristics of tumors. The content of citric acid, aconitase[5] and acid phosphatase in the prostatic adenoma is not impaired. In many respects the spheroidal disease of the prostate resembles fibroid tumors of the uterus except that epithelial proliferation is absent in the latter. Incompletely removed neoplasms usually regenerate and this explains the bad results of transurethral resection where it is impossible regularly or indeed frequently to remove all of the spheroids.

2. *Growth of the human prostate is not finite.* In his study of 733 human prostates Teem[6] quaintly but accurately observed "The prostate reached the adult size in the third decade of life, and from then on the curve for the average weight gradually rose." Benign prostatic hypertro-

phy was observed in 5 instances by Teem between age 30 and 39 years. Moore[7,8] did not encounter the disease before age 39. The disease increasingly affects the prostate with increasing age to the limits of life. In Moore's study 75-80 per cent of all men after 80 years of age had prostatic hypertrophy. The age influence is expressed in a homely way in the saw that "children have all of the urologic diseases of adults except pyelitis of pregnancy and benign prostatic hypertrophy."

3. *Only the medullary region of the prostate is involved by benign prostatic hypertrophy.* Tandler and Zuckerkandl[9] first expressed the concept that the disease is essentially pre-spermatic in origin and involves the periurethral regions exclusively and that the posterior region of the prostate does not become the seat of hypertrophy. It was the opinion of these scholars that the original lesions arose as budding of sub-mucosal glands of the urethra. Reischauer[10] and later Moore[8] stated that the earliest lesion was a sub-mucous nodule of stromal cells which were devoid of elastic tissue. Reischauer believed that the fibro-myomatous tumor often became invaded by epithelium. These findings are not consonant with our observation that the spheroidal nodules may arise in any part of the prostatic medulla.

Although the prostatic glands arise as buds from the urogenital sinus, it has been clear that a duality of structure exists in the prostates of many species. In the guinea pig and rat[11] as well as the monkey[12] a specific region of the prostate exists which is able to induce coagulation of the seminal vesical secretion. Further in the rat and mouse[13,14] this area—the anterior prostate or coagulating gland, responds differently to estrogen from the main body of the gland; the acinar epithelium becomes transformed to squamous cells in the anterior lobes while the dorsal and ventral lobes remain uninvolved.

In the dog the response to estrogen is clear cut in varying portions of the gland; only the posterior or dorsal segment of the gland responds to estrogen[15] by forming squamous metaplasia. In the presence of injected estrogen and androgen the ventral portion of the canine prostate responds by forming tall columnar epithelium while the posterior region undergoes squamous transformation.

In his classic embryologic study of the human prostate Lowsley[16] observed that the posterior lobe of the prostate arose as an independent structure originating from the floor of the urethra below the ejaculating ducts.

In man prostatic cancer usually arises in the cortical region of the prostate[17] and the difference in the type of tumors arising in the medullary region seems to indicate a fundamental difference in regions of the gland. Apart from the different types of neoplasms occurring in these regions of the gland, physiologic proof has been difficult to obtain concerning the duality of the human prostate. Subtle but definite effects are observed after estrogen administration which I shall present in a moment revealing regional differences in the human prostate.

Aside from the differentiation of the prostate into cortical (posterior lobe) and medullary portions (inner prostate, periurethral region), the prostate does not seem to have other lobes. At the present time a "median lobe" is commonly described but the terminology is inexact. Our observations coincide with those of Swyer[18] who states—"In most cases the fibroadenomatous nodules of early prostatic hypertrophy are found only in the lower parts of the prostate, and it is by the upward extension of these nodules that intravesical projections are generally formed. Rarely the projections take the form of a more or less complete collar around the internal urethral meatus, but it is much more common to find a median knob, often referred to as the uvula vesicae, behind the meatus. Very occasionally, a uvula vesicae may exist without there being any evidence of hyperplasia in the lower parts of the prostate; these are the cases of true subcervical or subtrigonal lobe hyperplasia." In most cases the median lobe or uvula can be traced to a lateral adenomatous nodule.

4. *The androgenic relationship.* Constantly in benign prostatic hypertrophy the prostatic epithelium consists of tall columnar cells 16-28μ in height.[19] In the dog and the rat castration causes a prompt decrease of height of the cell, which is restored by androgen. In man orchiectomy causes a decrease of cellular height and epithelial atrophy in the benign hypertrophy but at a rather slow rate compared to the laboratory animals. The epithelial cells were only slightly reduced 29 days after castration but marked atrophy was observed[19] at eighty-six and ninety-one days.

Orchiectomy produced a considerable relief of obstructive symptoms and a decrease in the size of the prostatic hypertrophy in our cases. However enucleable spheroids of muscle, fibroblasts and atrophic epithelium were present so that the neoplasm did not disappear—it merely shrank in size. Of importance in the etiology of benign hyper-

trophy is the fact that it has never been observed in man from whom the testes had been removed in early life.

The effect of estrogen on the prostate requires special comment. In the dog estrogen results in a rapid cessation of secretion and profound epithelial atrophy with pronounced epithelial metaplasia of the posterior segment of the gland. In man the effect is much less and slower. Moore and McLellan[20] injected estrogen for ten to thirty-one days in five patients with benign prostatic hypertrophy and observed an increased stratification of the transitional epithelium in the ducts and urethra; the acini and stroma of the nodules of benign hypertrophy showed little effect of the estrogen. In our experience with man estrogen administrated in dosage sufficient to cause breast growth (e.g. diethyl stilbestrol 130 mg. in fifty-seven days, of which 70 mg. were injected intramuscularly) caused no decrease in the amount of enzymic concentration of prostatic fluid; definite changes were observed in the acini of the inner prostate and none in the posterior lobe. In the acini of the medulla of the prostate a paleness of the cells, vacuolation and signs of mild injury such as a shift of the nucleus to the middle of the columnar cell were observed contrasted with the normal epithelial cells of the cortical prostate.

Discussion

In the hyperplastic prostate of dogs the lesion is primarily a great epithelial growth conditioned by 2 factors, the testis and time. Fibromas and myomas have not been observed. The epithelium is inefficient since the prostatic secretion is much reduced in quantity though qualitatively similar to the secretion of a normal young adult.

Since hyperplastic epithelium is the basis of the canine overgrowths theory suggests that the epithelial cells are the basic factors in the human prostatic enlargement. In most cases in man the lesion is an adeno-fibro-myoma; in those cases of pure myoma or fibroma the earlier presence of epithelium which has been "choked off" cannot be excluded. The nodular character of the process and its respiration indicate that the disease is a benign neoplasm. Since the prostate has the peculiar property of continued growth the frequent presence of abnormal growth processes is not unexpected.

In man the disease involves only the medullary part of the prostate. Comparative physiology has shown that there are 2 functionally dif-

ferent areas of the prostate in mouse, guinea pig and monkey. The evidence that the human prostate is composed of 2 different regions, apart from the capacities of the posterior lobe and the medullary region to form differing neoplasms, is based on differences of embryologic origin and response to estrogen of these regions.

Certainly in both man and dog prostatic enlargement is related to a stimulus acting for a very long time since the disease does not occur in early life. Presumably the stimulus is of testicular origin since the disease does not occur in the absence of the gonad. Obviously androgen is a basic factor in development if not the actual cause since tall epithelium is invariably present in the gland in prostatic hypertrophy, and the disease does not occur in feminized dogs. Also castration causes shrinkage[21] of this neoplasm which has never been known to develop in castrates. Finally androgen itself is a powerful stimulant of growth of selected cell areas.

It must be pointed out at this time that while estrogen is involved in the genesis of many tumors, androgen as yet has not been implicated as an inciting agent for tumors in any experiment.[22]

It is proven that androgen is a basic element in the etiology of benign prostatic hypertrophy. However in man in old age at a time when prostatic tumors are growing well there is a decreased secretion of androgen. Rusch and Kundert[23] first showed that the androgen excretion of men with prostatic hypertrophy is significantly lower than that of young males. Dingemanse and Laqueur[24] observed that both the urinary estrogens and androgens were less in men with benign prostatic hypertrophy than in old men without this lesion. The reduction in the amount of urinary androgens in old age has been confirmed by other groups[25,26,27] using both the comb growth assay technique and the Zimmermann reaction for 17-ketosteroids. Teem[6] found that the number of Leydig cells in the testis of men with benign prostatic hypertrophy is relatively reduced.

Growth of the prostatic hypertrophy in the face of greatly reduced androgen is well explained by the endocrinologic doctrine of threshold. The prostate has a lower threshold to androgen than the seminal vesicle. Working with crude extracts Moore and Gallagher[28] found that about 3 times as much androgen was required to show effects in the seminal vesicle as in the prostate. This has been confirmed with pure androgens.[29,30] There is a differential threshold in the prostatic lobes in the

rat to androgen. On the tenth day after castration involutionary changes were first detected cytologically in the anterior lobe (coagulating gland) although they had been noticed on the fifth day in the other prostatic lobes.[30] The evidence that there is a low threshold to androgen in human prostatic hypertrophy is based on the slowness of development of post-castrational atrophy and the resistance to estrogen in comparison to the laboratory animals.

Conclusion

The epithelium of the cortical prostate differs from that of the benign prostatic hypertrophy in its response to estrogen; this observation indicates that the prostate gland of man is composed of two different functional areas.

Benign prostatic hypertrophy in man consists of multiple spheroidal neoplastic nodules arising in the medullary portion of the prostate because of a testicular stimulus presumably androgen acting over a long period of years on a tissue which at that time has a low threshold to androgens.

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