

CARCINOMA OF THE PROSTATE
(A STUDY OF EIGHTY CASES DIAGNOSED
FROM 1930-1940 INCLUSIVE)

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TABLE OF CONTENTS

CHAPTER	PAGE
I. THE PROBLEM, MATERIALS AND METHODS	1
The problem	1
Materials and methods	1
II. REVIEW OF THE LITERATURE	3
Age incidence	3
Incidence of cancer of the prostate	3
Etiology	9
Symptoms	9
Clinical findings	12
Clinical classification	14
Survival figures	15
Duration of the lesion	16
Gross appearance	17
Spread of the tumor	17
Autopsy findings	22
Site of origin of carcinoma	23
Microscopic criteria of malignancy	26
Histological classification of carcinoma of the prostate	27
Phosphatases	34
III. HISTORY	38
Marital status	38
Occupation	38
Age	38

CHAPTER	PAGE
Family history of cancer	40
Previous genito-urinary tract disease	41
Complaints	41
Hematuria	43
Acute retention	43
Duration of symptoms before admission and diagnosis	44
IV CLINICAL FINDINGS	45
General condition of the patient on first admission	45
Rectal examination	46
Size of the gland	46
Consistency	46
Portion of the gland involved	47
Fixation	48
Cystoscopic examination	48
V LABORATORY FINDINGS	50
Laboratory and Roentgen studies	50
Plain films of kidneys, ureters and bladder (KUB)	50
Hemoglobin	50
Urinary sediments	50
Blood urea nitrogen estimations	51
Blood creatinine studies	51
VI CLINICAL CLASSIFICATION	52
Clinical classification of the American College of Surgeons	52

CHAPTER	PAGE
Ferguson's classification	53
VII. MICROSCOPIC CLASSIFICATION	58
The data obtained after microscopic classification . .	59
VIII. COMPARISON OF FERGUSON'S CLINICAL CLASSIFICATION AND	
EDWARDS' HISTOLOGICAL CLASSIFICATION	66
IX. OBSERVATIONS, SUMMARY AND CONCLUSIONS	69
Observations	69
Summary	72
Conclusions	73
BIBLIOGRAPHY	74
APPENDIX A. Records of Seven Cases where Review of Available	
Tissue Showed Evidence of Carcinoma either Lacking or	
Insufficient	79

LIST OF TABLES

TABLE	PAGE
I. Incidence of Cancer of the Prostate and Number of Deaths Due to the Disease in Manitoba from 1930-1949	4
II. Incidence Rates of Cancer of the Prostate in Manitoba during the Period of 1937-1949, per 100,000 Population .	5
III. Death Rates from Cancer of the Prostate per 100,000 Population in the Province of Manitoba, 1930-1949	6
IV. The Ten Year Averages of Death Rates per 100,000 Male Population due to Cancer of the Prostate, 1930-39 and 1940-49	7
V. Clinical Index of Malignancy after Ferguson ²³	15
VI. Reported Incidence of Latent Carcinoma of the Prostate in Cases over 50 Years of Age	24
VII. Occupations of the Patients of this Series	38
VIII. Age of the Patient at the Time of Diagnosis in Seventy- Seven Cases of Carcinoma of the Prostate	40
IX. Summary of Complaints, as Listed in the Histories	43
X. Duration of Symptoms of Prostatism before the First Admission	44
XI. Terms Used to Describe the Relative Size of the Prostate .	46
XII. Terms Used to Describe the Relative Consistency of the Gland, as Felt Per Rectum	47
XIII. Portion of the Gland Involved with Carcinoma, as Determined by Digital Examination Per Rectum	47

TABLE	PAGE
XIV. Lesions Recorded as Found by Cystoscopic Examination (Enlargement of the Lobes Excepted)	49
XV. Distribution of 80 Cases of Carcinoma of the Prostate, Classified According to the Method of The American College of Surgeons	53
XVI. Post-operative Survivals of 68 Cases of Carcinoma of the Prostate, Classified According to the Clinical Method of Ferguson	54
XVII. Showing Average Time of Survival from Date of Diagnosis for Each Class of this Series (Ferguson's Classification) . . .	55
XVIII. The Survivals (In Percentages) of Each Clinical Class Excluding Post-operative Deaths (68 Cases)	56
XIX. The Number and Percentage of this Series Showing One Type of Carcinoma (32 Cases or 40% of Series)	58
XX. The Number and Percentage of this Series Showing a Mixed Histological Picture	58
XXI. Table Showing the Duration of Symptoms and the Period of Survival after Operative Treatment (Time Given in Months) .	59
XXII. Survivals, Excluding Post-Operative Deaths, of those Cases which Showed a Pure Histological Type	63
XXIII. Summarizing Data of the Histological Types, of 80 Cases of Carcinoma of the Prostate	65
XXIV. Comparing the Distribution of Clinical Cases and Histological Types	66

TABLE

PAGE

XXV. Comparing those Cases Showing One Histological Type of
Carcinoma, Further Subclassified by Ferguson's Clinical
Method 67

LIST OF FIGURES

FIGURE	PAGE
1. Perineural lymphatic invasion by carcinoma. Tumor is also seen in an adjacent blood vessel	19
2. A mass of tumor cells found in a blood vessel in a shred of prostatic tissue	20
3. An example of duct carcinoma of the prostate	28
4. An example of acinar carcinoma of the prostate	29
5. Acinar carcinoma of the prostate showing the "back to back" arrangement of the acini	30
6. Anaplastic carcinoma of the prostate	31
7. An example of intratubular carcinoma of the prostate, showing multiple lumina and cells which have pale-staining cytoplasm.	32
8. An area of carcinoma of the prostate which shows the features of more than one histological type	33

LIST OF CHARTS

CHART	PAGE
1. The Trend of Cancer of the Prostate in Manitoba, 1937-1949 Crude Incidence Rates (Per 100,000 Population)	8
2. Showing the Distribution of the Ages of the Patients of the Series According to Five Year Groups	39
3. Survival Rates in Percentage of Sixty-eight Cases of Carcinoma of the Prostate, Classified According to the Method of Ferguson	57
4. The Length of Survival after Diagnosis of the Duct, Acinar and Anaplastic Histological Types	64

CHAPTER I

THE PROBLEM, MATERIALS AND METHODS

I. THE PROBLEM

There are large gaps in our knowledge of cancer of the prostate. Not only why or how the lesion begins, but also its rate of growth and mode of extension are not fully understood. The desirability of obtaining a microscopic classification, which would indicate the probable clinical course, has long been appreciated. The study of proven cases of carcinoma is an approach to the solution of the latter problem. Approximately one hundred and sixty-five clinical cases of carcinoma of the prostate were confirmed by tissue section in the laboratory of the Winnipeg General Hospital during the period between 1930-1940 inclusive. Only a few, if any, of these cases would be expected to survive until the present time, so that this series of cases may be expected to show a possible correlation between a clinical classification, a histological classification and the ultimate clinical course of the disease.

II. MATERIALS AND METHODS

Approximately one hundred and sixty-five cases of carcinoma of the prostate were diagnosed clinically and confirmed by tissue section in the Winnipeg General Hospital between 1930-1940 inclusive. The clinical histories and charts of these cases were reviewed and summarized. The data obtained were recorded on summary sheets based on the cancer

record sheets used by the American College of Surgeons and adopted by the Manitoba Cancer Institute. No history was recorded in thirty cases, and in a few others the information was insufficient. Tissue blocks sections of all cases were drawn from the files of the laboratory, except in eleven cases when neither paraffin blocks nor sections could be found. Approximately one quarter of the original paraffin blocks were re-cut and re-stained. Of those cases in which sufficient history had been recorded and sections were available, an attempt to determine the outcome and final history was made through three main sources: (a) the Manitoba Cancer Institute; (b) the hospital records; (c) the office records of the surgeons who had been in charge of the cases concerned. History subsequent to diagnosis and final notes were not obtained in twenty-four cases. Tissue sections, sufficient history and follow-up notes were obtained in eighty-seven cases. On review of the tissue sections, histological evidence of carcinoma was insufficient or lacking in seven cases, so these cases were not included in the series. Thus eighty cases were classified according to the clinical method of Ferguson, and the clinical method found on the summary sheets of the American College of Surgeons. The microscopic sections were classified according to the method proposed by Edwards (1950).

CHAPTER II

REVIEW OF THE LITERATURE

Age incidence. The average age at the time of clinical recognition of carcinoma of the prostate is between 61 to 66 years^{14,52}, although there is a wide clinical age range⁴⁵ and no adult period is entirely exempt²⁸.

Carcinoma of the prostate is extremely rare clinically before the age of 40 years^{2,14,15,46}. Some reported series^{4,5,16,28,52} include a few cases below the age of 40 years. In the opinion of Bumpus¹⁴ any case of prostatic tumor discovered before the age of 40 years should be considered a sarcoma clinically until proven otherwise. Huggins³², writing in 1943, had seen only one case (47 years old) younger than 50 years of age. Other authors^{3,28,36,37,39,43,54} report series which include an occasional case of carcinoma in a patient less than 50 years of age.

Incidence of cancer of the prostate. Cancer of the genito-urinary tract including the prostate contributed 16.2 per cent of the 84,108 male cancer deaths in Canada between the years 1931-1944 inclusive. Cancer of the prostate accounted for 8.9 per cent of these deaths. During the period of 1931-1944 inclusive, cancer of the digestive tract and the peritoneum was most common for men and women accounting for nearly 52 per cent of the 168,885 cancer deaths in Canada during that period. Cancer of the genito-urinary tract was

second most important cause of cancer deaths in males.*

Statistics dealing with the incidence and death rate of cancer of the prostate in Manitoba have been obtained through the co-operation of Miss P. L. Ellis of the Manitoba Cancer Institute. These figures are given in the following tables.

TABLE I

INCIDENCE OF CANCER OF THE PROSTATE AND NUMBER
OF DEATHS DUE TO THE DISEASE IN MANITOBA FROM 1930-1949.

Year	Number of Cases Reported	Number of Deaths Reported
1930	-	34
1931	-	19
1932	-	20
1933	-	27
1934	-	24
1935	-	34
1936	-	28
1937	43	40
1938	40	24
1939	51	35
1940	59	60
1941	58	45
1942	58	37
1943	54	37
1944	56	42
1945	61	34
1946	71	49
1947	83	53
1948	70	63
1949	83	61

* Reference--Cancer mortality in Canada and the provinces 1921-44. Vital statistics analytical report No. 3. The Dominion Bureau of Statistics, Department of Trade and Commerce. Canada. 1947.

TABLE II

INCIDENCE RATES OF CANCER OF THE PROSTATE IN MANITOBA
DURING THE PERIOD OF 1937-1949, PER 100,000 POPULATION.

Year	Crude Rates*			Age Adjusted*		
	urban	rural	general	urban	rural	general
1937	16.20	8.75	11.61	20.54	9.36	14.95
1938	11.87	10.00	10.72	14.18	10.62	12.40
1939	18.67	10.36	13.56	21.10	10.60	15.85
1940	22.03	11.64	15.64	23.84	11.90	17.87
1941	21.26	11.63	15.34	22.58	11.16	16.87
1942	17.09	14.47	15.49	16.88	13.78	15.33
1943	17.54	12.36	14.41	17.25	11.81	14.53
1944	17.22	13.27	14.85	15.84	12.13	13.98
1945	19.55	13.78	16.12	17.28	12.45	14.87
1946	25.47	14.56	19.04	22.12	12.61	17.36
1947	29.10	16.64	21.82	25.19	14.48	19.84
1948	19.05	17.40	18.10	15.63	14.38	15.00
1949	23.68	18.87	20.92	19.11	15.17	17.14

* Crude rates are expressed in terms of "rate per 100,000 population."

Age adjusted rates are the crude rates corrected to a standard population (1931) in order to eliminate the effect of changing age structure of the population from year to year.

TABLE III

DEATH RATES FROM CANCER OF THE PROSTATE PER 100,000
POPULATION IN THE PROVINCE OF MANITOBA, 1930-1949

Year	Age Adjusted		Crude	
	<u>urban</u>	<u>rural</u>	<u>urban</u>	<u>rural</u>
1930	16.80	11.54	9.67	9.16
1931	10.95	5.73	6.17	4.50
1932	13.56	3.90	8.94	3.12
1933	13.10	7.26	8.99	6.21
1934	10.32	7.13	6.98	6.19
1935	13.27	10.06	9.85	8.82
1936	10.38	8.29	7.80	7.47
1937	18.46	9.12	14.79	8.31
1938	9.35	5.93	7.68	5.65
1939	12.67	8.36	11.06	8.21
1940	22.49	13.12	20.65	12.93
1941	16.12	9.72	15.09	9.90
1942	10.19	8.99	10.26	9.64
1943	12.91	6.98	13.49	7.51
1944	10.37	9.98	11.26	11.06
1945	10.78	6.52	11.73	7.11
1946	15.84	8.49	18.29	9.55
1947	16.95	8.37	19.61	9.89
1948	15.56	11.36	19.05	14.28
1949	11.94	12.51	15.39	15.36

Note: Urban Manitoba includes Winnipeg and all its suburbs except Charleswood.

TABLE IV

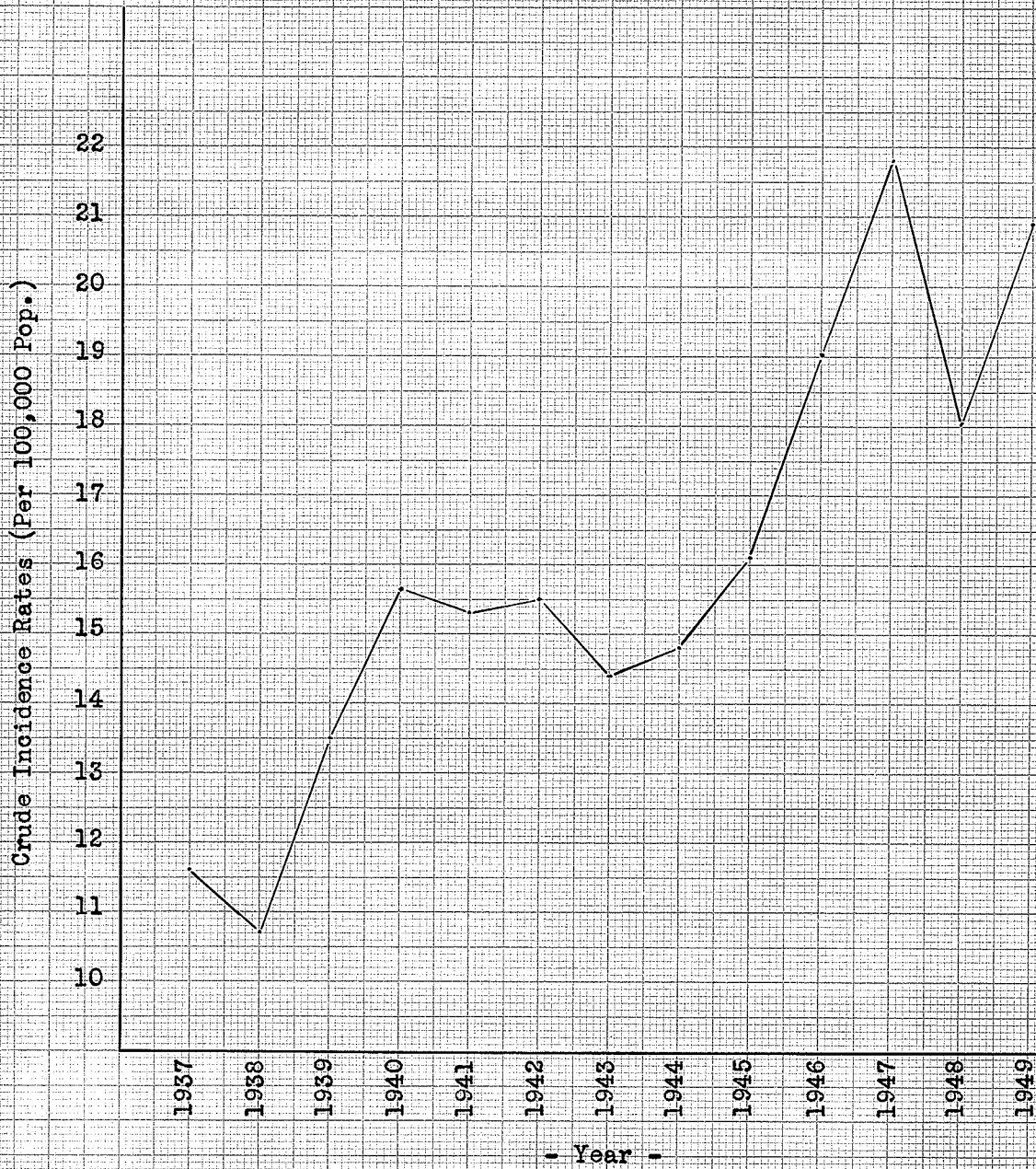
THE TEN YEAR AVERAGES OF DEATH RATES PER 100,000 MALE
POPULATION DUE TO CANCER OF THE PROSTATE, 1930-39 and 1940-49.

	1930-1939		1940-1949	
	<u>Age Adjusted</u>	<u>Crude</u>	<u>Age Adjusted</u>	<u>Crude</u>
Urban	12.89	9.19	14.32	15.48
Rural	7.73	6.76	9.60	10.72
Manitoba	10.31	-	11.96	-

The large increase in the crude rates is due to the increase in the population of the older age groups. In Winnipeg the number of men over the age of 70 years increased from 2895 in 1931 census to 6219 in 1946, an increase of 66 per cent in the average of the two decades. In rural Manitoba, the number of men over 70 years of age increased from 6818 in 1931 to 10,097 in 1946, an average increase of 29.6 per cent.

CHART 1

THE TREND OF CANCER OF THE PROSTATE IN MANITOBA, 1937-1949.
CRUDE INCIDENCE RATES (PER 100,000 POPULATION)



Etiology. In this connection, it is interesting to note that the development and maintenance of the prostate requires the male hormones of the normal testes¹⁸. Eunuchs have never been known to develop carcinoma of the prostate⁴². Kahler³⁷ could establish no relationship between carcinoma of the prostate and associated atrophy, nodular hyperplasia, inflammation, or calculi. Moore³⁹ on the other hand, believes that carcinoma is intimately associated with senile atrophy and that carcinoma rarely occurs in acini already hyperplastic. However, as with cancer occurring in other sites of the body, the etiology is not known at the present.

Edwards²¹, in agreement with Andrews², concluded on the basis of statistical analysis, that benign prostatic hypertrophy and carcinoma of the prostate showed a definite relationship, although the nature of this relationship remains obscure.

Symptoms. The onset of carcinoma of the prostate is elusive and without signs or symptoms²⁹. Even when the disease is moderately advanced, symptoms when present are not distinctive^{4,6} since carcinoma and benign prostatic hypertrophy both produce obstructive symptoms in the same age group⁴. Carcinoma of the prostate often begins in the periphery or in the posterior lobe of the gland at a distance from the urethral lumen, so that obstruction to urination appears late in the course of the disease¹⁸.

Symptoms depend upon (a) interference with urinary drainage by tumor invading the prostatic urethra and base of the bladder, (b) pain

produced by metastases to bone, (c) edema produced by metastases to lymph nodes, and (d) cachexia of carcinomatosis (Cf. Huggins³⁵).

The initial symptoms are either urinary⁶ due to obstruction¹⁰, or pain due to extension, or metastases. Barringer⁶ found frequency and difficulty the two most common initial urinary symptoms, occurring in 82 per cent of 280 cases. Other common initial symptoms are nocturia, retention, urgency and incontinence. There is considerable confusion in the literature regarding the importance of hematuria as an initial symptom, but the consensus appears to be that hematuria is uncommon³⁵ and of no significance¹⁰. Bumpus¹⁴ in 1000 cases did not find hematuria as an initial sign in any instance. Carnett¹⁵ states that hematuria and pyuria are found in only 1-2 per cent of cases when first seen. Usually patients complain of three or more symptoms at their first consultation. The most common triad in Barringer's⁶ series consisted of frequency, difficulty and nocturia.

Obstructive symptoms range anywhere between frequency of urination to complete retention. Frequency and nocturia head the list of urinary symptoms (initial) of any series. The onset is insidious. Gradually the frequency and nocturia may become so marked that the patient has no hour free from the demand to urinate. Difficulty in initiating the flow, stammering and inability to completely empty the bladder are added in time to the list of symptoms and compel the patient to seek advice, if hematuria, complete retention, or pain have not already done so. The onset of complete retention in the presence of relatively mild symptoms is considered to be suggestive of carcinoma

by some authors¹¹.

Pain may be manifest as painful urination, backache, sciatica, lower abdominal and pelvic pain or pain in the hips, groin, penis, rectum or perineum in that order of frequency⁶. Pain localized in the perineum, rectum, and penis is due to involvement of nerves by local extension of the tumor, while pain in the hips, low back, and long bones is due to distant metastases.

Vesical pain, which is infrequent in benign prostatic hyperplasia in the absence of calculus or infection¹⁵, is apt to be constant and independent of nocturia in carcinoma³⁶.

Extravesical pain associated with urinary symptoms should always be considered suspicious of metastases¹⁰. In one fifth of the cases of carcinoma reviewed by Carnett¹⁵, pain was an outstanding symptom in patients when first seen. In the series reported by Bumpus¹³, pain was absent in one quarter of all cases with metastases, and urinary symptoms were absent in approximately 11.5 per cent of those cases with metastases. Bilateral leg pain in men over fifty is commonly due to carcinoma. The pain may be only a soreness¹⁵. The onset of sciatica in a man over forty demands a rectal examination³⁵.

One of the chief causes of the bizarre clinical picture is the varying and widespread dissemination of the metastases³. The pelvis and the lumbar vertebrae are the common sites. Pain in the lower back, the hips and the pelvis is common. Metastases in the long bones are found in the proximal ends.

Several cases are well nourished and even obese in the presence

of advanced disease²⁶. Occasionally symptoms (such as diarrhoea and rectal bleeding) are referable to the gastro-intestinal tract⁶.

A considerable delay between the onset of symptoms and the time of the first consultation is noted by most authors. In Barringer's series⁶, twenty-four months was the average time between initial symptom and first examination. Bryan¹², writing in 1912, in an attempt to explain this delay states:

" . . . There is an unconscious adjustment of the patient to the condition. He pays no more attention to the increased calls for urination or the slightly stuttering stream than that patient who puts on spectacles for the first time: both conditions are regarded as one of the natural phenomena of advancing years. At the instant pain or haemorrhage is noticed, the patient now knows something is wrong and seeks the advice of a surgeon."

Clinical findings. Early clinical carcinoma is found as a firm nodule just beneath the capsule of the posterior lobe. The single hard nodule is to be differentiated from prostatic calculi, tuberculous infection, non-specific infection and benign prostatic hypertrophy³². The nodule is often masked by edematous prostatic tissue. The edema disappears after exposure to x-ray leaving the nodule clearly defined⁶.

The single nodule of carcinoma is not a common clinical finding. The literature contains many reports regarding the extension of the carcinoma at the time the patient is first seen. Thus, Barringer⁴ found the lesion confined to the prostate in only two, perhaps three, cases of a series of 145 patients. In another paper, Barringer⁵ states that in 98 per cent of cases the carcinoma had extended beyond the prostate when the patient was first seen. In one quarter of the cases

studied by Carnett¹⁵, bone metastases were demonstrable at the time the local lesion was diagnosed. Caulk and Boon-itt¹⁶ report that 51.3 per cent of 197 cases presented demonstrable lesions beyond the prostate when the patient was first examined. Only 36 cases of 1040 studied by Colston and Lewis¹⁷ were considered eligible for radical surgery. In the series reported by Wear and Schoenenberger⁵², 170 of 400 cases had metastases at the time of the first admission. These reports constitute only a fraction of the literature but illustrate the stage to which the disease has usually progressed when the patient first seeks advice.

The usual lesions fall into one of two groups: (a) the large bulky carcinoma which grows slowly, filling and infiltrating the pelvis, and (b) the small hard carcinoma which produces few local changes but which metastasizes relatively early in its history. Between these two extremes which in the pure type are rare, all gradations are seen⁴.

The usual type is a slowly growing tumor which is limited posteriorly by the limiting fascia of Denonvilliers and the base of the bladder anteriorly. The line of least resistance is followed and the tumor grows upwards into the lymphatics, around the seminal vesicles and metastasizes early in its history⁴.

In the well established case, the findings are fairly characteristic, for a high degree of clinical accuracy can be attained. The prostate is enlarged, firm or stony hard, nodular and fixed. Only one lobe may be involved. The median groove is often obliterated, although its presence does not rule out carcinoma⁶.

Metastases to lymph nodes may be very extensive and still not be

felt or reached by the examining finger¹³. The nodes must produce an abdominal mass or be increased to such a size to be felt per rectum¹³.

Clinical classification. A number of classifications have been proposed, none of which are entirely satisfactory. Each classification is based on different aspects of the disease. Barringer⁴ and Bumpus¹³ prefer to divide the cases into two groups: (a) those cases with large bulky carcinomata and late metastases, and (b) those cases with the small stony hard carcinomata and early metastases. Both extreme forms are rare and all gradations are found. Bothe¹⁰ proposes three types: (a) those cases which have urinary obstruction and no evidence of metastases where the prostate is stony hard and nodular; (b) those cases where there is evidence of metastases and no local evidence of the primary lesion, the variable symptoms depending on the site of the secondary tumors (occult); (c) those where there is no evidence of malignancy before study of the tissue after extensive sectioning (latent).

Ferguson's classification²³, given below in detail, recognizes three groups. The classification is based upon differences in prognosis, clinical findings and symptoms. The following table is taken from Ferguson's paper.

TABLE V
 CLINICAL INDEX OF MALIGNANCY
 AFTER FERGUSON²³

Index factors	Group A Least malignant	Group B Intermediate	Group C Most malignant
Age	More than 65	55 to 65	Less than 55
Residual urine	200 ml. and over. Frequently complete retention.	100-200 ml.	Less than 100 ml.
Duration symptoms	More than 20 months	10-20 months	Less than 10 months
Extent of disease	No pain. No demonstrable metastases.	Pain. No demonstrable metastases.	Pain and demonstrable metastases.
Prognosis, untreated cases	30 months to many years.	7-30 months. Average 18.	Up to 1 year. Average 6 months.
Percentage of 501 cases reviewed by Ferguson ²³	62 per cent	26 per cent	12 per cent

Survival figures. Survival figures are usually given as the length of life after the onset of symptoms and after the time of diagnosis. Bumpus¹⁴ in reviewing 485 untreated cases found the average duration of life from the onset of symptoms until death to be thirty-one months. Two thirds of those cases with metastases when first seen died within nine months, while those cases with no demonstrable metastases on their first examination averaged one year of life after the first consultation. Of the 485 cases, 58 per cent died within one year after

their first examination. Nesbitt and Plumb⁴³ give the figures for their series of 605 cases, in which the shortest duration of life from the onset of symptoms until death was two months, the longest 324 months, and the arithmetic mean was 50 months.

Survival figures actually mean very little when a case on hand is being considered from the standpoint of prognosis. An attempt of classification to correlate the clinical and pathological findings may be expected to reveal some constant factors. Foot²⁵ has attempted such a classification but could demonstrate no correlation between the histological picture and the time of survival.

Duration of the lesion. Any conclusions based on the study of reported series recording the duration of symptoms from onset to death will be erroneous and misleading with respect to the duration of the lesion. An estimation of the time from beginning to end is presumptive. When the facts regarding latent carcinoma and metastases are considered, it seems possible that the carcinoma of the prostate may exist for many years without causing symptoms or spreading from its place of origin²⁹. Flynn²⁴ reports a case of carcinoma which was proven microscopically nine years before there was evidence of local and widespread disease and twelve years before death. Such reports are rare. Ockerland⁴⁴ estimates on empirical grounds that the average victim of carcinoma of the prostate has had the lesion for five years by the time he seeks relief.

Gross appearance. The gland should be sliced with a sharp knife at regular intervals of not more than 4 mm thickness if early lesions are to be found. Thick pieces of punch material should be divided with the knife in the longitudinal plane. Tissue with yellow streaks and dots, which represent aggregates of degenerating and desquamated cells, should be blocked for section and staining as such areas are most likely to be carcinoma. While the lesions are usually firm, whitish-yellow or hemorrhagic compared with the oozing surface of the surrounding tissue, the following exceptions should be noted. The consistency varies with the amount of stroma and the degree of cellularity. Areas of fibrosis subsequent to a healed infarct or focal atrophy and chronic hyperplastic conditions may produce a firm lesion. White areas are produced by areas of fibrosis of old healed infarcts, while yellow colour is seen in areas of hyperplasia, tuberculous lesions and in acute or chronic pyogenic infections³⁷.

Spread of the tumor. The most characteristic mode of spread of the carcinoma is by way of the perineural lymphatics. Kahler³⁷ found the perineural lymphatics involved in practically all his cases regardless of size or microscopic grade. Moore³⁹ found carcinoma in the perineural lymphatics of 77 per cent of the 52 early cases reported. In 15 of the 17 early cases studied by Andrews² the perineural lymphatics were involved, while Edwards²¹ observed it in 12 of his 28 cases of latent carcinoma. Hinman²⁹ points out that the early invasion of the lymphatics does not necessarily mean distant metastases. According to

Hinman²⁹, this early invasion of the perineural lymphatics may be confined within the capsule of the prostate for a long time.

The size of the lesion often bears no relation to the extent of the metastases⁴². A small growth may give rise to widespread metastases^{5,15,19,26}, while in other cases⁵ the pelvis may be filled with tumor and yet no distant metastases have occurred. Distant metastases occur by way of the lymphatics and blood stream⁴², although spread by blood stream is late²⁹. Invasion of the blood vessels was not common in the series studied by Andrews² and not seen by Edwards²¹.

Bone and lymph node metastases constitute 66 per cent of the metastases of some series³. According to some authors the lymph node metastases are more frequent than those in bone and are less readily diagnosed clinically¹⁵. The lesions in the lymph nodes occur more frequently than is possible to demonstrate clinically because of the inaccessibility¹³ of the nodes. Graves and Melitzer²⁶ place metastases to lymph nodes second to those of the bone. With such a division, it is probable that the metastases to lymph nodes and bone are about equal.

The mechanism of bone metastases has been a matter of considerable speculation. Roberts⁴⁷ stated that spread occurred along the normal abdominal lymph drainage of the pelvic organs in probably all cases and suggested that the path of the lymph vessels and tissue spaces of the spinal laminae with associated ligaments may account for widespread metastases. Warren et al⁵¹ regarded the perineural lymphatics as pathways leading the cancer into intimate contact with cortical bone. Thence the growth through the ostia is relatively simple and invasion

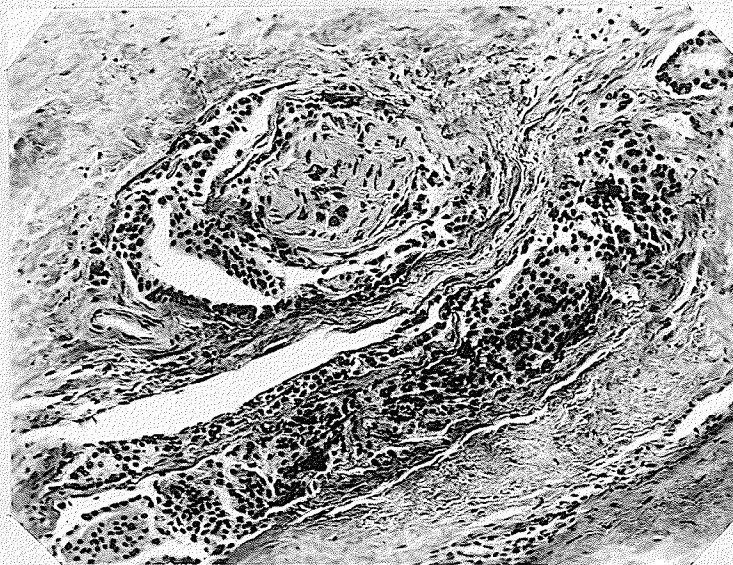


FIGURE 1

Perineural lymphatic invasion by carcinoma. Tumor is also seen in an adjacent blood vessel. Hematoxylin and eosin stain. 150 x.

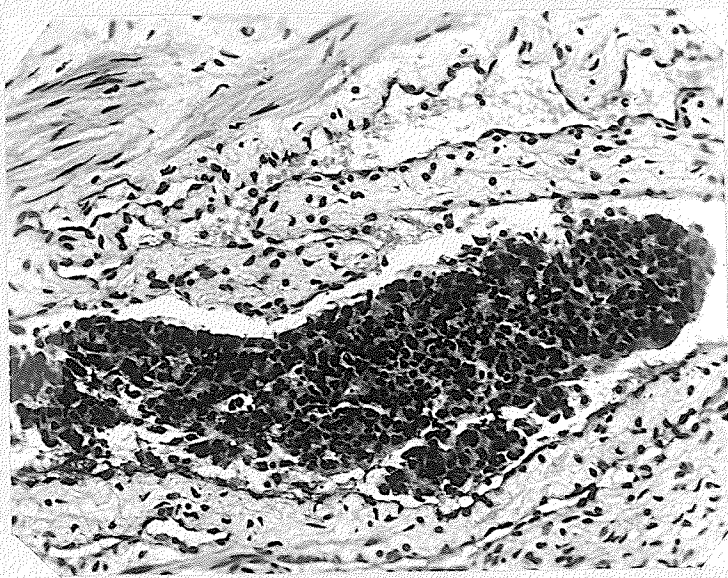


FIGURE 2

A mass of tumor cells found in a blood vessel
in a shred of prostatic tissue. Hematoxylin
and eosin stain. WGH 900-40. 200 x.

of the bone follows. Batson⁹ by injecting the deep dorsal vein of the penis was able to demonstrate connections between the veins draining the pelvic organs and the vascular sinuses of the sacrum, pelvis and head of the femora. Under certain conditions a retrograde flow was demonstrable. Batson⁹ has termed this system of veins, which is continuous with the veins of the skull, neck, viscera, vertebral column and body wall, as the vertebral system of veins.

Carcinoma of the prostate is the most common source of bone metastases in men^{15,22}. Kaufmann (quoted by Caulk and Boon-Itt¹⁶) states that 70 per cent of prostatic carcinoma, 37 per cent of thyroid carcinoma and 14 per cent of breast carcinoma give rise to bone metastases. The pelvis is always involved³². The pelvis and sacrum were involved in 85 per cent of cases with metastases in the series reported by Graves and Melitzer²⁶ and the lumbar spine in 59 per cent of the same group. Pathological fractures occurred in only 5 per cent of the cases. In a series of 50 advanced cases of carcinoma reported by Huggins³², 31 had x-ray evidence of bone metastases. The metastases are never found beyond the knee or elbow joint³².

The local spread of the tumor into the seminal vesicles and the base of the bladder are late manifestations in the natural history of the tumor, although by the time the tumor produces symptoms it is seldom confined within the prostate itself. Colston and Lewis¹⁷ found only 36 of 1040 cases suitable for radical extirpation of the tumor.

When an ulcerating tumor is found on the anterior wall of the rectum, it is usually an adenocarcinoma of the rectum, originating in

its mucosa and not an extension of carcinoma of the prostate into the rectum. Young⁵⁶ found that in 800 cases of prostatic carcinoma, the rectal mucosa was involved in only 12 instances.

Autopsy findings. The autopsy findings are usually those of the advanced case. Towards the latter part of the disease, the patient may have considerable pain and be bedridden, evidence of which is found at autopsy in the form of wasting of muscle and fatty tissue, trophic changes of the skin over pressure areas and edema of the extremities. Bronchopneumonia is a frequent contributing factor in the death of the patient. Tumor may partially or completely fill the true pelvis. Invasion beyond the capsule of the gland into contiguous tissue such as the base of the bladder and the seminal vesicles is common. The tumor may extend upwards and partially obstruct both ureters to produce hydro-ureter, hydronephrosis and pyelonephritis, the last being a common contributing factor in the death of the patient. If the obstruction of both ureters is more or less complete, terminal uremia may be present. Soft tissue metastases, for example, to the lung, liver and skin, are usually small and seldom explain symptoms of importance. Enlarged lymph nodes replaced by tumor tissue may form masses in the pelvis or along either side of the aorta. Secondary growths are usually obvious, but the real extent of these will depend upon the thoroughness of the examination. While it is impossible to examine all bony structures, special attention should be paid to any areas showing radiological changes. Approximately 90 per cent of the bony metastases are osteo-

sclerotic in nature.

Occasionally the carcinoma may be occult, in which case the primary tumor is small and the metastases widespread. Extensive sectioning of the prostate may be necessary to demonstrate the primary tumor.

Site of origin of carcinoma. That carcinoma begins most frequently in the so-called posterior lobe was first stated by Young and supported subsequently by several authors^{7,5,39,42,45}. When occult and latent carcinoma were studied, others found that the carcinoma begin in the periphery of the gland with no special predilection for the posterior lobe^{46,29}. Most authors^{6,7,39,42} agree that the vast majority of the carcinoma arise in the posterior lobe but can and do originate anywhere in the prostate gland or its accessory glands. Bugbee¹¹, however, found that the carcinoma originated in the median or lateral lobe in six of seven early cases diagnosed by tissue section where the lesion was small and the origin could be determined. Moore³⁹ in a study of 52 early carcinoma, in which only one lobe was involved, found 73.5 per cent in the posterior lobe, 8.8 per cent in the lateral lobe, 14.8 per cent in the anterior lobe and none in the median lobe. Of 40 foci of carcinoma found in 26 cases by Edwards²¹, 21 were in the posterior lobe, 13 in the lateral lobe and 6 anterior to the urethra. The foci may be multicentric in origin. Edwards²¹ found more than one carcinoma in 8 of 28 cases studied. As many as 5 foci were observed in a single gland in his series. The possibility must be considered,

however, that some of those cases interpreted to have multicentric foci, may merely represent irregular-shaped extensions of a single tumor cut in one plane.

Neller and Neuburger⁴¹ (1926) found in 40 cases of men dying from unrelated causes, 7 cases with atypical epithelium which they interpreted as beginning carcinoma. Since this time Muir⁴⁰, Moore³⁹, Rich⁴⁶, Kahler³⁷, Baron and Angrist⁸, Andrews² and Edwards²¹ have reported the incidence of latent carcinoma to range between 2.1 to 46 per cent. Much of the variation in the figures is due to the method of examination and the criteria of malignancy.

The following table summarizes the number of cases studied and the percentage of latent carcinoma found by different authors.

TABLE VI

REPORTED INCIDENCE OF LATENT CARCINOMA OF THE PROSTATE
IN CASES OVER 50 YEARS OF AGE

Author	No. of cases studied	No. of latent carcinoma found	Percentage of cases having lat. carcinoma
Neller and Neuburger ⁴¹	40	7	17.5
Muir ⁴⁰	54		13
Moore ³⁹	375	52	13.9
Rich ⁴⁶	292	27	
Kahler ³⁷	381	53	13.9
Baron and Angrist ⁸	50	23	46
Andrews ²	142	17	12
Edwards ²¹	150	28	18.7

The incidence of latent carcinoma of the prostate in males over the age of 50 years appears to be in the neighborhood of 15 per cent of all cases coming to autopsy. Only those reports should be considered which state rigid criteria of malignancy and which have included unselected series of consecutive autopsies except for age, where the lesion is small and confined to one lobe and not diagnosed clinically.

The study of latent carcinoma of the prostate is more than academic in importance. Data are being accumulated regarding the site of origin and the association of the early lesions with other conditions of the prostate. It is only possible to make such studies on autopsy material, so that the important question of how these tumors might behave in living patients is still incomplete. Tissue obtained at operation does not lend itself to determining the important question of how many of these latent carcinomas become clinically manifest. The entire gland is not removed usually at operation. Only adenomas are removed in the suprapubic approach so that the true prostatic tissue compressed in the periphery of the gland is left in the "rim" or "capsule." Most of the early or latent carcinomas are found in the periphery of the gland. Much of the tissue removed by transurethral resection is median lobe tissue, in which latent carcinoma is seldom found. If carcinoma is found in a shred of tissue removed by transurethral resection, the lesion is probably advanced. In the present series a few cases were reported as early or even latent, but on further examination the tumor was found on the edge of one shred and it is likely that the surgeon's knife touched the tumor at its periphery.

Microscopic criteria of malignancy. The criteria of malignancy in the prostate are similar in many respects to those of carcinoma elsewhere. A few features are unique. Many cases are straightforward and present no problem. Small lesions and lesions present in one or two shreds of punch material often require considerable study. Distortion of the microscopic picture by a previous operation and infection may produce a lesion simulating carcinoma. Andrews² and Moore³⁹ have given their criteria of malignancy of the prostate in detail.

The relationship of the epithelium to stroma is very important^{2,39} since adenocarcinoma is often composed of small, well differentiated acini in which nuclear changes and mitotic figures are rare or absent². In the normal prostate, the acini are surrounded or invested by a narrow band of collagenous connective tissue devoid of capillaries. This layer, which is termed the tunica propria, follows all the irregularities of the acinus. In the earliest malignancies, a loss of the tunica propria occurs and the acini are arranged irrespective of the whorls of smooth muscle, connective and elastic tissue. A "back to back" arrangement results where the acini are found in close approximation with no intervening stroma. An abnormal stromal relation together with any nuclear changes or lymphatic or blood vessel invasion, supports a diagnosis of malignancy.

The acini may be small, round or oval with no papillae but an irregular lumen border. Many of the acini are distorted with the lumen narrowed to a slit-like space. The cells may be two layers thick or

there may be intra-acinar proliferation. The basal layer of epithelial cells is not present. The cells lining the acini have a faintly eosinophilic staining cytoplasm which is usually finely granular. They are usually cuboidal but there is wide variation in shape and size. Variation in staining qualities is noted together with relatively larger than normal nuclei (Cf. Moore³⁹ and Andrews²).

Often the diagnosis is made using a low power magnification in which the details of stroma and acinus relationships may be appreciated. Inclusion of epithelial elements with muscle bundles is diagnostic. At times the muscle fasciculi appear to be "fractured." Perineural lymphatic invasion is an early and reliable sign of malignancy^{2,37}. The tumor cells may be arranged in sheets and cords with no attempt to form acini.

Histological classification of carcinoma of the prostate.

Edwards (1950) noted the similarity between the histological picture of carcinoma of the prostate and carcinoma of the breast. On the basis of microscopic appearance, he proposed a descriptive terminology and divided carcinoma of the prostate into four groups, namely: (1) duct carcinoma, (2) acinar carcinoma, (3) intratubular or intra-acinar carcinoma, and (4) anaplastic carcinoma.

(1) Duct carcinoma. The histological picture of duct carcinoma is characterized by small, irregular or incomplete glands, which are frequently single and have intervening stroma. The epithelium is low and cuboidal, with scanty cytoplasm and large hyperchromatic nuclei.

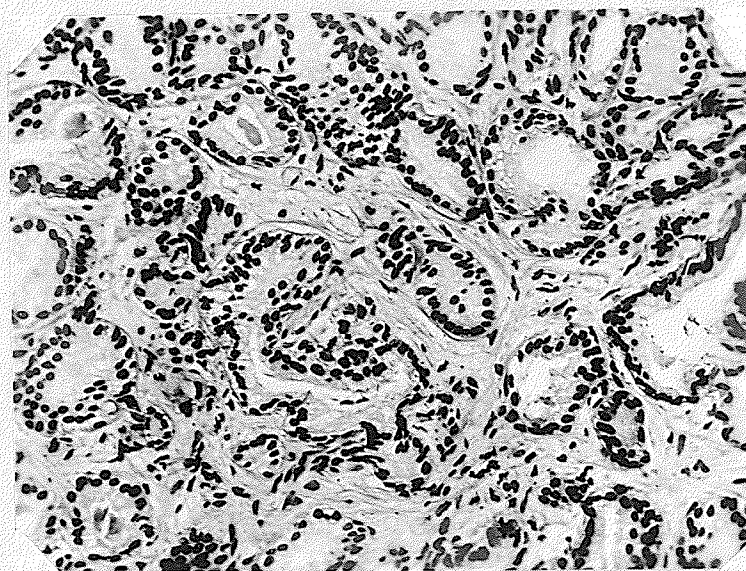


FIGURE 3

An example of duct carcinoma of the prostate. The cells are small, have deeply staining nuclei and there is abundant intervening stroma. Hematoxylin and eosin stain. WGH 1717-36. 200 x.