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ENDOCRINE CONTROL OF PROSTATIC CANCER[1,2]

By Dr. CHARLES HUGGINS

THE DEPARTMENT OF SURGERY, THE UNIVERSITY OF CHICAGO

THERE is a high incidence of abnormal growth processes—of tumors, in the prostate gland of certain species in senescence. These species are man, the dog and the lion. For technical reasons, observations can be carried out with greater facility on the first two types than on the king of the beasts.

The most common neoplasia involving the prostate gland are benign nodular hypertrophy and carcinoma. The benign hypertrophy has been found[3] to involve the prostate gland in 45 per cent. of men over forty years in otherwise unselected autopsy material. Cancer of the prostate occurs[4,5] in at least 9 to 17 per cent. of men over fifty years; while many of these tumors are microscopic in size and, remaining latent, seldom are factors in morbidity or mortality, others invade and spread and become the cause of death of about 5 per cent. of men older than fifty years[6] in the United States. Plainly, neoplastic processes are usually present in the human prostate gland after the fifth decade, while a normal prostate is less common in old white men. Barringer, an eminent student of prostatic cancer, recently stated:[7] "The control of prostatic carcinoma presents one of the most difficult problems in the field of cancer. Many urologists believe seriously that its control is impossible."

[1] Address delivered on the occasion of the first award of the Charles L. Mayer Prize administered by the National Science Fund of the National Academy of Sciences, May 19, 1943.

[2] This investigation was aided by a grant from the Committee for Research in Problems of Sex, the National Research Council.

[3] M. B. Teem, *Jour. Urol.*, 34: 692, 1935.

[4] A. R. Rich, *Jour. Urol.*, 33: 215, 1935.

[5] R. A. Moore, *Jour. Urol.*, 33: 234, 1935.

[6] E. Baron and A. Angrist, *Arch. Path.*, 32: 787, 1941.

[7] B. S. Barringer, *Surg. Gynec. and Obst.*, 62: 410, 1936.

The prostatic cancers most commonly encountered consist either of undifferentiated sheets of cells or of adenocarcinomas wherein tiny glands are reproduced. These types have been observed in a very few animals, namely in one monkey[8] and three dogs,[9] and have not been produced experimentally. In rats, the implantation in the prostate of the carcinogen, 1 : 2, benzpyrine, was followed by squamous carcinoma,[10] a type rarely encountered in man; adenocarcinoma has not been reproduced experimentally.

The prostate is not known to produce a hormone and a considerable function of the gland is external secretion. The nature of the external secretion is of importance, since this fluid contains several unusual components; what seems bizarre is of the greatest interest to scientists, far overshadowing routine and predictable phenomena. Human prostatic fluid contains rather large amounts of calcium,[11] citric acid[12] and two enzymes, fibrinolysin—a moiety capable of rapidly destroying fibrin[13] and acid phosphatase, an enzyme of some importance, as will be seen.

The prostate gland is dependent for its existence in the adult or secretory state upon endocrine products and as far as is known upon only two types of hormones, androgens and estrogens. The male sex hormones or androgens cause an increase of size and the initiation and maintenance of the function of prostatic epithelium and in excess produce, fundamentally, hyperplasia. The estrogens, or female sex hormones in excess, cause a decrease in size and cessation of function of the tall columnar secretory epithelial cells —metaplasia. Further these fat-soluble compounds have the interesting physiological capacity of neutralizing the action of each other with respect to the prostate, when administered in appropriate amounts; nothing is known of the mechanism of antagonism of androgens by estrogens except that it is not a neutralization in the sense that acid neutralizes alkali. These basic reactions of the prostate to hormones may be easily demonstrated by the surgical procedure of prostatic isolation in dogs,[14] which permits frequent assay of the prostatic secretion for many months.

One of the directions that cancer research now is taking is the functional or physiological approach to the problem of tumors. The functional approach contrasts sharply with the descriptive approach—with the methods of classical pathology. It is concerned with the entire living organism rather than with sections or segments of the dead organism. In the functional approach the measure is of first importance: How much cancer activity is present? How can the activity be increased or decreased? Assay of a disease in a laboratory obviously removes much of the uncertainty inevitably associated with bedside observation, particularly in cancer. The yardstick in prostatic cancer concerns certain enzymes, the phosphatases.

"The metabolism of living cells is carried on by a diverse and intricate mosaic of enzyme catalysis. Under normal conditions and over the greater part of the life of the host, each tissue presents a steady and consistent enzymic pattern."[15]

The phosphatases are important in energy production in the cell. An enzyme capable of hydrolyzing phosphoric esters was discovered by Grosser and Husler[16] in intestinal mucosa in 1912; Robison[17] found that this enzyme was rich in growing bone and that it had its optimum activity at about pH 9. In certain bone diseases where there was abnormally increased osteoblastic activity, Kay[18] found that the "alkaline" phosphatase value of serum was abnormally increased; among these bone diseases is prostatic cancer which often metastasizes and involves bones, flourishing in this location.

Another phosphatase, with optimum activity at pH 5, was discovered in 1934, independently by Davies[19] and Bamann and Riedel,[20] in liver and kidney. Kutscher and Wolbergs[21] found that this "acid" phosphatase was rich in concentration in the prostatic secretion of man. The extensive and elegant studies of A. B. Gutman and Ethel Benedict Gutman have greatly elucidated the prostate-phosphatase relationships. The enzyme does not appear in appreciable amounts in human or monkey prostate tissue until puberty,[22] either naturally occurring or artificially induced with androgens,[23] when large amounts form. Cancer of the prostate also contains large amounts of the enzyme.[24] In certain patients with cancer of the prostate when the tumor has spread to lymph nodes or

[8] E. T. Engle and A. P. Stout, *Am. Jour. Cancer*, 39: 334, 1940.

[9] C. F. Schlotthauer and J. A. S. Millar, *Jour. Am. Vet. Med. Asn.*, 99: 239, 1941.

[10] R. A. Moore and R. H. Melchionna, *Am. Jour. Cancer*, 30: 731, 1937.

[11] C. Huggins, W. W. Scott and J. H. Heinen, *Am. Jour. Physiol.*, 136: 467, 1942.

[12] B. Scherstén, *Skand. Arch. Physiol.*, 74: suppl. 9, 1936.

[13] C. Huggins and W. Neal, *Jour. Exp. Med.*, 76: 527, 1942.

[14] C. Huggins, M. H. Masina, L. Eichelberger and J. D. Wharton, *Jour. Exp. Med.*, 70: 543, 1939.

[15] J. P. Greenstein, *Jour. Nat. Cancer Inst.*, 3: 419, 1943.

[16] P. Grosser and J. Husler, *Biochem. Zeits.*, 39: 1, 1912.

[17] R. Robison, *Biochem. Jour.*, 17: 286, 1923.

[18] H. D. Kay, *Brit. Jour. Exp. Path.*, 10: 253, 1929.

[19] D. R. Davies, *Biochem. Jour.*, 28: 529, 1934.

[20] E. Bamann and E. Riedel, *Zeits. für physiol. Chem.*, 229: 125, 1934.

[21] W. Kutscher and H. Wolbergs, *Zeits. für physiol. Chem.*, 236: 237, 1935.

[22] A. B. Gutman and E. B. Gutman, *Proc. Soc. Exp. Biol. and Med.*, 39: 529, 1938.

[23] A. B. Gutman and E. B. Gutman, *Proc. Soc. Exp. Biol. and Med.*, 41: 277, 1939.

[24] E. B. Gutman, E. E. Sproul and A. B. Gutman, *Am. Jour. Cancer*, 28: 485, 1936.

bone, acid phosphatase values are increased in the blood,[25,26] constituting an important diagnostic test when high values are obtained. In many patients with advanced prostatic cancer both phosphatases are increased in serum; alkaline phosphatase because the bones are frequently involved with resultant increased osteoblastic activity and acid phosphatase because the tumor is prostatic in origin. Gomori[27] demonstrated by an ingenious histochemical staining method that acid phosphatase is elaborated by the normal secretory cells as well as by cancerous prostatic epithelium.

It then became apparent that the increased phosphatase values of adult secretory prostatic epithelium represented a secondary sex characteristic of an enzymic nature, and that usually prostatic cancer cells were at such a mature level that secretion occurred; this was of interest since in the past most cancers have been conceived to be composed of tissue resembling embryonic or primitive epithelium. It was known that with the possible exception of the anterior lobe of the prostate of guinea pigs[28] all secretory prostatic epithelium in mammals underwent diminution in size and function when the androgens were reduced in amount or in activity. Therefore, it was necessary to determine the effect of vitiation of androgens on prostatic cancer.

In a series of patients with advanced prostatic cancer the androgens were reduced by surgical removal of the testes or by estrogen administration, using as a yardstick the elevated serum phosphatases which were determined at frequent intervals.[29] Characteristically in man, such androgenic reduction is accompanied by a sharp fall in the amount of acid phosphatase to or towards normal and by a slower rise of alkaline phosphatase which after some weeks likewise decreased. These changes in alkaline phosphatase values apparently reflect healing in the bony lesions. The converse obtains in that the injection of androgen increases acid phosphatase values in prostatic cancer and aggravates the disease.

The inhibition of prostatic cancer by androgen control is not limited to beneficial effects on enzymes in blood serum. Among the earliest changes occurring in man are an increased appetite and relief of pain, often within several days after initiating treatment.[30] It is striking to see patients emaciated from malignant disease develop a voracious appetite. Pain in advanced prostatic cancer usually is severe and requires sedatives; this pain often disappears soon after castration. The increased food intake and decrease of pain promote a sense of well-being and more tangibly a gain in weight and increased blood formation so that the anemia accompanying the tumor frequently disappears, still further interrupting the vicious circle of the cancerous disease. Often there is a pronounced decrease in size of the neoplasm so that the palpably involved tissues, wherever they may be, return to normal; in deep recesses this apparent disappearance of the disease may be well followed in roentgenograms. Several patients with paralysis due to involvement of the spinal cord or nerve trunks with this cancer have had a disappearance of the neurologic changes and a return to a normal functional state.[30,31]

There have been no adverse psychic effects encountered, but certain undesirable effects attend androgen control. After castration most people develop the vasomotor phenomena known as hot flushes identical with those which are physiologic in occurrence in women at the menopause. Following estrogen administration men develop pain and swelling of the breasts. Moreover, in both instances whatever sexual activity remains, commonly slight, is usually abolished.

All in all, the improvement occurring after castration or estrogenic administration in prostatic cancer far outweighs the undesirable effects. It must be emphasized that the results are not uniformly successful and that they fall into three groups; one group, less than 5 per cent. of patients received no or slight benefit from endocrine treatment; the other groups, larger and nearly equal in number, obtained respectively an improvement pronounced but unsustained (less than eighteen months), or a pronounced and more prolonged regression of the disease. The improvement is greater than palliation, when technically the patient is merely made more comfortable in the face of advancing disease. The benefit in prostatic cancer often includes disappearance of the tumor, at least in the gross, and is considered as neoplastic inhibition. In clinical patients, castration seems to give somewhat better results than occur from estrogenic therapy.

The failure cases, where either no or an unsustained improvement occurs, are of great interest. As stated, in some of these cases endocrine modification produces a temporary atrophy, both of the original tumor and of the spread, to be followed in some months by reactivation of the disease; the recrudescence is always greater in the metastases than in the primary tumor. This is a strange phenomenon[32] when the previously

[25] A. B. Gutman and E. B. Gutman, *Jour. Clin. Investigation*, 17: 473, 1938.

[26] B. S. Barringer and H. Q. Woodard, *Trans. Am. Asn. Genito-Urin. Surgeons*, 31: 363, 1938.

[27] G. Gomori, *Arch. Path.*, 32: 189, 1941.

[28] E. D. Sayles, *Jour. Exp. Zool.*, 90: 183, 1942.

[29] C. Huggins and C. V. Hodges, *Cancer Res.*, 1: 293, 1941.

[30] C. Huggins, R. E. Stevens and C. V. Hodges, *Arch. Surg.*, 43: 209, 1941.

[31] R. M. Nesbit and R. H. Cummings, *Jour. Am. Med. Asn.*, 120: 1109, 1942. B. G. Clarke and H. R. Viets, *Jour. Am. Med. Asn.*, 121: 499, 1943.

[32] C. Huggins, *Ann. Surg.*, 115: 1192, 1942.

hard, enlarged and nodular prostate gland becomes and remains soft and atrophic in the presence of the advancing neoplastic process elsewhere in the body. Clearly the prostatic tissue in bone marrow and lymph gland is located more strategically for its growth than in the original neoplastic site. Among possible causes of the failure cases are the production of significant quantities of androgen in extragonadal loci, as well as differences in the nature of original tumor. It has been established that varying, and at times, large, amounts of androgen are produced in the adrenal cortex of man; the adrenal androgens have been incompletely studied in prostatic cancer but obviously if significant amounts of androgens are produced in this region in certain patients, castration will effect incomplete regression of the tumor. It has been found that glandular types of prostatic cancer often but not always respond more favorably than undifferentiated tumors.

The urinary excretion of hormones in prostatic cancer has been studied.[33] The 17-ketosteroid excretion is reduced in amount as compared with vigorous young men, but not more so than in normal males of the same age group; following orchiectomy there is a decrease in their level followed in several weeks by a rise greater than the pre-operative values. The excretion of gonadotrophic agents is slightly increased after castration.

The concept of autonomy of the cancer cell in recent years has influenced thinking about cancer; according to this idea the malignant cell is dependent for its survival on few or no extraneous influences and proliferates even when solely dependent on catabolic effects of a starving host for its energy and growth. The present observations demonstrate that this concept is not general in application in the tumor field, since the prostatic cancer in man often is dependent on androgen for its survival.

In summary, it is possible by reducing the amount or the activity of circulating androgens to control, more or less but often extensively, far advanced prostatic cancer in large numbers of patients. In this special case, androgen control seriously disturbs the enzyme mosaic of the cancer cells at least with respect to the important energy producing protein-catalysts, the phosphatases. As a contribution to the problem of cancer treatment, it is well to emphasize that any interference with an important enzyme system of a cell, normal or malignant, will cause in that cell a decrease of size and function.

COLORBLINDNESS AND THE DETECTION OF CAMOUFLAGE

By Dr. DEANE B. JUDD
NATIONAL BUREAU OF STANDARDS

ACCORDING to newspaper reports, colorblind observers have frequently been successful in spotting otherwise perfectly camouflaged positions. In order to show whether these reports can be believed, a brief analysis of the ways by which a normal observer can detect off-color camouflage must first be given.

NORMAL VISION

A normal observer can make color discriminations of three kinds: light-dark, blue-yellow and red-green. If a camouflaged position appears neither lighter nor darker, neither bluer nor yellower and neither redder nor greener than the surrounding terrain, the observer with his naked eye can not detect it because of its color; it is therefore perfectly colored and matches its background perfectly.

RED-GREEN BLINDNESS

The two most common forms of colorblindness are called deuteranopia and protanopia. Deuteranopes and protanopes are called colorblinds because they can not make red-green discriminations. To hide a position from such an observer as these it is sufficient to make it neither lighter nor darker, and neither bluer nor yellower than the background. It is not necessary to worry about whether the position is redder or greener than the surrounding terrain. These observers find it hard to pick out ripe strawberries from green or to pick out a rotten apple from a barrel of red apples, since the color differences involved are chiefly red-green differences. Since they can make yellow-blue discriminations quite as well as the normal observers, they are sometimes said to be only partially colorblind.

RED-GREEN WEAKNESS

There are two other forms of abnormal vision which have to be considered. They are forms of vision intermediate between normal vision and deuteranopia and protanopia, respectively. The form intermediate between normal vision and deuteranopia is known as deuteranomalous vision, that tending toward protanopia as protanomalous vision. There are more

[33] W. W. Scott and C. Vermeulen, *Jour. Clin. Endocrinol.*, 2: 450, 1942. A. L. Dean, H. Q. Woodard and G. H. Twombly, *Jour. Urol.*, 49: 108, 1943.