A CLINICO-PATHOLOGICAL STUDY

OF

THE PROSTATE GLAND

WITH SPECIAL REFERENCE TO

ITS RESPONSE TO EXPERIMENTAL INJURY.

A Thesis

presented by

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with

130 ILLUSTRATIONS.

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Section I.

A Clinico-pathological Study of Prostatic Carcinoma.

Section I.

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Preface.

Shortly after completing an investigation with Professor G.H. Cooray into the aetiology and pathology of Uterine cancer in Ceylon, one of us (G.H.C.) wished to continue the studies in tumour pathology. The prostate gland was selected for study and the investigation was well under way when I left for the United Kingdom.

For my part, I had planned a study on the pathological aspects of Carcinoma of the prostate gland in Edinburgh. Hence, on my arrival at Edinburgh, and subsequently joining the Department of Pathology of the University, I set about investigating the possibilities of such a study. To my delight I found that no previous work had been done in this field. Further to my advantage was the fact that there was a wealth of material at my disposal, for the Pathology Departments of the University and Royal Infirmary receive a large number of both biopsy and autopsy specimens. The results of this study are embodied in Section I of my thesis.

While gathering information on the subject of prostatic carcinoma from the recorded literature, I found that there was a certain lack of information on the gross morbid anatomical appearances of unsuspected Carcinoma of the prostate, despite the fact that there were many contributions on this particular aspect of the subject. Thus I soon found/

found myself engaged in Section II of my thesis. In the course of my general reading I came across a most fascinating article on Breast carcinoma by Sir John Fraser (1927) in which he discusses the importance of elastic tissue in the local spread of Breast Carcinoma. This stimulated my interest and before long I began an investigation to study this particular feature in unsuspected carcinoma of the prostate. The results of this work are also incorporated in Section II.

My former chief, Professor W. A. E. Karunaratne was closely associated with Professor G. R. Cameron for a number of years. This friendship was spoken of by my chief in many interesting anecdotes to me and my colleagues who were on the staff of the Pathology Department in the University of Ceylon. These reminiscences made a deep impression on me so much so that I hoped that I would be able to meet this dynamic personality some day. My hopes were fulfilled when I was invited down to London by one of my colleagues to meet Professor Cameron in his department at University College Hospital Medical School. The subject of Section III of my thesis is the outcome of a most interesting discussion on Regeneration in different organs and tissues.

The above is a brief account of the development of my thesis. In conclusion may I add that I have divided the thesis into three sections in order to illustrate three phases of the subject of/

of Pathology namely, the Clinical aspects of Pathology, pure Morbid Anatomy and Histology, and lastly Experimental Pathology.

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Section I.

(1) INTRODUCTION.

A large volume of literature on carcinoma of the prostate gland has appeared within recent years, particularly from the United States of America. The only major study on the surgical anatomy and surgical pathology of simple prostatic hypertrophy in Edinburgh is the brilliant monograph of Wade (1914). In this work he refers to 14 cases of carcinoma of the prostate gland out of a total of 134 prostate glands. Stewart (1944) in a Honyman-Gillespie Lecture discussed management in prostatic surgery with special reference to operative risk. In this study of 406 prostate glands 12% were found to be carcinomatous. My histological survey is on 2,458 prostate glands received from 1936 to 1952, supplemented by an examination of the clinical records of 369 cases of carcinoma of the prostate gland, which had been followed up by the Radio-therapy Department of the Royal Infirmary during the period 1932 to 1952.

It is only by such periodical reviews that one is able to get an accurate appraisal of the behaviour of this type of carcinoma, the importance of early diagnosis, the pathology and complications of the disease, the success or otherwise of any special mode of treatment, the life expectancy or prognosis of cases under the different forms of therapy, and the provision of adequate nursing facilities and adequate/

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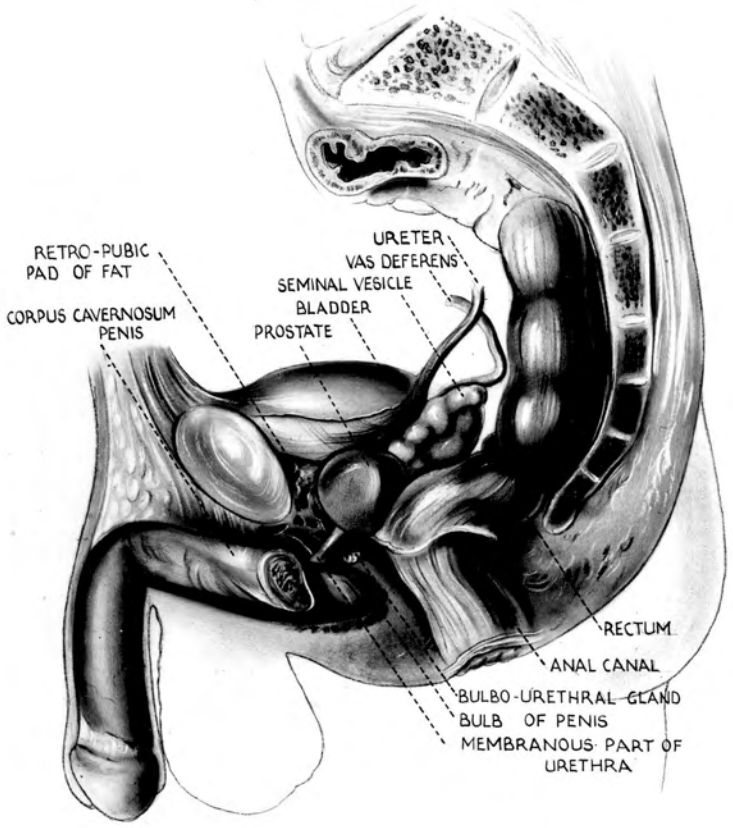
adequate hospital accomodation. I have discussed as many as possible of the features of the above problem in the light of the data which I have accumulated with painstaking care and accuracy.

There are many problems that still await solution. I have sketched very briefly a plan as to how information on cancer of the prostate gland could be gathered together, analysed by a team of research workers and then further research planned on the data so obtained. I must apologise to the reader for the number of diagrams, tables and graphs which appear in this thesis - my plea for inserting them is purely to present in as interesting and as striking a manner as possible the otherwise dull reading of a statistical study. I regard this section as a useful contribution to the field of Geriatric Medicine.

(2) ANATOMY AND PHYSIOLOGY OF THE PROSTATE GLAND.

(a) Anatomy of the prostate gland.

The prostate gland is a partly glandular, partly muscular organ of a dark brown-red colour which surrounds the beginning of the urethra in the male. It lies within the pelvis behind the pubic symphysis and is enclosed by a dense fascial sheath. Through the various connections of this sheath the prostate is firmly fixed within the pelvic cavity. The ejaculatory ducts traverse the upper part of the prostate in their course to join the urethra. The size of the prostate varies considerably, but usually/



DISSECTION OF PENIS AND PELVIC ORGANS FROM LEFT SIDE

(FROM CUNNINGHAM'S TEXT-BOOK OF ANATOMY 1951)

Figure 1.

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usually its greatest transverse diameter is 1½ inches, its antero-posterior diameter ¾ of an inch, and its vertical diameter 1¼ inches. Superficially the prostate is separated from the bladder by deep, wide lateral grooves and by a narrow posterior groove.

The prostate has an apex which is directed downwards, a base looking upwards, a posterior surface, and a pair of lateral surfaces. The base is directed upwards against the inferior aspect of the bladder in the neighbourhood of its urethral opening. The greater part of the base is structurally continuous with the bladder wall ; only a narrow portion remains free on each side and forms the lower limit of the deep groove which marks the separation of the bladder and prostate. The lateral surfaces of the prostate are convex and prominent, especially in their posterior and upper portions, and rest against the fascia covering the levatores ani muscles. They are directed for the most part laterally, downwards, and slightly forwards, and meet together in front in a rounded anterior border, sometimes called the " anterior surface " of the prostate. The posterior surface, is flat and triangular, and is directed backwards and very slightly downwards against the anterior wall of the rectum, through which it may be felt in the living subject. The apex points downwards and is in relation to the fascial covering of the sphincter urethrae muscle. From the apex, the anterior/

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anterior border passes upwards in the median plane behind the pubic symphysis and retropubic pad of fat; and it is interrupted in its lowest part by the passage of the urethra.

When its fascial sheath is stripped off, the prostate has a more rounded outline, and the surfaces just described are not so clearly defined. The anterior border may now appear to be a surface rather than a border, and the antero-posterior diameter is considerably reduced.

The urethra enters the prostate at a point near the middle of its base, and leaves it at a point on its anterior border immediately above and in front of the apex.

The ejaculatory ducts enter a slit immediately in front of the posterior border of the base and run downwards and forwards to open into the prostatic portion of the urethra at the margins of the mouth of the prostatic urticle.

The wedge-shaped portion of the prostate which separates these ducts from the urethra is called the median lobe. It projects upwards against the bladder, and is continuous with the bladder-wall immediately behind the urethral orifice. When hypertrophied, as it often is in old men, the median lobe of the prostate may cause a considerable elevation in the cavity of the bladder, which is of surgical interest, and to which the term uvula of the bladder is applied. The remaining part of the prostate is described as a pair of large lateral lobes, which are, however, not marked off from one another/

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another superficially.

In front of the prostate, between it and the pubis, there is a close venous network called the prostatic plexus, with which the deep dorsal vein of the penis communicates. That plexus is continued backwards, round the sides of the prostate, and joins the large, thin-walled veins which are collected for the most part in the deep sulcus between the bladder-wall and the prostate, and from the prostatico-vesical plexus. Most of the veins of the plexus lie embedded in the fascial sheath of the prostate.

Fascial sheath of prostate : This sheath is a dense fibrous portion of the pelvic fascia, and closely invests the prostate. Inferiorly the sheath becomes continuous with the fascia on the sphincter urethrae muscle and, through it, gains attachment to the sides of the pubic arch. In front and at the sides, it is fused with the pubo-prostatic ligaments, by which it is connected with the pubic bones and the fascia on the levatores ani. Between the two medial pubo-prostatic ligaments there is a shallow depression, the floor of which is formed by a thin layer of fascia which connects the anterior part of the sheath of the prostate with the back of the pubic symphysis. The medial (or anterior) edges of the levatores ani muscles are immediately below the pubo-prostatic ligaments, and, when followed backwards, they are seen to embrace the lower part of the prostate.

Posteriorly/

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Posteriorly the upwards prolongation of the sheath is continuous with the fascial layers which enclose the ampullae of the vasa deferentia and the seminal vesicles, and it is adherent to the peritoneum of the recto-vesical pouch. In this position it is spoken of as the recto-vesical septum.

(b) Physiology of the prostate gland.

A brief account of the physiology of the prostate gland will help the reader to get a clearer understanding of the biochemical estimation of acid phosphatase in the diagnosis of prostatic carcinoma, the rationale of oestrogen therapy, and the oestrogenic effects on carcinoma of the prostate :-

The following will be discussed :-

i) General structure of the prostate gland.

ii) Characteristics and composition of prostatic fluid.

iii) Function of prostatic fluid.

iv) Phosphatase in the prostate gland.

v) The effects of Androgens and Oestrogens on the prostate gland.

(1) General structure of the prostate gland.

The prostate gland does not appear to have any endocrine function. It is composed of branched tubuloalveolar glands grouped into about twenty lobules. Its stroma is fibroelastic in nature and contains many bundles of smooth muscle. The alveoli of the glands drain into some twenty ducts which discharge into the urethra. The alveolar epithelium secretes prostatic fluid which is thin and opalescent and/

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and gives the semen its characteristic odour. It secretes approximately 0.5 to 2 cc. per hour of fluid continuously, and much larger amounts during coitus. The secretion of prostatic fluid is increased by stimulation of parasympathetic (sacral outflow) and sympathetic nerves (hypogastric). Secretions from the seminal vesicles and from the prostate gland are added to the sperm ; of the two, the former appears to be of the greater importance for the viability of the spermatozoa, or at any rate for fertilization, as this is possible after the removal of the prostate but not after the loss of the seminal vesicles.

(2) Characteristics and composition of prostatic fluid (Carroll, 1947).

Specific gravity 1.022 (approx.)

Slightly acid in reaction (pH 6.4)

Inorganic salts-calcium and citrate esp. 30 and 50 mEq respectively.
Sodium, potassium, phospherus and chlorides
2.5% proteins, cholesterol, traces of glucose, enzymes, acid phosphatase and fibrinolysin.

} Total solids 7 % (approx).

(3) Functions of prostatic fluid.

It has been common knowledge that very little intracellular nutrient material is present in spermatozoa and that for this reason the sperm would be unable to survive in seminal fluid were it not for an adequate and readily available supply from/

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from extracellular sources. The seminal plasma is a mixture of secretions derived from the accessory sex glands. It furnishes the bulk of high energy yielding nutrients which appear to be utilised efficiently by the normal sperm. Little was known about the complex chemical constituents until citric acid was discovered in seminal vesicular and prostatic fluids by Schersten in 1929, prostatic phosphatase by Kutscher and Wohlbergs (1936) and phosphorylcholine in seminal vesicular fluid by Lundquist (1946).

The processes going on in semen after ejaculation is as follows : the fluid secretion from the vesicular glands is mixed with prostatic secretions (and other secretions in small amounts), resulting in immediate formation of a clot consisting of a substance very similar to fibrin. The fibrinolytic enzyme from the prostate gland attacks the fibrin, which subsequently liquifies. The breakdown products are then attacked very effectively by aminopeptidase and probably one more enzyme, giving rise to a high concentration of free amino acids which may possibly be of some use for the spermatozoa (Wolstenholme, 1953).

(4) Phosphatase in the prostate gland.

An enzyme which splits the phosphate radical from organic phosphorus compounds is known as phosphatase. Phosphatases occur in many tissues, and in general differ in properties with their tissue of origin. They fall into two broad groups, those/

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those with a maximum activity in acid solution and those with a maximum activity in alkaline solution. These are known as acid or alkaline phosphatases respectively. In addition to differing in a pH optimum, phosphatases differ in their activities on various substrates. Few phosphatases are highly specific for any one substrate. The prostate gland contains small and unimportant amounts of alkaline phosphatase (0.5 - 1.3 units/Gm) in the capillary walls.

Acid phosphatase.

In 1935 and 1936 Kutscher and his co workers showed that the prostatic extracts and prostatic secretion contained an acid phosphatase which would split phenyl phosphate alpha and beta glycerophosphate and hexose diphosphate. Since then many studies have shown that extracts of numerous tissues had acid phosphatase activity but that, in man, the activity of the prostate was a hundred or more times as great as that of any other tissue. Gutman and Gutman (1938) found that in the human the acid phosphatase activity of the prostate gland was low in childhood and rose rapidly at puberty to adult levels. The acid phosphatase content is large in man. Fluid expressed from the resting gland by digital compression contains 100-200 units of acid phosphatase per 100 cc: fluid secreted during a period of sexual excitement contains 1900-4000 units. Acid phosphatase is found in the prostate in the following concentration in units /gram :-

new born child 1.5 ; adolescent 70 ; adult 500-2,300./

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2,300. The increase in acid phosphatase content after puberty is due to the action of testosterone.

The normal serum acid phosphatase content is only three units or less per 100 cc : it is derived from many organs, the prostate being a quite unimportant source because the enzyme cannot get through the walls of the prostatic vessels into the circulation. The serum acid phosphatase is thus approximately the same in children and women as in adult men.

The physiological role of the prostatic acid phosphatase is unknown : if a suitable substrate (like hexosephosphate) were present in the gland with consequent release of inorganic phosphate, large amounts of calcium phosphate would be precipitated owing to the rich calcium content of prostatic fluid. Adult male urine contains 3-5 times as much acid phosphatase as the urine of women and children. If acid phosphatase is injected intravenously it disappears from the blood in 3 - 6 hours : the normal level of serum acid phosphatase thus depends on a nice balance between its discharge into the blood from many organs and its removal from the blood.

Carcinoma of the prostate gland and acid phosphatase/

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phosphatase.

The cells of the carcinoma form acid phosphatase to a varying degree ; on an average the enzyme content of the cancer is 1/20 that of normal prostate (the range is 19 - 280 units / g.). When the growth metastasizes the secondary deposits, like the parent growth, also form acid phosphatase. When the deposits occur in the bone marrow and lymph glands the enzyme can pass fairly readily into the blood stream with the result that the serum acid phosphatase level rises from 3 units /100 cc. to 10-700 units. A serum value exceeding 10 units /100 cc. is diagnostic of metastasis of prostatic carcinoma. Secondary deposits in bone for some unknown reason stimulate osteoblastic activity and so raise the local concentration of alkaline phosphatase with a corresponding rise of serum alkaline phosphatase e.g. to 70 units/ 100 cc.

(5) The effects of androgens and oestrogens on the prostate gland.

(a) Androgens. The term androgen is used to describe any substance which has masculinizing properties i.e. which promotes the growth of the accessory organs of reproduction in castrated male mammals. The androgen secreted by the testis is testosterone./

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testosterone. Two weaker derivatives androsterone and isodehydroandrosterone, are found in urine and represent degradation products of testosterone. They are neutral 17-ketosteroids.

Androgens can also be extracted from the adrenal cortex. Methyltestosterone is an artificially prepared androgen which is active by mouth.

The liver is the main site of inactivation and modification of androgens.

Effects of androgens on the prostate gland :

(1) Naturally secreted testosterone is responsible for the development of the accessory organs of reproduction and the other secondary male sexual characters at puberty.

(2) Androgens overcome the degenerative changes in the accessory sexual organs resulting from castration. Thus castration produces atrophy of the prostate and degeneration of the glandular epithelium.

Oestrogens and the normal prostate gland.

(b) The term oestrogen is used to describe any substance which produces oestrous growth in vagina, uterus and mammary glands and female secondary sexual characters. Oestrogens can be extracted from the ovary (both the Graafian follicle and the corpus luteum); the placenta, the adrenal cortex, the testis, and normal adult male as well as female urine.

Action of oestrogens.

Zuckerman and Parkes (1935-36) have shown that injections of oestrogens into monkeys causes prostatic/

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prostatic hypertrophy, fibromuscular overgrowth of the whole prostate, together with epithelial stratification and distension of the uterus masculinus. Such effects can be counteracted by injection of male hormone (testosterone). Inglis (1948) describes the effect of stilboestrol on the normal human prostate, the drug having been administered because of suspected prostatic cancer. The prostate was not obviously enlarged although on section there was generalised cystic change. The colliculus seminalis was obviously hypertrophied and had the white flat appearance associated with sodden squamous metaplasia. The changes produced showed a remarkable similarity to that described in experimental animals.

The epithelial cells of a prostatic adenocarcinoma are dependent for their growth and activity, as is the normal epithelium of the prostate, upon the male hormone. It is upon this basis that castration has been employed in the treatment of prostatic cancer, the malignant growth, in many cases, undergoing regression after operation.

The relationship between the prostate gland and the testes was initiated on a scientific basis by John Hunter, (1786) who observed the fact that prostate diminished in size after removal of the testes. This knowledge came to be applied clinically at the end of the 19th. century when White suggested that castration be used for the

treatment/

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treatment of enlarged prostate in the elderly male. About the same time Astley Cooper (1829) drew attention to the relationship between the breast and ovaries. Interest in the problem of the hormonal control of malignant disease, especially carcinoma originating in the sex glands, was stimulated by the work of Huggins on the treatment of carcinoma of prostate by castration and Stiboestrol. Huggins' (1939) clinical work was based on a long series of ingenious animal experiments. He demonstrated that the administration of androgens stimulated prostatic activity and increased the flow of prostatic fluid. It was shown that the administration of oestrogens stopped the production of prostatic fluid. A certain degree of metaplasia was also produced-at times sufficient to simulate cancer. Androgens caused a return to normal. Huggins (1941) further showed that after surgical castration prostatic secretion stopped. It then occurred to him that as malignant disease of the prostate was frequently merely an overgrowth of adult epithelial cells, castration, by removing the main sources of natural androgens, would have a restraining effect on the growth. Males also excrete oestrogenic hormones in their urine, the sources of these being taken as the adrenals. After castration, therefore, the output of oestrogens should remain constant, thus bringing about a shift in the androgen/oestrogen ratio towards a higher oestrogen and lower androgen level. Obviously the administration of oestrogens per se would bring about a similar sort of shift.

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The control of the response to such treatment was made by the estimation of serum acid and alkaline phosphatase levels. (Gutman, Sproul and Gutman 1936) The level of acid phosphatase indicates the activity of the cancer. Alkaline phosphatase is produced in excess by bone as a defence mechanism, where there are bony metastases, the activity of the bone defense is indicated by the amount of alkaline phosphatase in the blood. In 1941 Huggins and Hodges noted that castration or injection of Stilboestrol or Oestradiol benzoate produced a fall in acid phosphatase and a rise followed by a fall in alkaline phosphatase. This is accompanied by a remarkable improvement in the patient's general condition. Testosterone proprionate injections produced a sharp rise in acid phosphatase. Actually, it was found later (Dean, Woodward and Twombley, 1944) that from the point of view of excretion of hormones, castration and the administration of oestrogens apparently do not produce their effects in the same way. Castration causes a decrease in oestrogen excretion, while the excretion of androgens, as measured colorimetrically as 17 Ketosteroids by the Callow-Zimmerman test tends to remain the same or rise slightly. Actually, the figures they give are not raised significantly. On the other hand they found that Stilboestrol causes a decrease in excretion of 17 Ketosteroids and a rise in oestrogen excretion.

While a prompt response has been noted to anti-androgenic therapy in many patients with metastatic prostatic cancer, frequent failures have necessitated continued/

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continued investigation. Many possibilities have been suggested to explain these failures ; differences in histologic or biologic characteristics of prostatic carcinoma (Nathanson et al, 1952), inherent cell differences ; the establishment of autonomy by prostatic epithelium and its independence of androgenic influence : (Huggins & Scott, 1945, Deming & Hovenian, 1948, Deming, 1949) the influence of extragonadal sources of androgen upon prostatic tissue and possible basic metabolic differences in the host (May et al, 1948). A clearer understanding of the failures had been gained from an investigation of adrenal physiology. Gonadectomy in susceptible strains of mice results in the development of benign or malignant tumours of the adrenal cortex preceded by cortical hyperplasia (Burrill & Green, 1939). The intact hypophysis stimulates adrenal hyperactivity in the absence of gonadal hormones. Such laboratory evidence has been substantiated by clinical observations. In patients no longer responding to anti-androgenic treatment enlargement of the adrenals to several times their normal size has been observed (Nathanson 1952). The successful use of adrenal substitution materials Cortisone acetate and pituitary adrenocorticotropin (ACTH) in 3 patients with advanced carcinoma of the prostate with metastases is reported, by Huggins and Bergenstal (1952).

Table I.

CANCER OF PROSTATE (DEATHS)

(M.O.H. Edinburgh).

Years	Age groups.						Total
	15-25	35-45	45-55	55-65	65-75	75+	
1936	Nil	1	2	2	10	6	21
1937	Nil	Nil	Nil	1	8	10	19
1938	Nil	Nil	Nil	4	14	8	26
1946	Nil	1	2	2	18	16	39
1947	Nil	Nil	Nil	4	5	10	19
1948	1	Nil	Nil	3	18	18	40
1949	Nil	Nil	Nil	5	17	13	35
1950	Nil	Nil	Nil	4	19	16	39
1951	Nil	Nil	2	3	16	15	36

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(3) HISTORICAL ASPECTS.

Prostatic malignancy is not a modern disease. Archaelogical surveys have shown that fossil remains of prehistoric man and animals contain secondary growths of this disease. It was first recognised as a distinct entity in 1817 by Langstaff. The term "metastasis" was first used by Reconvier in 1829 to signify the secondary growth from this disease. It is to Sir Henry Thompson that we owe the first clear description of carcinoma of the prostate. He showed a case in 1854 at a meeting of the Pathological Society. Prior to the present century malignancy was seldom recognised for in 1899 Richard Wolff was only able to review the small number of 83 cases reported in the world up to that date. This was probably due to the fact that it was confused with simple enlargement, a feature stressed by Sir Henry Thompson. However, with the increasing aids to diagnosis and other features such as a sense of awareness of the condition 1300 cases were reported by Birdsall (1948).

(4) INCIDENCE.

Hoffman (1934) states that the death rate from Carcinoma of the prostate in England, Wales and Scotland in 1921 was 2.98 per 100,000 of population and in 1930 it was as high as 7.47. The reports of the Medical Officer of Health for Edinburgh during the years 1946-1952 gave the deaths from cancer of the prostate as listed in Table I. An examination of this table shows that the number of elderly/

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elderly males dying from carcinoma of the prostate is not significantly increased. This table serves to illustrate the erroneous impression given by such statistics. Owing to the inherent difficulties of death certification as it now exists, as for instance when the medical attendant at times does not know the true cause of death and he states the immediate cause of death, e.g. bronchopneumonia, then again the stigma attached to the word "cancer" by the laymen is, at times, a strong factor in deterring the general practitioner from inserting it in the death certificate. Sometimes the most significant sign is inserted as the cause of death, namely "Uraemia" for the simple reason that there is a failure to appreciate the true underlying pathology, e.g. carcinomatous change in a prostate which has undergone simple enlargement.

When the case incidence of Cancer of the prostate is considered amongst hospital admissions to a General Hospital such as the Royal Infirmary of Edinburgh certain difficulties arise. For instance, not every prostate removed at operation is sent to the Pathologist for histological examination. The similar age incidence of Paget's disease and carcinoma of prostate, also, the fact that the radiological appearances in these two conditions, are often indistinguishable (McWhirter, 1953) is an added source of error in arriving at an accurate estimation of the incidence of prostatic carcinoma. All that could be said with some certainty, is that, when new therapeutic measures such as the introduction/

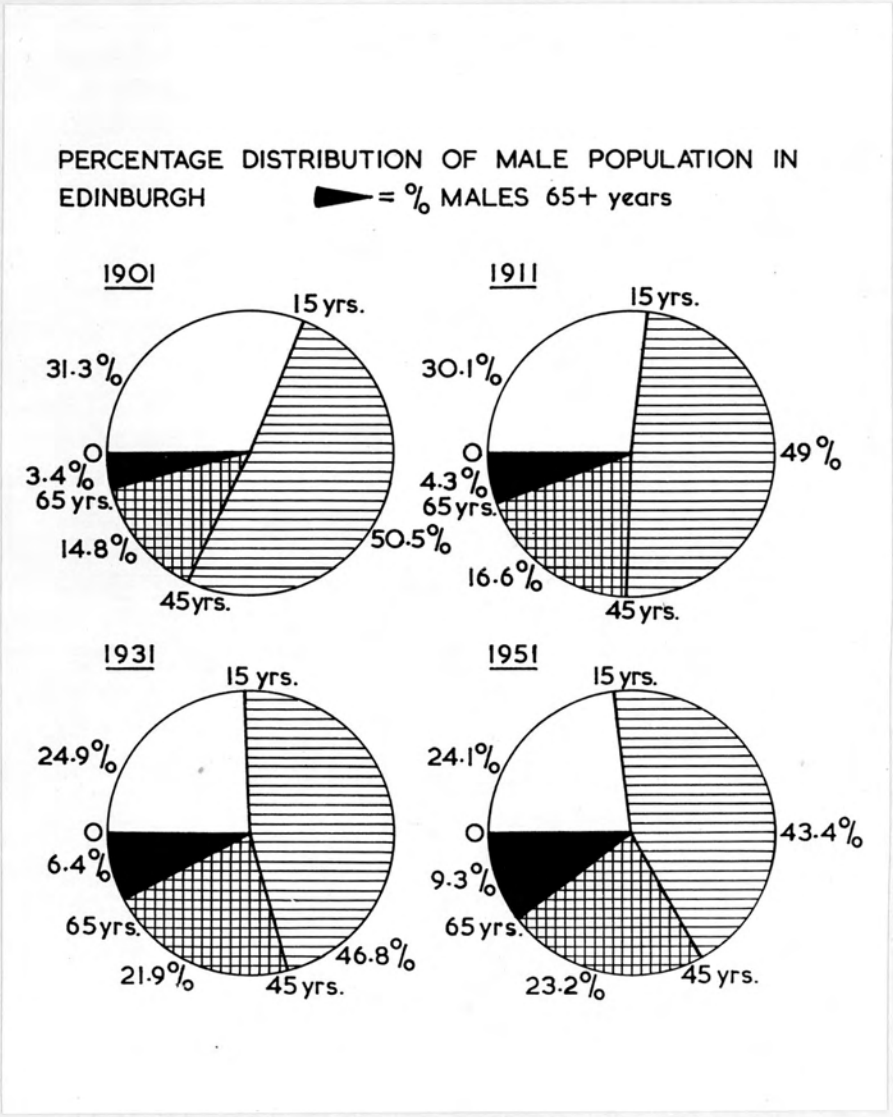
PERCENTAGE DISTRIBUTION OF MALE POPULATION IN EDINBURGH
= % MALES 65+ years
1901
15 yrs.
31.3%
3.4%
65 yrs.
14.8%
50.5%
45yrs.
1911
15 yrs.
30.1%
49 %
4.3%
65yrs.
16.6%
45yrs.
1931
15 yrs.
24.9%
6.4%
65yrs.
21.9%
46.8%
45 yrs.
1951
15 yrs.
24.1%
43.4%
9.3%
65 yrs.
23.2%
45 yrs.

Figure 2.

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introduction of antibiotics, and the fruits of preventative medicine combine to produce a sharp decline in the mortality of the middle aged and a marked rise in survival during the sixth and subsequent decades, the numbers that are likely to develop carcinoma of the prostate will increase. Table 2 gives a numerical picture of the percentage distribution of the male population of Edinburgh for the years 1901, 1911, 1931 and 1951 respectively. It shows quite clearly the progressive increase.

Table 2.

Percentage distribution of male population. Year.	age group. 45-65 yrs. %	65 + yrs. %
1901	14.8	3.4
1911	16.6	4.3
1931	21.9	6.4
1951	23.2	9.3

This demonstrates without a shadow of doubt that, in the near future, many cases of cancer of the prostate will be seen in Edinburgh.

Improved diagnostic methods will also, undoubtedly, influence the detection of cancer of the prostate and consequently bring about an apparent increase in the numbers of cancer cases.

(5) AGE DISTRIBUTION.

The greatest majority (38%) of cases amongst the biopsy material of Carcinoma of Prostate of the Royal Infirmary series was in the age group 71- 80 years./

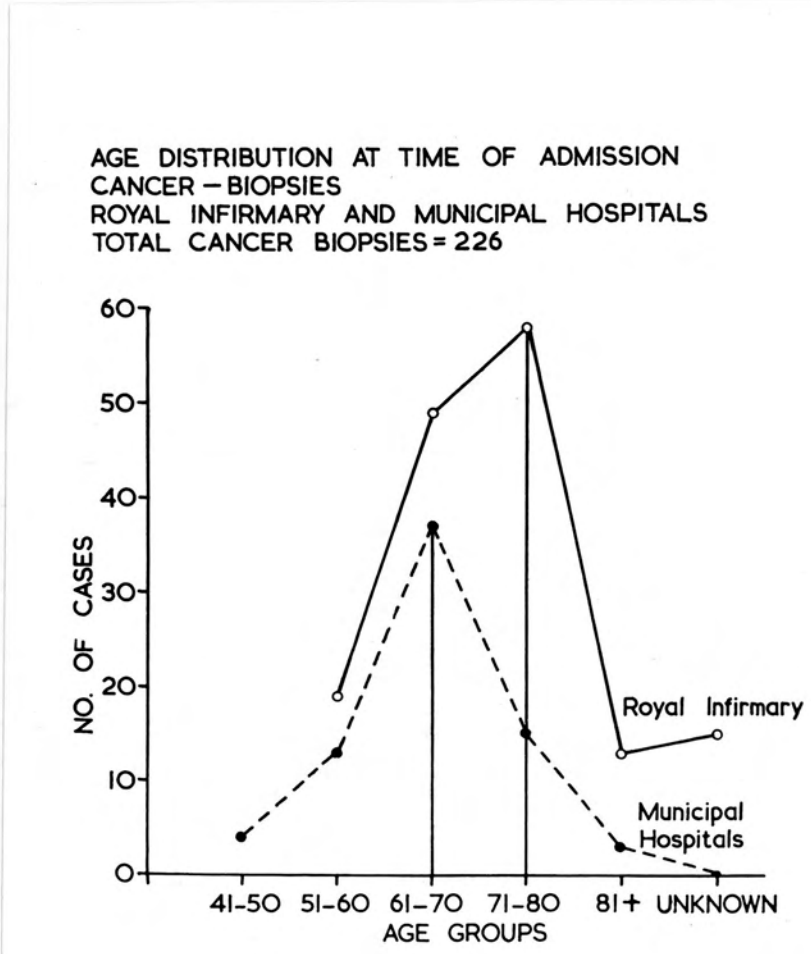
AGE DISTRIBUTION AT TIME OF ADMISSION
CANCER – BIOPSIES
ROYAL INFIRMARY AND MUNICIPAL HOSPITALS
TOTAL CANCER BIOPSIES = 226
NO. OF CASES
60
50
40
30
20
10
0
Royal Infirmary
Municipal Hospitals
41-50
51-60
61-70
71-80
81+
UNKNOWN
AGE GROUPS

Figure 3.

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years. See Table 3. In the Municipal Hospital cases the age group containing the greatest number of cases was 61-70 years (51%). (The age stated was that ascertained at time of admission). This discrepancy in ages is probably due to the fact that the patients are admitted to the Municipal Hospitals (Western General in particular) at an earlier date.

Table. 3.

Age distribution of Carcinoma of Prostate.

(Biopsy)

Decade	No. of cases.	% R.I.E. Cases (154)
71-80	58	38.31
61-70	49	31.18
51-60	19	12.33
81+	13	8.44
Unknown 15	15	9.74

Decade	No. of Cases.	% M.H.B. (72)
61-70	37	51.3
71-80	15	20.83
51-60	13	18.05
41-50	4	5.5
81+	3	4.16

With regard to the autopsy Cancer cases we find in the Royal Infirmary series, the greatest number of cases (49%) occurred in the decade 61-70 years ; the same findings were noticed in the Municipal Hospital series.

Table 4./

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Table 4.

Age Distribution Cancer autopsies (R.I.E.)

Decade (yrs)	No. of cases.	% R.I.E. (33) Autopsies
61-70	16	48.5
71-80	10	30.3
51-60	4	12.1
81+	1	6.1
31-40	1	3.0
Unknown	1	3.0
Total	33	

Table 5.

Age Distribution. Cancer autopsies. (Municipal Hospitals).

Decade (yrs)	No. of cases.	% Municipal Hospitals (25)
61-70	14	56
71-80	6	24
51-60	2	8
81+	2	8
10-20	1	4
Total	25	

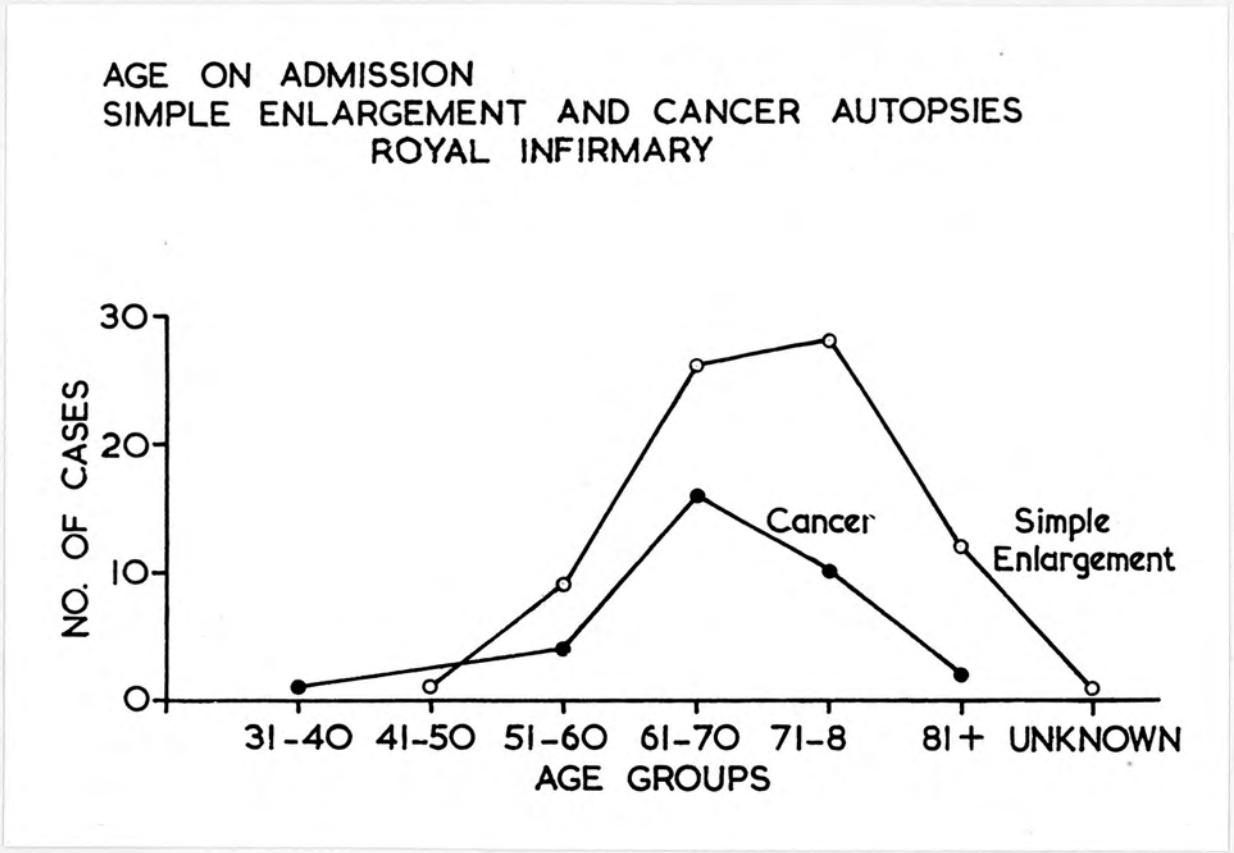

Figure 4.

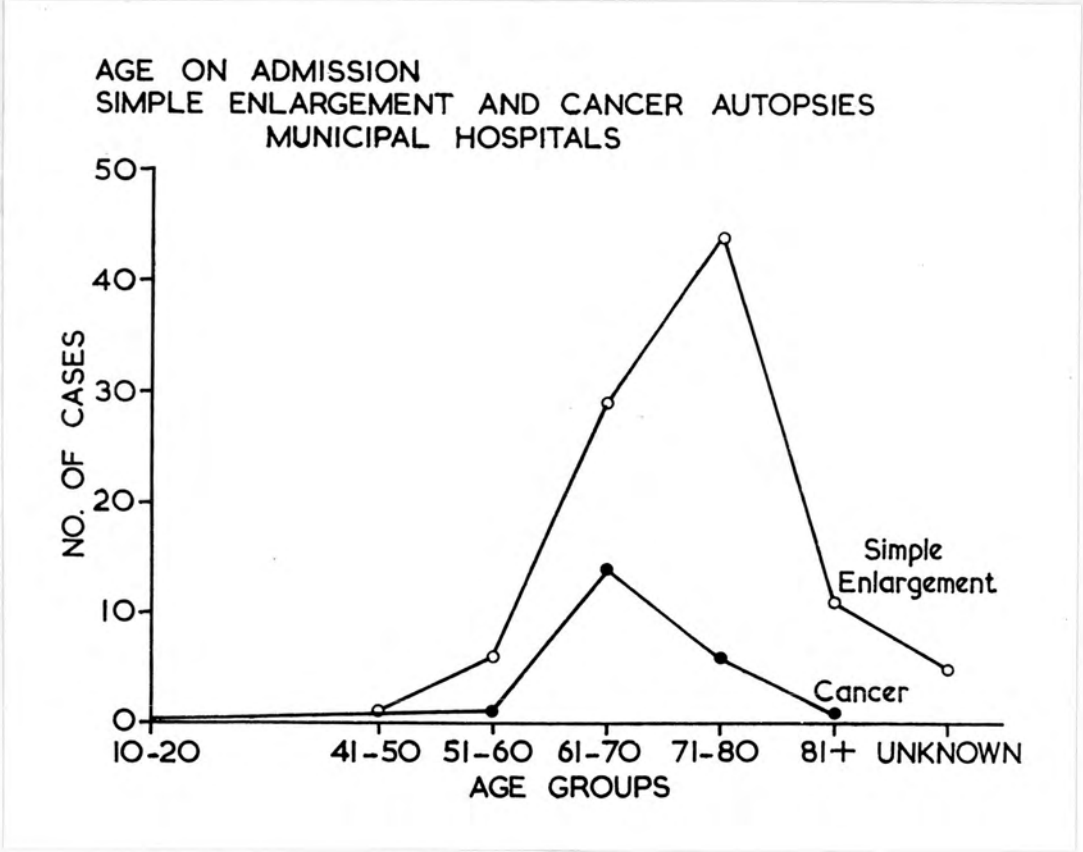

Figure 5.

23.

A comparison of the figures for the age incidence of cancer of the prostate as quoted in the literature is tabulated below.

Table 6.

Observations from the Literature.

Age Distribution of Carcinoma of Prostate.

Decade	YOUNG (1909) 111 Cases. %	BUMPUS (1921) 361 Cases. %	DEMING (1922) 100 Cases. %	BARRINGER (1931) 280 Cases. %	AUTHOR (1953) * 226 Cases. %
40-50	1.8	2.7	3.0	3.9	2.2
50-60	22.5	21.6	17.3	29.9	15.0
60-70	45.5	31.2	45.0	41.3	41.0
70-80	27.0	2.1	25.0	4.1	30.0
80-90	3.6	1.2	10.0	1.7	6.0

* (Royal Infirmary and Municipal hospitals combined).

Thus it is seen that the maximum age incidence of the cancer patients occurs in the 60-70 age decade (41%), this is in agreement with the observations of other workers.

(6) ANATOMICAL SITE OF CARCINOMA OF THE PROSTATE GLAND.

It was not possible to ascertain the frequency of lobe involvement of the carcinomatous process in the cases reviewed by me owing to lack or failure to record these important details. This lack or failure to record important details delays progress/

24.

progress in the field of Clinical Research. It is for this reason that I advocate the use of a stenographer in the operating theatre. This individual will be able to record all such detail in a previously prepared form and in this manner will be able to record a vast volume of useful data for future analysis.

(7) OCCUPATION AND CARCINOMA OF THE PROSTATE GLAND.

I was able to ascertain the occupation in 143, (i.e. 90%) of the 154 Cancer of prostate biopsies of the Edinburgh Royal Infirmary. The occupation was not stated or not known in over 70% of the Municipal Hospital series and consequently had to be omitted from this section.

The results are tabulated below :-

Table 7.

% Occupational distribution of Cancer Cases.

	No.	%
Professional	7	4.5
Skilled	66	42.8
Unskilled	24	16.2
Retired	46	29.8
Unknown	11	7.1
	154	100.4

This table shows the largest number of cases occurs in the group of skilled workers (42.8%). The smallest number (4.5%) is seen amongst the professional/

25.

professional class. This simply means that the professional class does not seek treatment in the Royal Infirmary. The Infirmary class of patient is drawn from the remaining three groups. Thus Carcinoma of the prostate gland occurs amongst all classes.

There does not appear to be any special trade or profession which is particularly associated with Carcinoma of the prostate gland.

I have given details of the differenent occupations in the Appendix.

(8) MARITAL STATUS AND CARCINOMA OF PROSTATE GLAND.

An analysis of the biopsy series of the Carcinoma of prostate gland (154) with regard to marital status reveals the fact that no less than 66% of the cases occurred amongst those who were married.

Table 8.

Marital Status and Cancer.

	No.	%
Married	102	66.2
Unmarried	40	24.1
Unknown	12	7.7
	154	100.0

At the present time there is no satisfactory explanation for this increased incidence amongst the married male. We must wait for future research to/

26.

to unravel this mysterious factor which influences unfavourably the married male. This observation has been noted by other workers too (Crowell 1940).

(9) RELATION TO SIMPLE PROSTATIC ENLARGEMENT.

The fact that the two conditions - simple enlargement of the prostate and carcinoma occur commonly in the elderly male has given rise to many views as to the relationship of these two conditions. This is indeed a perennial question.

Young (1909) is of the opinion that it does not arise as a degeneration in a previously benign process. Albarran and Halle (1900) insist upon a definite relationship between simple enlargement and carcinoma. Among 865 cases of simple prostatic enlargement they found in 12, epithelial changes which they thought to be different grades of carcinomatous degeneration. They suggest that prostatic hypertrophy has its origin in pathologic processes in the glands which may develop into benign adenomatous formations or, on the other hand, into malignant neoplasms. Ewing (1940) criticises this observation by stating that " early or suspicious changes are much more frequent than is the established disease. " Some of these areas are undoubtedly the result not of excessive epithelial proliferation, but of overgrowth of the periacinar-fibrous tissue, leading to partial obliteration of the prostatic glands. (Muir, 1934). Willis (1948) very correctly leaves the matter undecided when he states - " While it is quite possible, even probable/

27.

probable, that hyperplasia and neoplasia of the prostate are related, it remains for future research to prove and define the relationship." I agree with Willis (1948) for I was unable to detect any relationship between simple enlargement of the prostate and carcinoma in the 2,458 prostate glands examined in the course of this study.

(10) THE PROBLEM OF DIAGNOSIS.

I consider this aspect of the study extremely important. In no other type of malignant growth is the problem of early diagnosis more difficult. Diagnosis is dependent upon the history given by patient and thorough clinical examination. As applied to prostatic carcinoma the symptoms produced at time of examination were :-

Table 9.

Frequency of Symptoms.

Frequency	40%	Overflow incontinence	3%
Difficulty with Micturition	27%	Pain	1%
Acute Retention	18%	Haematuria Oedema of legs and sacrum	1%
Dysuria	6%		

The symptoms listed above indicate that they are not considered sufficiently serious to warrant early medical examination. Haematuria and pain account for 1% and less than 1% respectively of cases seeking admission. The only symptom which compels them to obtain medical relief is acute retention/

28.

retention (18%). So, it is not unnatural to understand the reasons for patients not coming into hospital until more serious symptoms arise.

With regard to the prostate gland itself - the gross morphology of prostatic cancer may be described as " typical " only when the disease is advanced (Gordon, 1941).

Kahler (1939), who made a very careful study of 195 cases of carcinoma of prostate says that the failure to recognise these tumours is due to the absence of characteristics sufficiently distinct to differentiate them from normal or simple prostatic enlargement tissue.

Early diagnosis is difficult. The disease is insidious, causing few symptoms until late in its course (Brendler 1952). Caulk (1937) stresses the difficulties in defining the features of an early case - " the nature of the disease is progressive and deadly. Indeed, I am incompetent to state what is an early case since I have seen numerous instances of small localised palpable lesions in what appeared to be an otherwise normal gland. "

Boyd (1942) states clearly that "early carcinoma of prostate is symptomless. The first symptoms are most often due to prostatic obstruction. Usually these first symptoms are ignored by the patient as the usual thing in a man of his age and it is often years before advice is sought. Frequency and difficulty of urination in the mind of the laity is not suggestive of a malignant condition and so no fears are aroused. "

It/

29.

" It is thus evident that the slightest urinary derangement in men beyond middle life should demand an immediate investigation of its cause, with suspicion of malignancy of this organ in mind. " (Caulk, 1937).

Under these circumstances it is imperative that other diagnostic methods should be applied, such as :

(a) Histological examination of biopsy material.

(b) Radiological examination.

(c) Chemical estimation - Serum acid phosphatase.

(d) Cystoscopy.

(e) Cytological examination of prostatic secretion after prostatic massage.

(11) PATHOLOGICAL FEATURES OF PROSTATIC CARCINOMA.

Having decided that the prostate gland has undergone malignant change the next most natural question is " What type may it be ?" The answer to this question and others dealing with the pathological features of carcinoma of the prostate gland will now be discussed in the following manner.

(1) Gross morbid anatomy — Cut surface / Consistence

(2) Morbid histology.

(3) Pathologic complications.

(1) Gross morbid anatomy.

i) Size
ii) Shape
iii) Surface
iv) Section, i.e. cut surface.

i) Size.

In/

30.

In the early phase of carcinoma of prostate gland, i.e. when the malignant growth is confined to the prostate gland no obvious alteration in size is seen. If the cancerous process occurs in a gland which has already undergone simple prostatic hypertrophy then it will be enlarged. On the other hand, malignancy might occur in a gland which is not enlarged. This fact was demonstrated very strikingly in the routine series of prostate glands examined in the study on unsuspected Carcinoma of the prostate.

ii & iii. Shape and Surface.

Normally, the prostate gland is described as having the shape of a horse chestnut. When it undergoes hypertrophy it loses its smooth contour and appears nodular. When the malignant growth breaks through the capsule or when it is just inside the capsule - a small, raised swelling or nodule is produced. This nodule is generally of a yellowish-white or creamy colour. The naked eye appearance is not unlike that of a tuberculous nodule. This appearance resulted in a diagnosis of Tuberculosis of the Genito-Urinary Tract in one case in the autopsy series of the Royal Infirmary. It was only on microscopic examination that the presence of carcinoma was detected.

Below is a summary of the morphological characteristics of prostatic carcinoma, as noted on clinical examination and at autopsy.

Table 10./

31.

Table 10.

Morphological Appearance. Cancer of Prostate.

	Clinical Examination	Autopsy
Size	Enlarged (67%)	Enlarged (84.8%)
Shape	Small (4%)	Small (6%)
Consistence	Stony hard (66%) Nodular (23%)	Hard (66.6%) Not stated.
Colour	-	White (33.3%) Yellow (18%) Grey (9%)

iii. Cut Surface.

The appearance of the cut surface is extremely variable. The wide range of variety is dependent upon such things as the size of the growth, the changes that have occurred in the main mass of the tumour owing to secondary degenerative changes, whether it occurs in a gland which has undergone simple enlargement, etc. In general the growth is homogeneous, firm and of a yellowish-white to grey colour. It is quite impossible to detect early malignant change with certainty by mere naked eye examination (Chandler Foot, 1952). Kahler (1939) too states emphatically " In most instances gross inspection is of no assistance in localizing a tumour or in determining its size. " On cutting the gland there is a characteristic hardness - a sensation which is only experienced when cutting the prostate gland. No words can adequately describe this. It is not a grittiness, for grittiness can be produced by the minute greyish-blue firm particles/

32.

particles one often sees in the cut surface embedded in minute spaces (corpora amylacea). This hardness is seen in a relatively early stage of carcinoma of the prostate. I have succeeded in showing (in a later section) that this hardness is probably due to an increase of elastic fibres in the stroma of a gland containing the malignant growth. The elastic fibres are not so heavily distributed in the actual site of growth.

The observations made by other workers on the morphological characteristics of prostatic carcinoma are summarised below. My observations are in agreement with those of other workers.

Table 11. /

33.

Table 11.

Observations from the Literature.

Morphological appearance - Carcinoma of Prostate.

AUTHOR	DESCRIPTION OF PROSTATE GLAND
1. Young (1909)	Hard consistence ; rough surface.
2. Young Geraghty (1906)	Hard, tense ; gritty sensation. Greyish yellow areas. Tissue does not bulge on cutting gland.
3. Muir (1934)	Small, scattered dark particles seen on section.
4. Boyd (1942)	Hard, tense, gritty sensation, dry, without lobulation, small in size, yellow in colour.
5. Kahler (1938 & 1939)	Yellow; white or haemorrhagic areas, increased consistence, homogeneous surface.
6. Gordon (1941)	Small or large size, hard or soft, depending upon whether scirrhous or medullary type of growth.
7. Thomson-Walker (1948)	Hard, even cartilaginous ; whitish nodules or hard throughout.
8. Hey (1948)	Large, irregular, nodular if adeno-carcinomatous. Small, stony hard, fixed if scirrhous.
9. Kimbrough (1951)	Hard nodule in posterior lobe.
10. Chandler Foot (1952)	Stony hard ; granular, whitish, opaque.
11. Landes et al (1951).	Stony hard region in single lobe. Marked induration of whole gland.

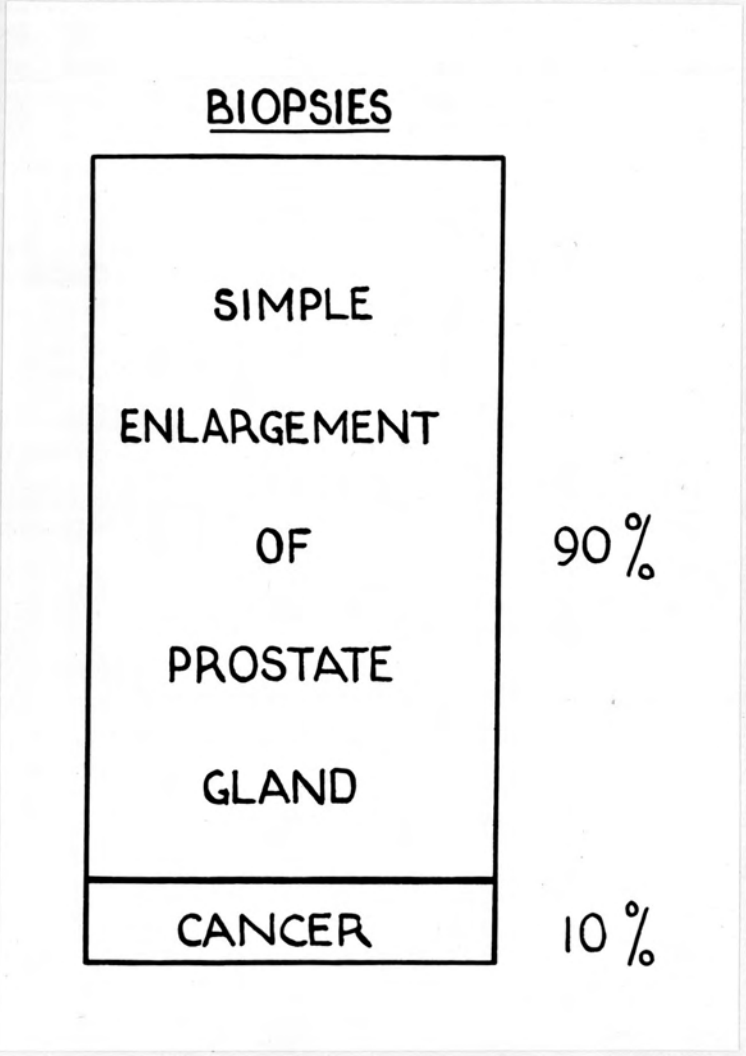
BIOPSIES
SIMPLE ENLARGEMENT OF PROSTATE GLAND
90 %
CANCER
10 %

Figure 6.

34.

Summary. The prostate gland containing the malignant growth presents a varied picture depending upon the extent of the growth. In the early stages the features are not very striking for the simple reason that the lesion is too small to be detected naked eye. It is not uncommon for the pathologist who handles the whole prostate, sections it himself, and still fails to see any evidence of malignancy. At this early stage there is no departure from the normal size, shape and weight of the gland. Should the malignancy occur in a gland which has already undergone simple hypertrophy then the prostate will be larger than normal, and perhaps a little nodular. The cut surface will show microcystic spaces and white strands of fibrous tissue running across and so dividing it into irregular islands. When the growth is moderately advanced the malignant growth appears in a variety of colours - white, opaque, yellow, grey. The consistence is firm and at times, stony hard. When the cancerous process has extended beyond the capsule a button-like, hard, nodular area could be palpated, especially in the posterior lobe.

(2) Morbid histology.

A classification of malignant disease of an organ which has at its basis the histological differentiation of cells is both simple and readily understood. Consequently, it enjoys a wider appeal. A further reason for adopting a histological classification arises out of the fact that the morphological appearances of carcinoma of the prostate offer no distinctive types of growth as one sees/

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sees, for example, in Carcinoma of the stomach. Unfortunately, there is a serious drawback in this method of classification, namely, the fact that there is no uniformity of structure of the growth ; the same tumour presents a variable microscopic appearance in different and in adjacent portions. Any classification which is based upon the cytological detail of a small section of the growth is apt to be misleading. At this moment I am reminded of the words quoted by John Fraser (1927) in his study on Malignant diseases of the breast - "T'is but a part we see and not a whole. " (Pope). However, this difficulty is surmounted by taking a number of sections from different parts of the gland. In this way a more accurate interpretation of the type of growth is obtained.

Willis (1948) describes the histological picture of prostatic carcinoma under the following types - Adenocarcinoma and spheroidal-celled carcinoma. The adenocarcinoma type was further subdivided into tubular, acinar forms, cystic and papillary. Spheroidal cell carcinoma is described in two forms - scirrhous and the cellular or anaplastic form. He, too, admits that several or all of these variants may be seen in the same tumour.

Ewing (1940) describes it as an adenocarcinoma which rarely occurs in a pure form : it has a tendency to merge into an alveolar type. He describes another pseudoalveolar form - where the acini are in small groups. This type, he says, is a/

36.

a more malignant form of adenocarcinoma. The scirrhous form is observed in rare cases.

Kahler (1939) is quite outspoken when he states that the " suggested classifications of prostatic carcinoma are at present both numerous and confusing. " Despite this remark he does not attempt to simplify the position when he goes on to divide the carcinoma into squamous cell carcinoma and adenocarcinoma. Those two are further subdivided according to grades of malignancy as formulated by Broder. I will not bore the reader any further by stating the numerous classifications in the literature, but I will sum up the position by quoting Gordon (1941). The need for a central " registry ", in order to establish a standardised simple nomenclature, is apparent when the many classifications for carcinoma of the prostate are reviewed.

The classification I have adopted is by no means the ideal. However, it is based on the degree of differentiation of cells. By differentiation I mean the extent to which the cancer cell pattern or architecture resembles the pattern seen in the normal gland, or the extent to which it alters or differs from the normal arrangement. Thus there is a well-differentiated form, a moderately well-differentiated form and a poorly differentiated form.

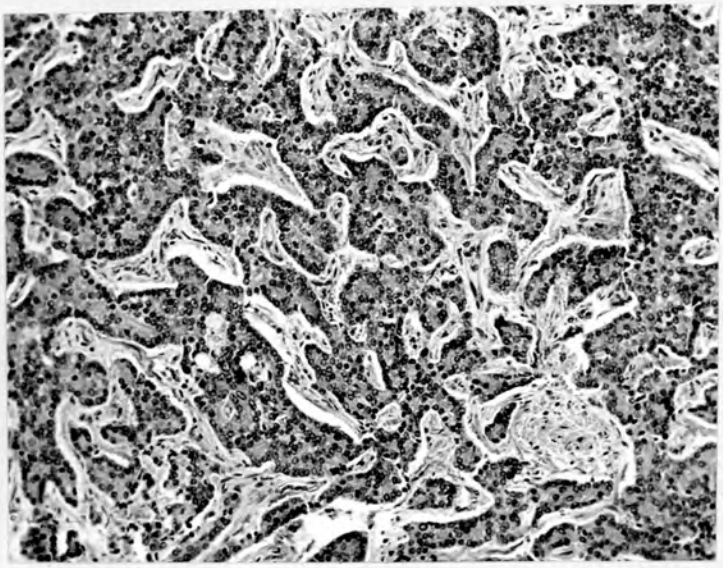

Fig. 7. Prostate. Well differentiated adenocarcinoma. Haematoxylin & Eosin x 150.

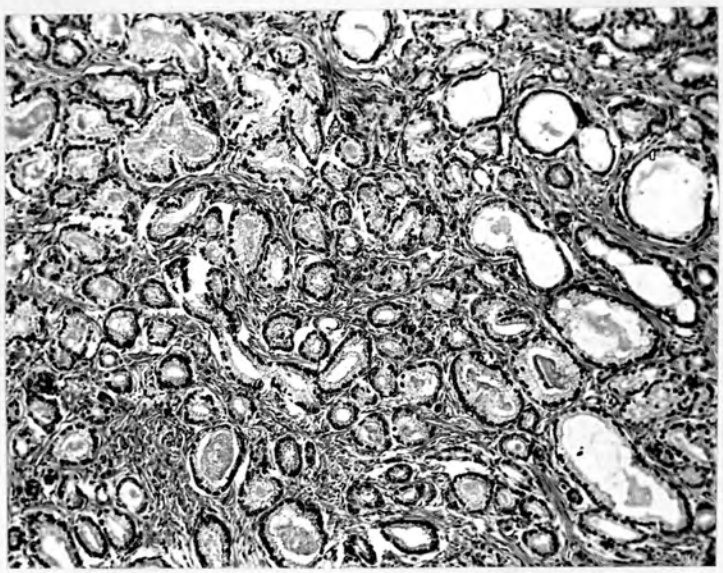

Fig. 8. Prostate. Well differentiated adenocarcinoma. Haematoxylin & Eosin x 90.

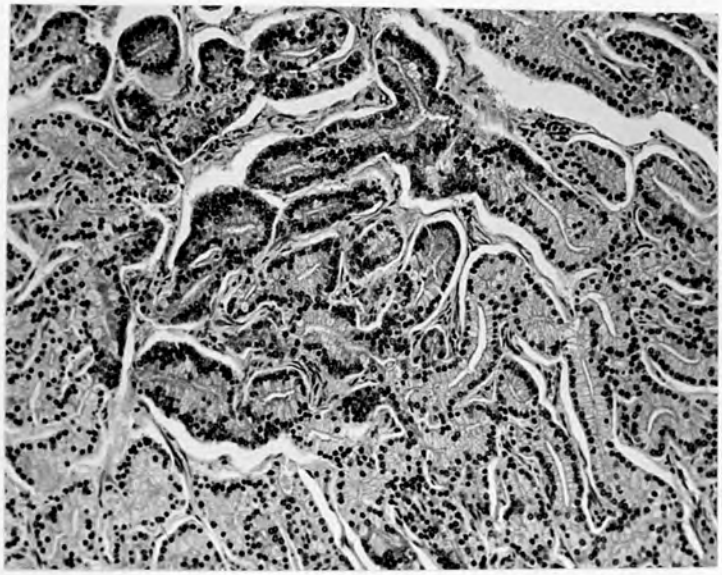

Fig. 9. Prostate. Well differentiated adenocarcinoma. Haematoxylin & Eosin x 150.

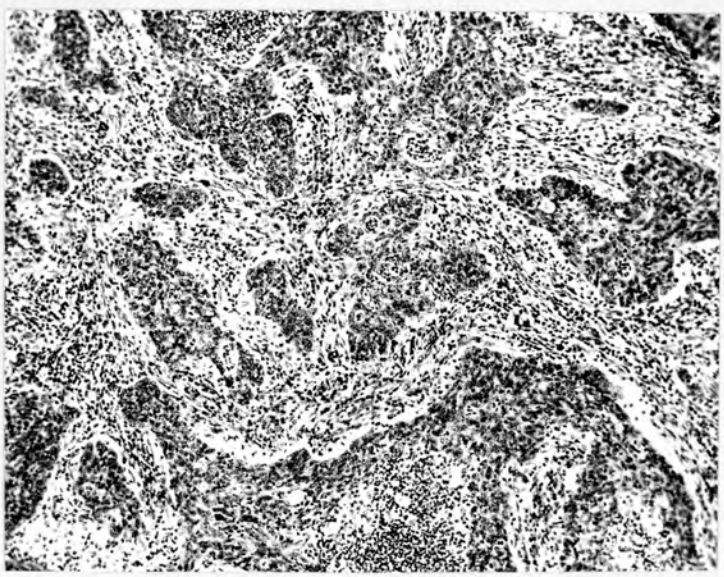

Fig. 10. Prostate. Moderately well differentiated adenocarcinoma. Haematoxylin & Eosin x 90.

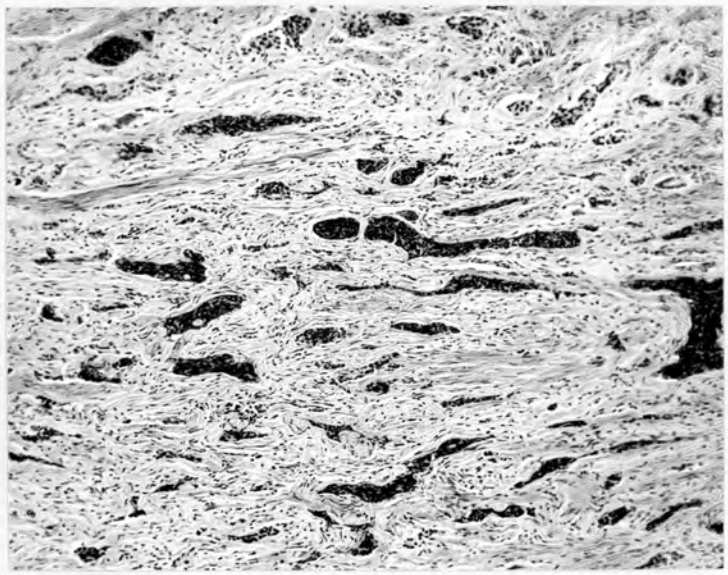

Fig. 11. Prostate. Poorly differentiated adenocarcinoma. Haematoxylin & Eosin x 90.

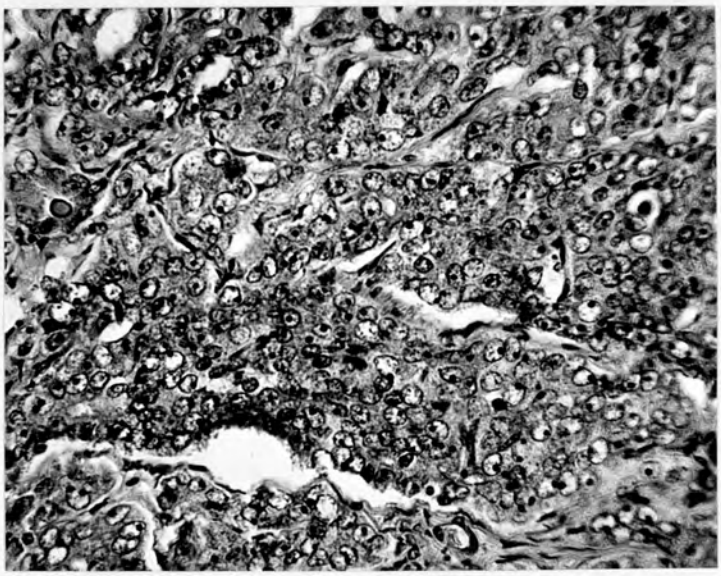

Fig. 12. Prostate. Anaplastic type of carcinoma. Note hyperchromatic nuclei. Haematoxylin & Eosin x 300.

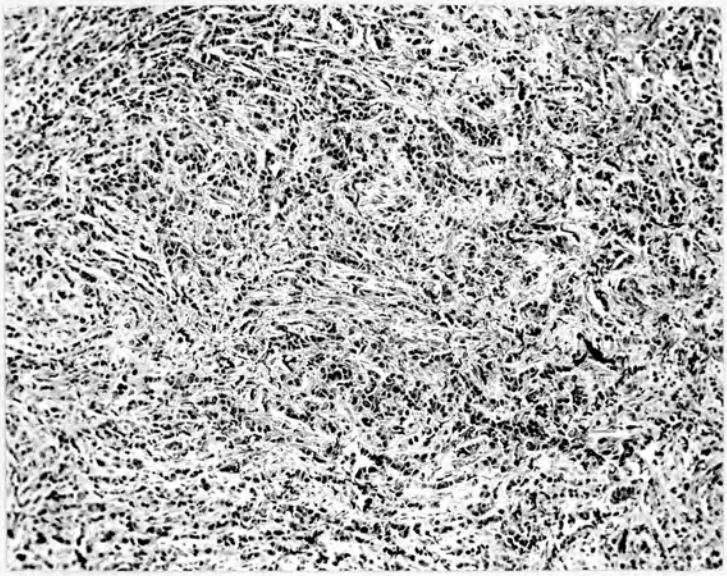

Fig. 13. Prostate. Undifferentiated adenocarcinoma.
Haematoxylin & Eosin x 90.

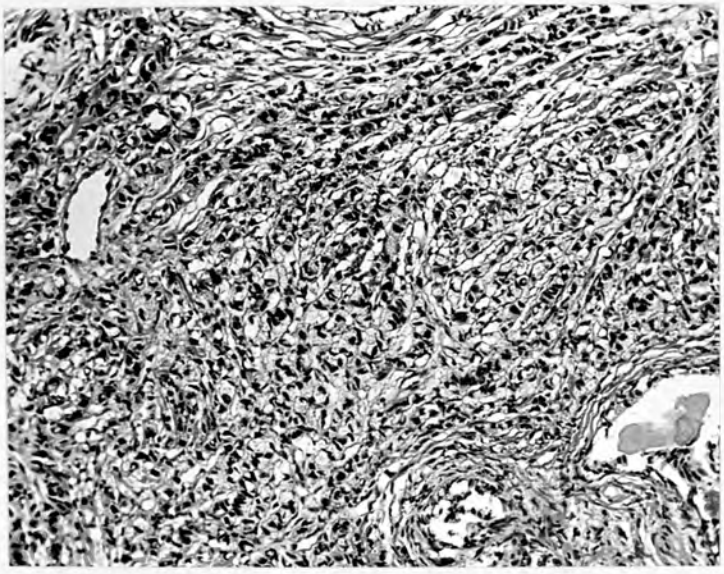

Fig. 14. Prostate. Scirrhous carcinoma.
Haematoxylin & Eosin x 150.

37.

Next there is the type that is not very cellular - the proportion of fibrous tissue (generally) exceeds the amount of glandular tissue, also there are a few spheroidal shaped cells amidst muscle and fibrous tissue strands. This I designate the SCIRRHOUS AND SPHEROIDAL CELLED types.

Finally, there is a SARCOMA of the prostate gland. This type rarely occurs in the prostate and many of the reported cases are of uncertain nature. Kaufmann (1902) collected only 24 authentic cases, but discards many other for lack of microscopical report (Ewing, 1940). Willis (1948) makes no reference to this form of malignant growth ; he quotes Cappell (1944) by stating that diffuse carcinoma may simulate and has no doubt often been misdiagnosed as sarcoma. This type of growth may occur at any age, but in most of the recorded cases it has occurred in the first decade of life. The simplest pathological classification is that given by Stevens and Barringer (1953). According to these two authors, sarcoma of prostate may be divided into two major groups (a) the primary group includes the Rhabdomyosarcomas, Lymphosarcomas and sub-group in which are classified the spindle-cell sarcoma, fibrosarcoma, myxo-sarcoma, round cell sarcoma, and giant cell sarcoma.

(b) the second group includes the anaplastic carcinoma actually resembling lymphosarcoma.

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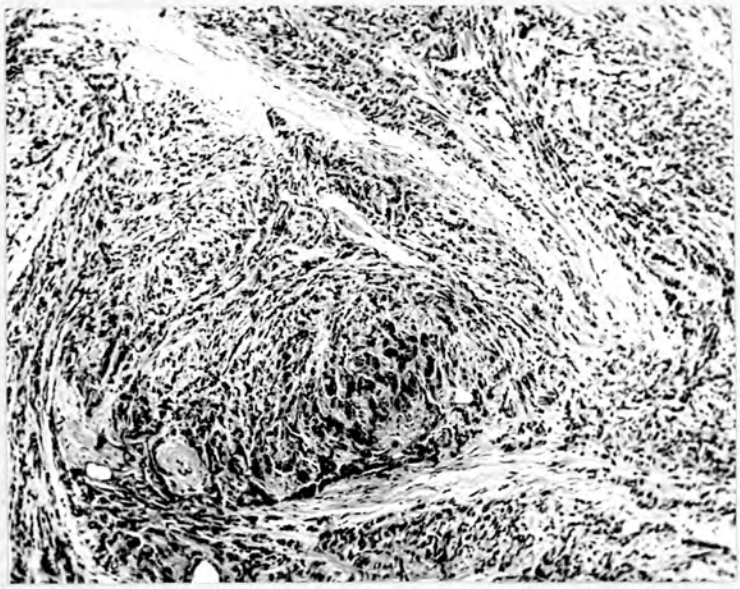

Fig. 15. Prostate. Spheroidal cell carcinoma. Haematoxylin & Eosin x 120.

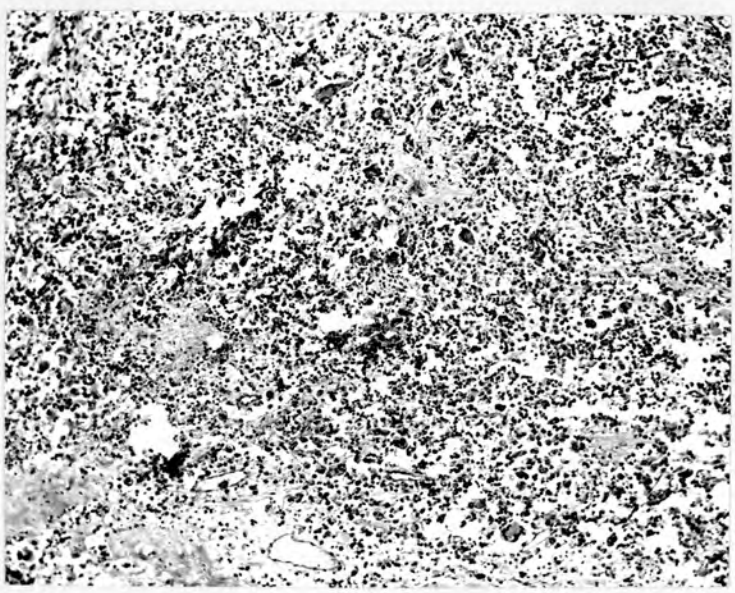

Fig. 16. Prostate. Lymphosarcoma. Haematoxylin & Eosin x 60.

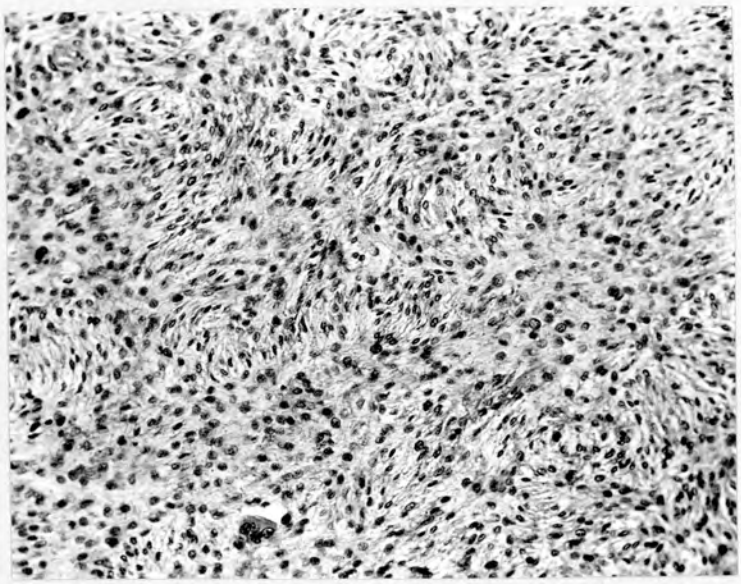

Fig. 17. Prostate. Spindle cell sarcoma.
Haematoxylin & Eosin x 120.

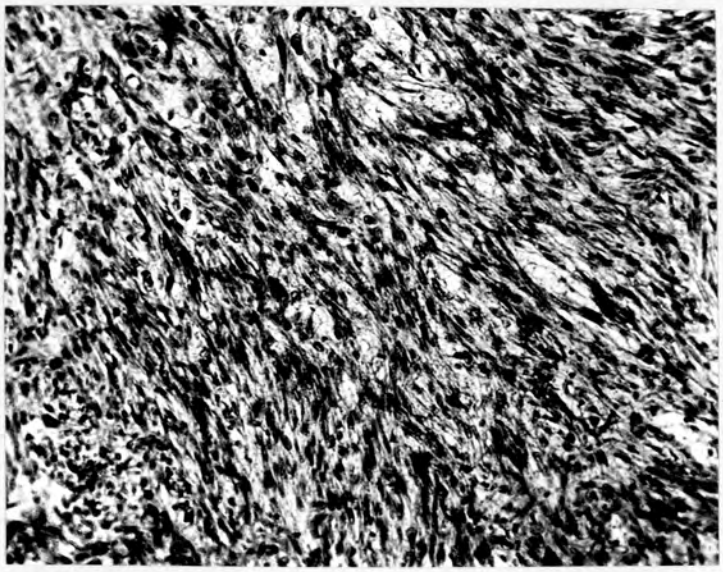

Fig. 18. Prostate. Spindle cell sarcoma.
Haematoxylin & Eosin x 150.

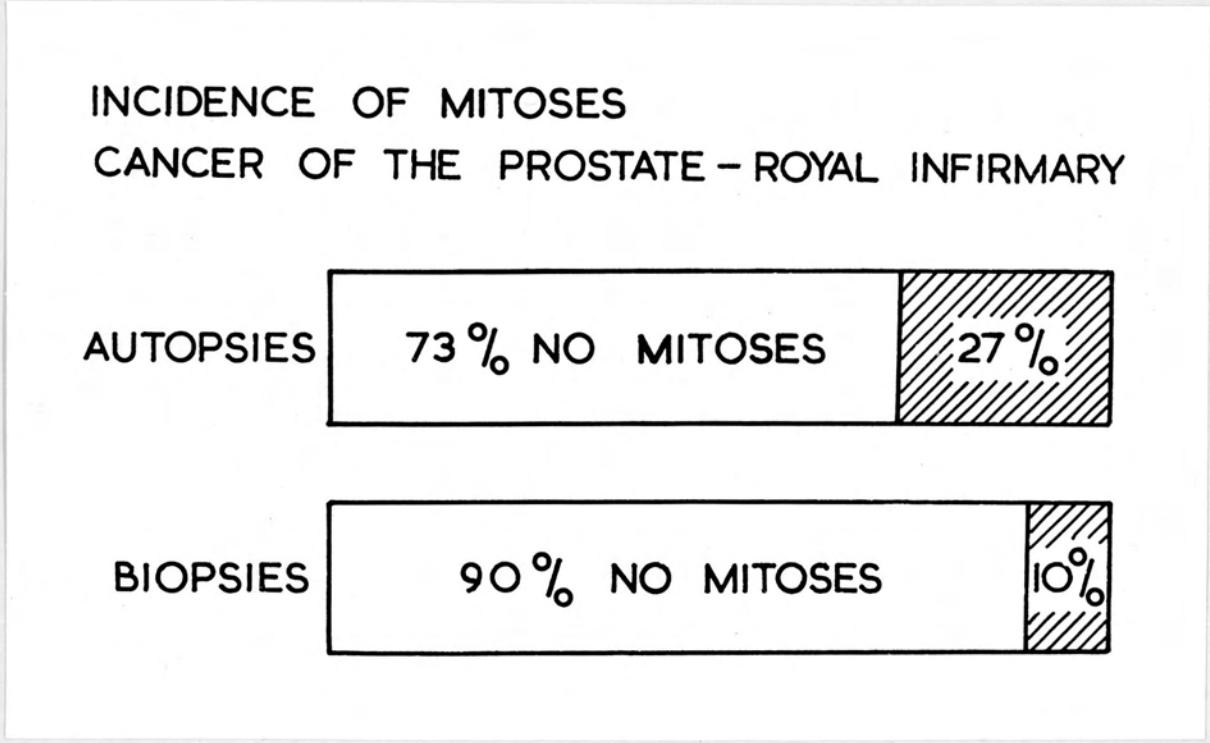
INCIDENCE OF MITOSES
CANCER OF THE PROSTATE – ROYAL INFIRMARY
AUTOPSIES
73 % NO MITOSES
27 %
BIOPSIES
90 % NO MITOSES
10%

Figure 19.

38.

In the histological sections reviewed by me I found only three cases of (1) lymphosarcoma of prostate gland in a boy 16 years of age (Case CHA. 64) and (2) leiomyosarcoma in a man 52 years of age (Vol. XLV - No. 856/ 1948, R.I.E.). The microscopic appearances are illustrated below. There is some degree of distortion in the cellular detail owing to the effects of both oestrogen therapy and pituitary irradiation. (3) spindle cell sarcoma in a man 48 years of age. (Biopsy No. 494/ 1945 R.I.E.).

Regarding the histological types of Carcinoma seen amongst the biopsy series of the Royal Infirmary Cases the results were :

Table 12.
Histological Type of Cancer.

	No.	%
Simple enlargement + Moderately well differentiated adeno-carcinoma	66	42.8
Anaplastic	28	18.2
Moderately well differentiated adenocarcinoma	25	16.2
Well differentiated adeno-carcinoma	17	11.0
Spheroidal Cell carcinoma	12	7.8
Scirrhous Carcinoma	3	1.9
Sarcoma	3	1.9
	154	99.8

Thus/

39.

Thus it is seen that Carcinoma of the prostate gland is very commonly associated with simple enlargement of the prostate (43%). The Anaplastic variety was encountered in 18% of the cases. The moderately differentiated adenocarcinoma was seen in 25 cases (16%). This analysis reveals the important fact that anaplastic forms are seen fairly frequently despite the fact that, in the majority of cases, there was only a delay of approximately 6 months before hospital treatment was obtained. It further stresses the need for early diagnosis. The observation that Carcinoma was associated with simple enlargement in no less than 42.8% of cases emphasises the importance of a histological examination of every prostate gland removed at operation. Of course it might be argued that since the gland has been removed in toto it matters very little as to the pathologists report of the presence of malignancy. The Surgeon will in all probability make a note of this fact but he will not worry the patient by giving him oestrogen therapy and thereby produce a sort of cancer neurosis. It is debateable whether this is the correct attitude that a Surgeon should adopt. As I am a pathologist I make no attempt to voice an opinion on this highly debatable issue.

On examining the Cancer autopsy cases of the Royal Infirmary the results on microscopic examination were :-

Table 13. /

40.

Table 13.

Histological Types - autopsy series.

	No.	%
Well differentiated adenocarcinoma	11	33.3
Moderately well differentiated and simple enlargement	9	27.3
Moderately well differentiated	4	12.1
Anaplastic	3	9.1
Scirrhous	3	9.1
Spheroidal cell	3	9.1
	33	100 %

It was found that, in general, Carcinoma of the prostate gland did not exhibit many mitotic figures. Only 10% of cases in the biopsy series and 27% of cases of the autopsy series showed mitotic figures. Thus mitoses were seen more often amongst the autopsy series. This is in keeping with the finding that the autopsy series in general showed a more advanced growth.

Summary.

The commonest type of growth seen in the biopsy series is the moderately differentiated adenocarcinoma in a gland which has undergone simple enlargement. Anaplastic carcinoma was the second most common type of growth seen.

The autopsy series included a greater percentage of cases showing mitotic figures. This was/

41.

was in keeping with the advanced stage of the cancer in the autopsy cases.

(3) Pathological complications.

It was interesting to compare the ante mortem diagnosis with the post mortem findings in the fifty-eight cases of the autopsy series (Royal Infirmary and Municipal Hospitals).

The condition was correctly diagnosed in 51.7% of the cases. This demonstrates in no uncertain manner the greater number of cases that could be diagnosed with the aid of all auxilliary methods of diagnosis. However, there are still as many cases that are either incorrectly diagnosed or remain undiagnosed. This fact stresses the importance of a postmortem examination of every patient dying in hospital and also the practice of routine examination of the prostate gland.

The following tables set out clearly the results of the analysis.

Table 14.

Pathological Diagnosis in Carcinoma of Prostate.

	No. of cases.	%
Correctly diagnosed	30	51.7
Incorrectly diagnosed	20	34.4
Diagnosis not known	8	13.9

42.

Antemortem diagnosis	No. of cases.
Carcinoma of bowel	3
Carcinoma of stomach	1
Secondary carcinoma in liver	1
Mediastinal tumour	1
Uraemia	8
? Pernicious anaemia	1
Vesical haemorrhage	1
Subdural haematoma	1
Coronary thrombosis	2
Pneumoconiosis	1
	20

It will be noted that in the majority of cases noted above, the diagnosis made before death was that of a complication of the primary neoplasm, the primary growth being undetected.

As a corollary to this section I have analysed the additional postmortem findings besides the main lesion, namely Carcinoma of the prostate gland. These features are arranged in order of frequency :-

Table 15.

Additional pathological changes.

Pathological change	No. of Cases	%
Hydronephrosis	13	42
Hydroureter	13	42
Pyelonephritis	13	42
Cystitis & Pyelitis	5	15.1
Cardiac infarction	4	12.1
Pleural effusion	4	12.1
Bronchopneumonia	4	12.1
Left ventricular hypertrophy	3	9.2
Dilatation & Hypertrophy of bladder	2	6.06
Nephrosclerosis		
Pulmonary infarction		
Infection of pelvic tissues	1	3.03
Gynecomastia	1	
Anaemia	1	
Osteomyelitis of bone	1	
Acute yellow atrophy of liver		
Pathological fracture		

43.

It is not unnatural to find Hydronephrosis, Hydroureter, Pyelonephritis, Cystitis and Pyelitis being the most frequently occurring complications. These are all produced, in the main, as a result of obstruction to outflow of urine by the enlarged prostate gland. (The gland was found to be enlarged in the majority of the cases of Carcinoma of the prostate). Infection of the bladder resulting from stasis of urine occurred in only 15.1% of the cases. One would have thought that this complication would be seen more frequently. This relative paucity of cases might be explained by the fact that the patients do not live a sufficiently long period for the full blown lesion to appear more often. No doubt the end of the ureters are involved by the cancerous process in quite a number of cases - following direct extension into the bladder. The bladder was noted as being the third most common site for metastasis, but, as a result of lesions elsewhere, for example, Bronchopneumonia (12.1%) death intervened and so cut short the likelihood of developing a pelvic cellulitis. The development of Serous effusion as a complication of prostatic carcinoma is extremely interesting. In fact, it is more significant when one sees that it occurs as often as 12.1% in so small a series as thirty-three autopsies. This information may not be alarming to a pathologist who is well aware of the fact that the lung is the commonest site for secondary deposits of blood borne metastases from a primary growth in the prostate ; but, the general practitioner will benefit/

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benefit in no small measure from this knowledge. The true significance of this statement is illustrated very well by Case No.1. I will not describe the details here as it will break the continuity of the subject under discussion. I would ask the reader to refer to the Appendix for further details of this interesting case.

Cardiac infarction.

The association of cardiac infarction with atherosclerosis is a well known factor in the pathogenesis of coronary artery disease.

Cardiac infarction was seen as an additional post mortem finding in 12.1% of the autopsy cases of Carcinoma of the prostate gland. This observation is an extremely interesting one. There is evidence that there is an increased incidence of atherosclerosis amongst women after the menopause (Kornerup, 1950). This fact throws light on the pathogenesis of atherosclerosis. Other endocrine factors probably also play a role in the pathogenesis of atherosclerosis (Heinbecker, 1951), especially since serum cholesterol may be a precursor of the adrenal cortical hormones (Conn et al, 1950). Related to this also is the demonstration that Cortisone and adrenocorticotropic hormone may produce changes in serum cholesterol levels (Adlesberg et al, 1950) and alter the rate of development of experimental atherosclerosis (Oppenheim et al, 1952). These statements will now be examined in relation to Carcinoma of the prostate gland. In the first place the age period of/

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of the onset of the male menopause is still obscure. The only indication at the moment, is the occurrence of simple enlargement of the prostate gland. It is for future research to clarify this situation (See later - future progress section). However, it might be stated that with the onset of the male menopause there is an increased incidence of atherosclerosis. It is known that adrenal cortical hormones are closely linked up with the behaviour and growth of Carcinoma of the prostate and therefore there is a very great probability of the influence of these hormones in the serum cholesterol level and eventually on the incidence of coronary disease in the aged male. Therefore the fact that 12.1% of the cancer cases show evidence of coronary infarction is of great significance. The use of oestrogens in the treatment of coronary occlusion emphasises further the close inter-relationship between coronary artery disease - hormonal balance and Carcinoma of prostate.

Left ventricular hypertrophy : Nephrosclerosis, Hypertrophy and Dilatation of the Urinary bladder are all pathological changes following obstruction to the prostatic urethra. The very carefully written monograph by Wade (1914) throws light on this observation in these words " during the post mortem examination of patients who have died of various diseases in the medical wards of the hospital, there can frequently be observed, in male subjects over the age of fifty years, indications of a mild degree of chronic prostatic disease with associated damage to the urinary tract above. It is usually unsuspected: /

46.

unsuspected: in these cases, however, the ureter and renal pelves are dilated to a moderate extent and there is present a recent interstitial nephritis throughout both kidneys."

Gynecomastia was noted only in one case. One might have expected to find this change in the nipples occurring more frequently in view of the fact of the wide use of oestrogens in the treatment of Carcinoma of the prostate gland.

Anaemia was present in one case. This is probably not the true frequency of this complication when one considers the frequency of secondary metastatic involvement of bone.

Acute yellow atrophy and osteomyelitis of bone are in all probability merely incidental findings. Consequently they do not merit further discussion.

Pathological fracture. This is due to deposit, either in a localised or diffuse form, of the primary growth travelling via the blood stream and finally settling down in the medullary cavity. The metastases are generally osteoblastic in nature and therefore give rise to increased density of the bone. At times the new bone thus formed is spongy and of a soft texture - osteolytic deposits. Von Recklinghausen believed that the tumour cells blocked the sinuses and gave rise to a condition of congestive hyperaemia leading to the growth of osteoid tissue and bone (Muir 1934). The first indication of the presence of deposits in bone is pain, sciatic or lumbar in distribution, and often worse on sitting down (Riches, 1948). This complication occurred/

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occurred in one case.

(12) MODE OF SPREAD AND DISTRIBUTION OF METASTASES OF PROSTATIC CARCINOMA.

(a) Mode of spread.

Malignant growths, in general, may spread in the following ways :-

(1) Direct extension.
(2) Lymphatic spread.
(3) Blood spread.

(1) The spread of carcinoma of the prostate is no exception to this rule. The structures most commonly involved by direct extension are the rectum, bladder, pelvic tissue and ureters.

In discussing the involvement of the rectum by cancer of the prostate Lazarus (1946) describes three stages of spread. He states " in the first place the rectal lumen may be occluded by pressure of the pelvic structures involved in a diffuse invasion which binds the prostate, seminal vesicles, bladder and rectum into a firm mass to the pelvic bones. Or the tumour may extend into the wall of the rectum and start to grow there as an intra-mural tumour causing occlusion of the lumen without actually eroding the mucosa." Finally the tumour may extend directly through the entire thickness of the rectal wall and present itself as a fungating growth in the lumen (Jackman and Anderson 1952).

(2) Lymphatic spread.

The lymph vascular system is a common route along which malignant disease is conveyed either as emboli or by permeation. Shields Warren and co-workers (1936) stress the part played by perineural lymphatics/

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lymphatics in the spread to the pelvis and lumbar vertebrae, but Willis (1948) criticises this work in the following terms - " this opinion was based on the frequent finding of cancerous permeation of these lymphatics in the periprostatic tissues in 7 cases with metastases in these bones. It must be noted, however, that 4 of the 7 cases had visible metastases in the lungs, that there is no record of microscopical search of the lungs for tumour emboli in the other 3 cases, that only the pelvis and lumbar vertebrae were subjected to special examination, and there was no necropsy study of the distribution of tumours in other parts of the skeleton, and that the authors admit while perineural permeation was common in the periprostatic tissues - " very little evidence was found of involvement of nerves or of their lymphatics extending towards the bony pelvis. " Roberts (1927) also throws some light on the role of lymphatics in the spread of carcinoma of the prostate gland. He suggests the lymphatics of the intra-spinous ligaments and the lymphatics in the loose connective tissue lying on the surface of the levatore ani and coccygeus muscles might constitute an important route for the spread of prostatic carcinoma in axial skeleton.

(3) Blood spread (usually distant).

The blood stream affords a ready means by which malignant emboli may be widely disseminated. It is logical to assume that the arterioles and capillaries will lodge the tumour emboli in the first instance. The lungs will, in all probability harbour/

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harbour the emboli conveyed there by way of the systemic veins and the lymphatic vessels. Those emboli travelling in the portal vein will finally rest in the liver and lastly the emboli traversing the pulmonary veins and left ventricle will be distributed far and wide in the peripheral organs by way of the systemic circulation. In the series under discussion there are many examples of the spread of carcinoma of the prostate. These will be referred to later. They will also be illustrated by photo-micrographs. The suggestion put forward by Batson (1940) regarding the role of the vertebral venous system in the spread of carcinoma of the prostate is noteworthy. This intricate venous system was first described by Breschet in 1832. However, it was left to Batson to demonstrate its importance in the spread of Carcinoma of the prostate gland. Batson showed that the pelvic connections of the deep dorsal vein of the penis are the same as those of the prostatic plexus. Thick radio-opaque material injected into the dorsal vein of the penis of the adult cadaver passed into the prostatic plexus, along the vessels of the lateral pelvic wall and could be forced into the sacral canal and the veins of the iliac bones. The whole pattern is a replica of the spread of carcinoma of the prostate and under certain conditions material injected into the dorsal vein could be made by direct spread to enter the veins in and about the sacrum and lumbar vertebrae and proceed up the spine eventually extending into the intercostal veins. Willis (1948) suggests/

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suggests spread to bone via systemic arteries after passing through caval circulation. The work of Coman and others (1951) which consisted of injecting suspensions of viable tumour cells into the femoral veins of rats and rabbits while slight abdominal pressure was applied throws light on this mode of spread. The animals were later killed and the distribution of the tumour studied. The results were in accord with the concept that the frequency of spontaneous tumour metastases to the vertebral column from pelvic tumours in man depends on the entrance of tumour cell emboli directly into the vertebral system by passing the lungs. This experimental work confirms Batson's work. We have further confirmation of this work in a very recent study by Franks (1953) who injected suspensions of barium via the dorsal vein of the penis and later radiographed the bodies of the human material. He has demonstrated very beautifully a direct communication between the prostatic veins, the vertebral venous system and the veins of the pelvic bones.

(b) Distribution of metastasis in Prostatic Carcinoma.

i. Lymph node. ii. Skeletal. iii. Visceral.

In the entire series of 58 cases (Royal Infirmary (33) and Municipal Hospital (25) autopsies) no less than 95.4% showed lymph node metastases. There were visceral metastases in 82.9% of the autopsies examined and 32.9% showed metastases in skeletal structures, such as bone, muscle and pelvic tissues. This latter figure represents the lower limit of the incidence in skeletal structures for routine examination of the skeleton had not been performed./

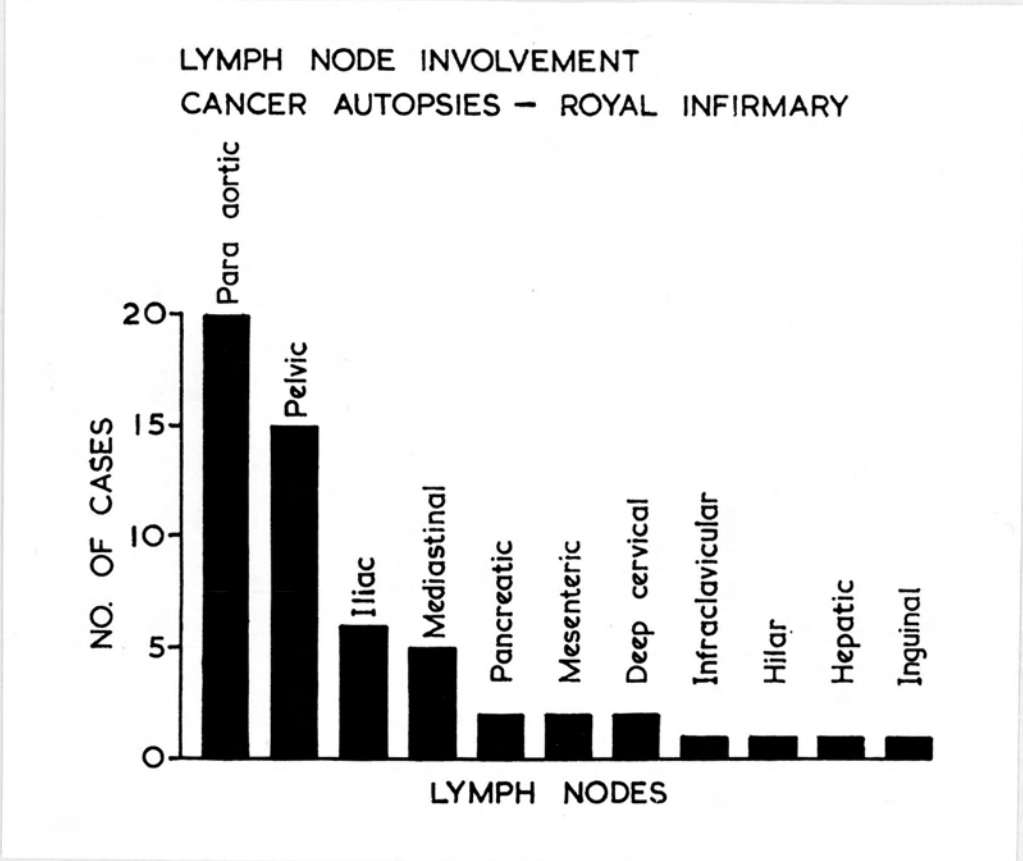
LYMPH NODE INVOLVEMENT
CANCER AUTOPSIES – ROYAL INFIRMARY
NO. OF CASES
0
5
10
15
20
Para aortic
Pelvic
Iliac
Mediastinal
Pancreatic
Mesenteric
Deep cervical
Infraclavicular
Hilar
Hepatic
Inguinal
LYMPH NODES

Figure 20.

51.

performed. The actual figures would therefore be very much higher.

(i) Lymph node involvement.

The prostate gland is very richly supplied with lymphatic vessels (Sappey), therefore it is not unnatural to find that 95% of the autopsy cases showed lymph node involvement. The commonest node showing carcinomatous deposit was the para-aortic (46.7%). The next most common site of involvement were the pelvic nodes (34.4%). The iliac nodes were involved in 17.2% of the cases.

Table 16.

Observations from the literature - Lymph node involvement in Carcinoma of prostate.

Author	Material	Percentage of lymph node involvement.
Pasteau (1898)	Autopsy	Iliac (87), Retro- peritoneal (27), Inguinal (36).
Wolff (1899)	Autopsy	Pelvic (45.5), Inguinal (8.8).
Kaufmann (1902)	Autopsy	Pelvic (85), Axillary (5).
Young (1909)	Surgical	Inguinal and pelvic (19.8).
Motz & Majewski(1917)	Autopsy	All lymph nodes (99).
Bumpus (1926)	Surgical	Inguinal (.18), Cervical (10).
Dossot (1926	Autopsy	Pelvic (55.2), Common iliacs (55), iliacs (44.7), retroperitoneal (86.8).
Muir (1934)	Autopsy	Int. iliac (73), Ext. iliac (50), Lumbar aortic (42), Inguinal (23), Thoracic (19), Supra-clavicular(19).
Crowell (1940)	Autopsy	Pre-aortic (38), Inguinal (2.5), Pelvic (2.5).
Thomson-Walker (1948)	Surgical	Inguinal (16).
Willis (1948)	Autopsy	All nodes (65).
Author (1953)	Autopsy	Para-aortic (46.7), Iliac (17.2), Pelvic (34.4), Inguinal (2.2).

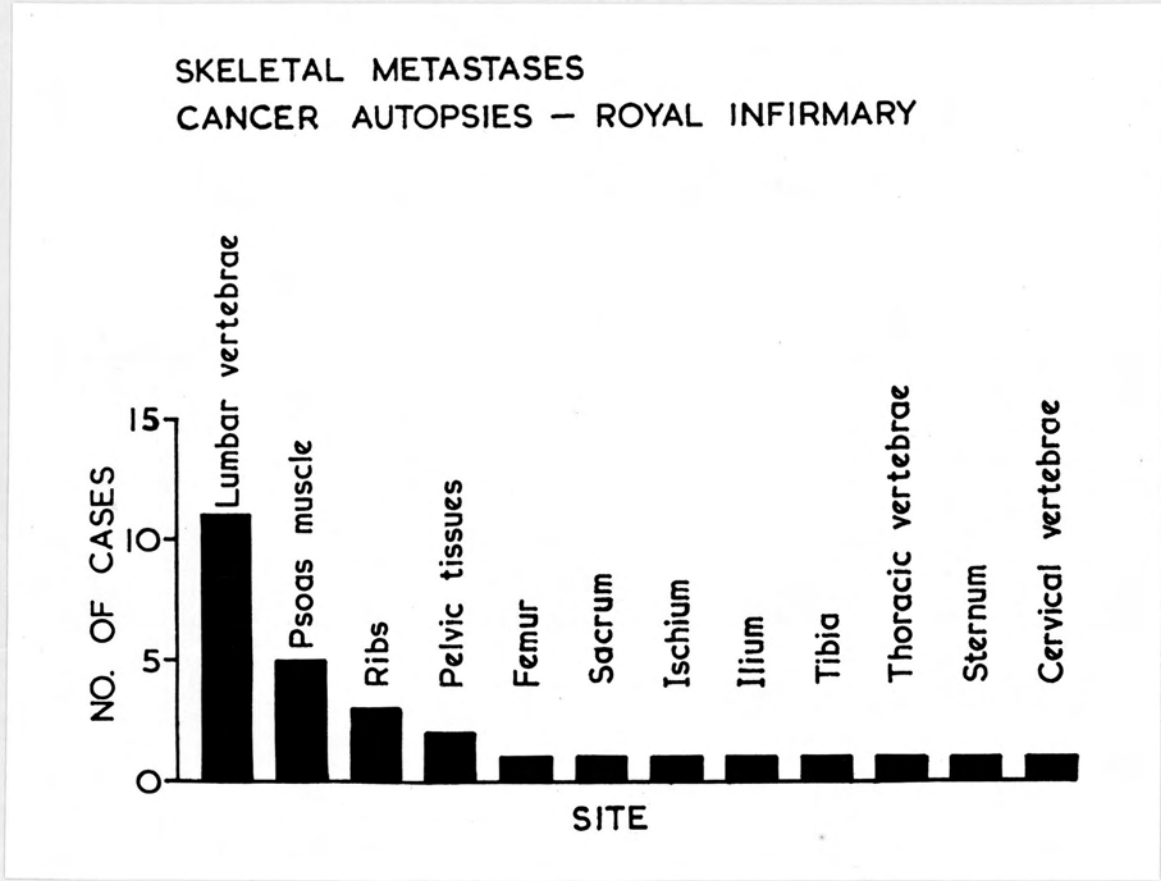
SKELETAL METASTASES
CANCER AUTOPSIES — ROYAL INFIRMARY
NO. OF CASES
0
5
10
15
Lumbar vertebrae
Psoas muscle
Ribs
Pelvic tissues
Femur
Sacrum
Ischium
Ilium
Tibia
Thoracic vertebrae
Sternum
Cervical vertebrae
SITE

Figure 21.

52.

A survey of the literature with regard to lymph gland involvement reveals the following facts -

(a) In clinical series of carcinoma of the prostate, the commonest set of lymph nodes involved is the Inguinal (16.18 %).

(b) In autopsy series, the iliac nodes (para-aortic, ext. iliac, int. iliac) are the commonest group involved.

(ii) Skeletal metastases.

Skeletal metastases were seen in 31.8% of the series investigated by me. The lumbar vertebrae were involved to the extent of 35.1%. The next most common site was the psoas muscle (18.5%). The ribs were involved to the extent of 10.7%. The pelvic tissues were the site in 7.1% of cases.

The cancer deposits examined radiologically (See fig. 22)revealed the fact that the metastases were distributed in the following order of frequency - Pelvis, Lumbar vertebrae, Ribs, Thoracic vertebrae, Femur and Sacrum.

Below is a table showing the observations of other workers.

Table 17. /

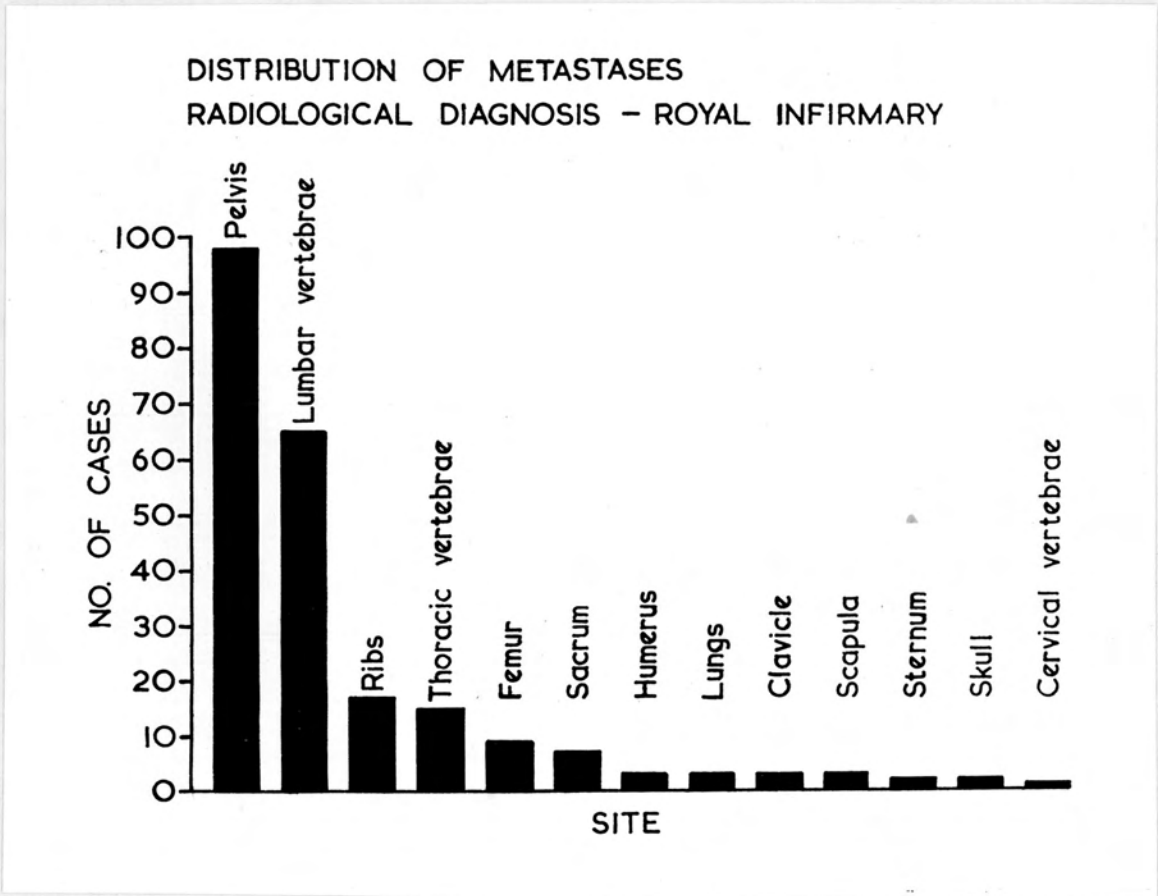
DISTRIBUTION OF METASTASES
RADIOLOGICAL DIAGNOSIS – ROYAL INFIRMARY
NO. OF CASES
0
10
20
30
40
50
60
70
80
90
100
Pelvis
Lumbar vertebrae
Ribs
Thoracic vertebrae
Femur
Sacrum
Humerus
Lungs
Clavicle
Scapula
Sternum
Skull
Cervical vertebrae
SITE

Figure 22.

53.

Table 17.

Observations from Literature - Skeletal metastases.

Author	Observations.
Kaufmann (1902)	Lumbar vertebrae 79.41% ; Femur 67.6 %; Ilium 61.7 % ; Ribs 61.7 %
Purckhauer (1929)	Lumbar vertebrae 90% ; Femur 36.6 % ; Pelvis 23.3 % ; Ribs 13.3%.
Copeland (1931)	Pelvis ; Vertebrae ; Femur Tibia ; Skull.
Mintz & Smith (1934)	Vertebrae 95.2 % ; Ribs 47.6 % ; Pelvis 61.9 % ; Femur 14.2 % ; Skull 9.5 % ; Clavicle 4.7 %.
Muir (1934)	Vertebrae ; Pelvis ; Ribs ; Femur ; Skull ; Clavicle.
Blumer (1934)	(1) Vertebrae ; (2) Ribs ; (3) Pelvis ; (4) Femur ; (5) Skull ; (6) Sternum ; (7) Humerus ; (8) Tibia ; (9) Scapula ; (10) Clavicle ; (11) Fibula ; (12) Forearm.
Willis (1948)	Lumbar vertebrae 52.9 % Femur 22 % ; Ribs 57.3 % ; Skull 35.2 % ; Pelvis 19%.
Arnheim (1948)	(1) Vertebrae ; (2) Ribs ; (3) Pelvis ; (4) Sternum ; (5) Femur ; (6) Skull ; (7) Clavicle.
Author (1953)	Lumbar vertebrae 35.1 %; Psoas muscle 18.5 %.; Ribs 10.7 % ; Pelvic tissues.

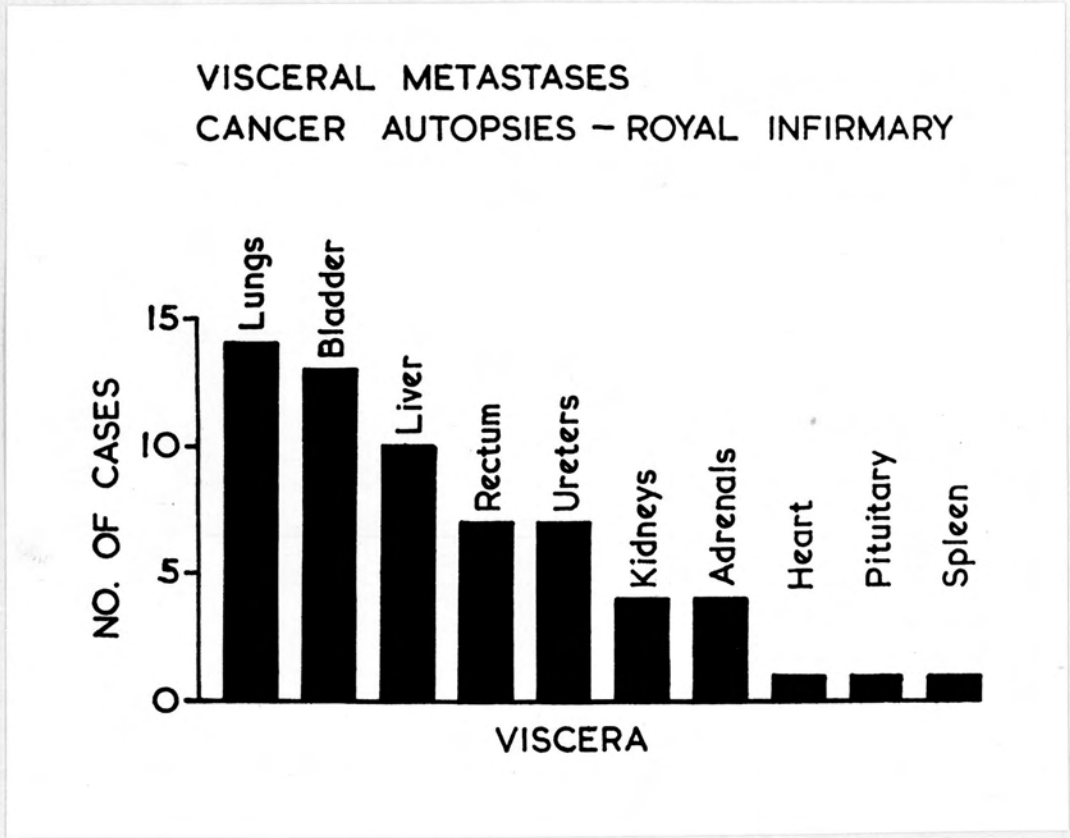
VISCERAL METASTASES
CANCER AUTOPSIES – ROYAL INFIRMARY
NO. OF CASES
15
10
5
0
Lungs
Bladder
Liver
Rectum
Ureters
Kidneys
Adrenals
Heart
Pituitary
Spleen
VISCERA

Figure 23.

54.

It will be seen, therefore, that of the vertebrae the lumbar are the most commonly involved. The ribs appear to be the next most common site, and then the pelvis : of the leg bones, the femur is the site of choice for a metastatic deposit of prostatic carcinoma.

(iii) Visceral metastasis.

Visceral metastases from prostatic carcinoma were found in 82.9% of the total series of eighty eight autopsies. The distribution was as follows :

Lungs 23.2 % : Bladder 21.9% : Liver 16.4 % : Rectum and Ureters 10.9 % : Adrenals 6.8 % : Kidneys 5.4 % : Heart ; Spleen ; and Pituitary were each 1.3 %.

I tabulate below the findings of other workers for comparison :-

Table 18. /

55.

Table 18.

Observations from the Literature - Visceral Metastases.

Author	Observations.
Willis (1948)	Lungs 40% ; Liver 20% ; Spleen & Adrenals 6.6 %.
Arnheim (1948)	Lungs : Liver : Pleura : Adrenal gland, Kidney, Peritoneum, Spleen. Skin : Pancreas : Brain : Stomach : Small intestine : Colon : Mesocolon : Gall bladder.
Mintz & Smith (1934)	Lungs 24 %; Liver 20%; Kidneys 3%; Ureter, Suprarenal, Pancreas, Gall bladder, Pericardium, Eye, Penis, Skin, 1%.
Muir (1934)	Lungs 19% ; Liver 15% ; Suprarenals 8% ; Kidneys, Skin, Dura mater, Heart and Wall of ureter 4% each.
Author (1953)	Lungs 23.2 % ; Bladder 21.9 %; Liver 16.4 % ; Rectum and ureters 10.9% ; Adrenals 6.8 % ; Kidneys 5.4 %; Spleen, Heart, and Pituitary 1.3 %.

Summary - The lungs are the commonest site of blood borne metastatic deposits ; secondly the bladder ; the liver was the next most common organ involved. The involvement of the Adrenals is much commoner than one would expect.

(13) OESTROGENIC EFFECTS OF PROSTATIC CARCINOMA.

The changes that occur have been described by others - Huggins, Scott and Hodges (1941) ; Huggins and Hodges (1941) ; Kahle, Schenken and Burns (1945) ; Reynolds, Schulte and Hanner (1950). Ferguson and Franks (1953) have attempted/

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attempted to correlate the changes produced by the oestrogens with the clinical picture. McCarty (1947) has described the effects of oestrogen therapy on osseous metastases.

There have been no studies describing the changes produced by oestrogen therapy both on the primary growth and also on the metastatic deposits.

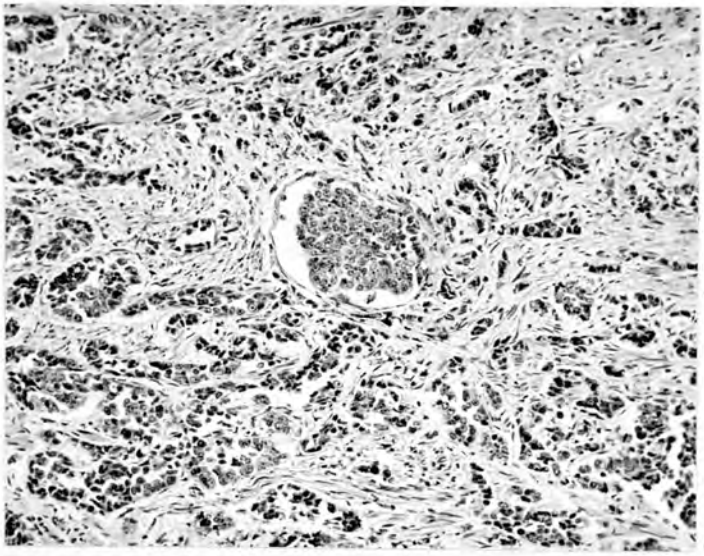
Although I have been able to gather together only ten cases from amongst the autopsies performed during the period 1936-52 which have been treated with oestrogens, still it will serve to illustrate some of the changes produced by prolonged oestrogen therapy. Amongst the biopsy material I was able to collect sixteen cases which had been treated with oestrogens. The fact that these patients were readmitted after oestrogen therapy had been instituted proves that this form of treatment does not cure the condition. There is always the possibility of a recurrence of obstructive symptoms. The photomicrographs shown below illustrate (i) the changes seen in the primary growth and the metastases (ii) the difference in response shown by metastases in different organs, and in lymph nodes and bone.

The changes I have been able to demonstrate are similar to what has been described in the literature.

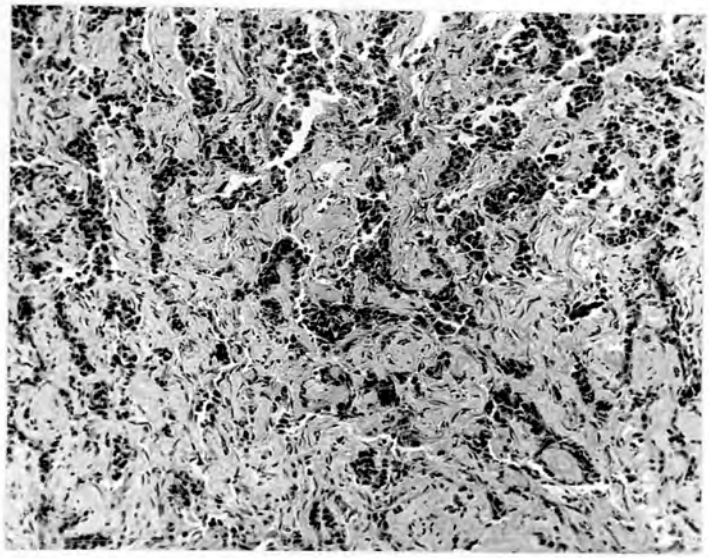
To summarise the changes seen :-

A. <u>Primary growth</u>.

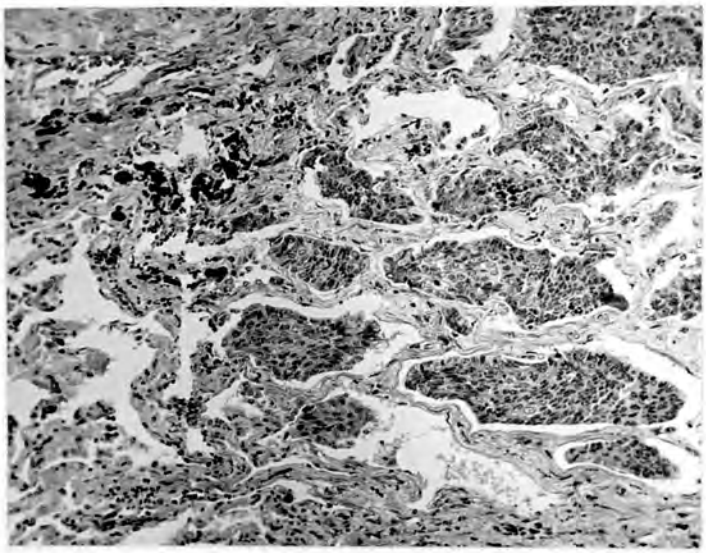
1) Reduction in number of papillary infoldings and/



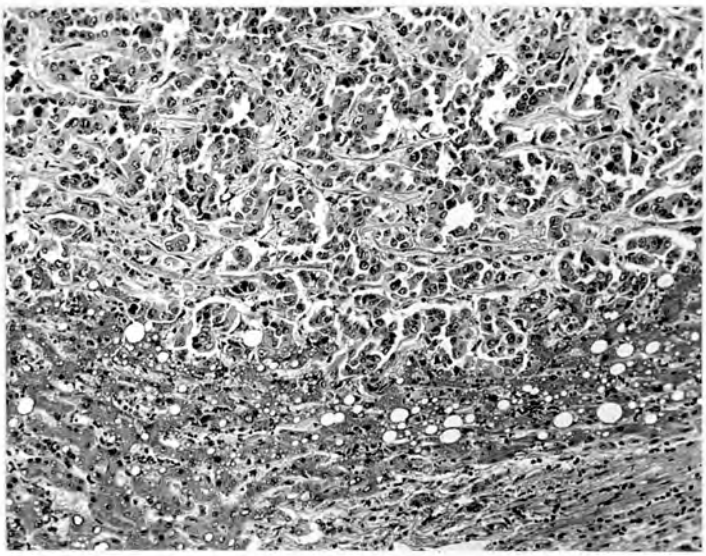
MHA. 3308. Prostate (1). Moderately well differentiated adenocarcinoma after 3 months oestrogen therapy. Note regressive changes in some acini and also formation of fibrous tissue in stroma. Anaplastic areas with mitotic figures not affected by oestrogens. Haematoxylin & Eosin x 120.



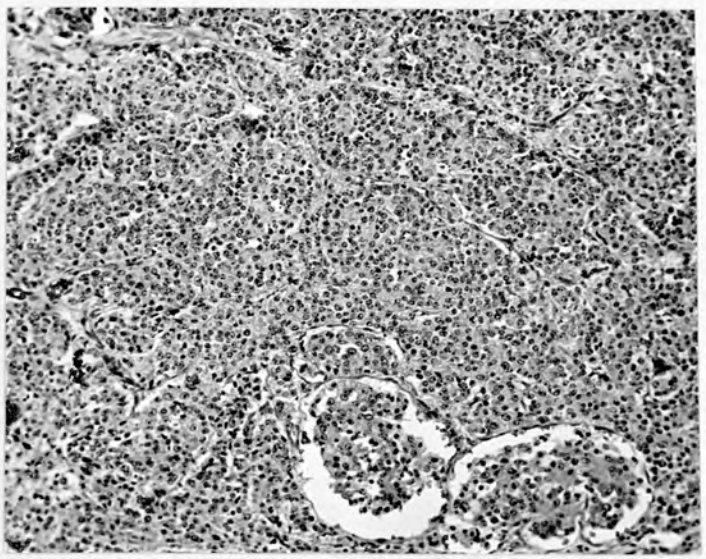
MHA. 3308. Prostate (2). Another area showing marked scirrhous reaction of stromal tissue. Note the " pyknotic " nuclei of the glandular tissue indicating response to oestrogen therapy. Haematoxylin & Eosin x 120.



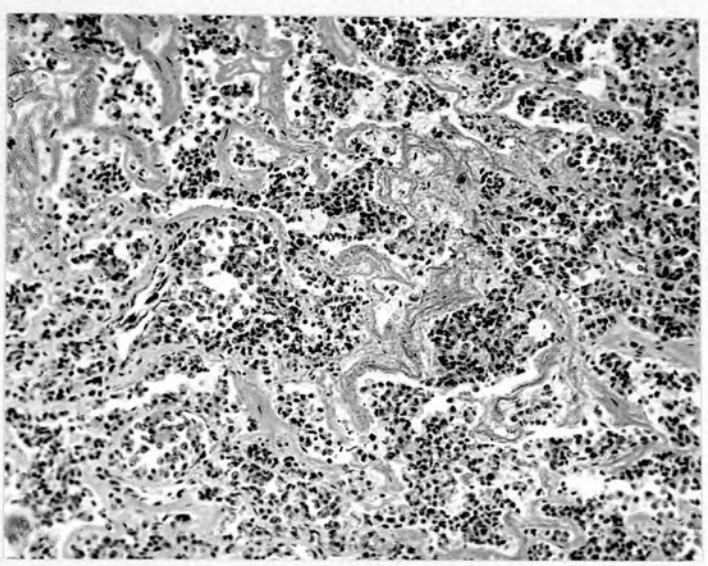
MHA. 3308. Lung. Anaplastic type of adenocarcinoma. Poor response to oestrogen therapy. Haematoxylin & Eosin x 120.



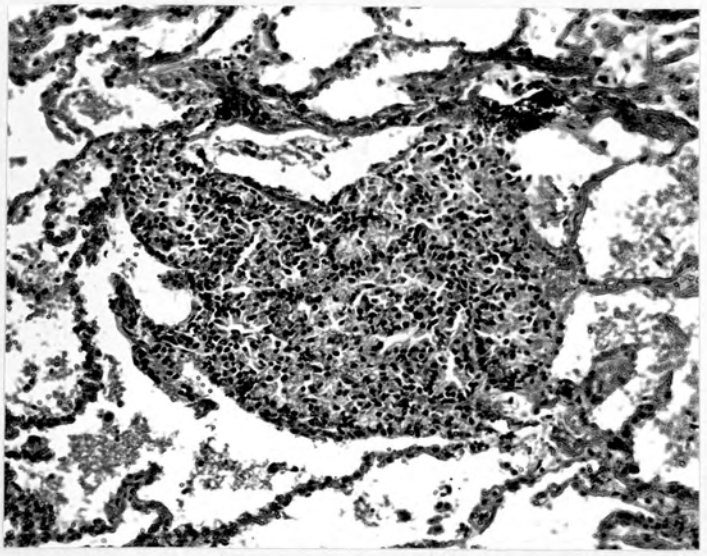
MHA. 3308. Liver. Anaplastic carcinomatous deposit with hyperchromatic nuclei and numerous mitotic figures. Poor response to oestrogen therapy. Haematoxylin & Eosin x 120.



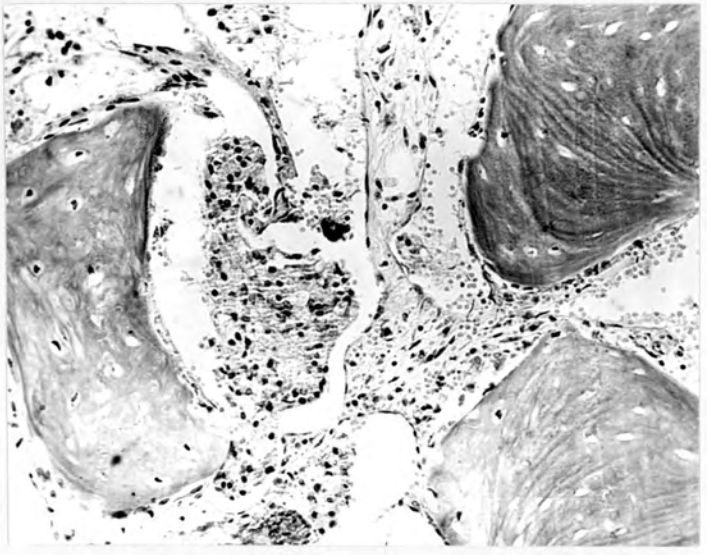
B. 2936. Prostate(1). Anaplastic adenocarcinoma. Numerous mitoses. Haematoxylin & Eosin x 120.



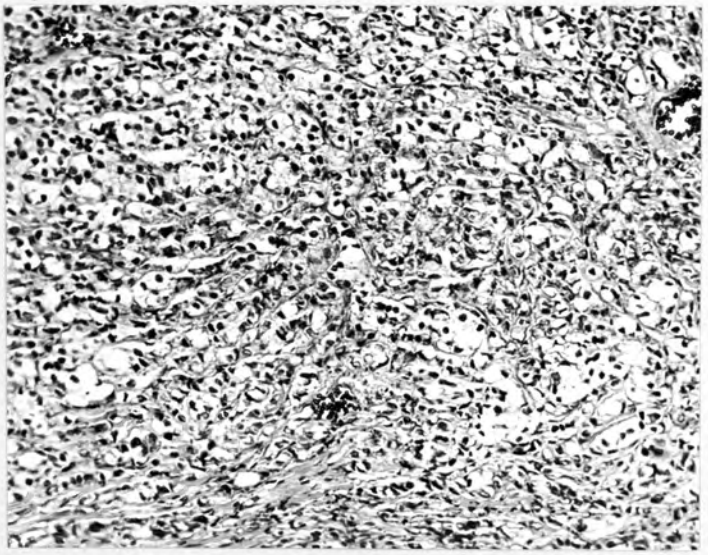
MHA. 2936. Prostate(2). Same case. Note coarse strands of fibrous tissue amidst the pyknotic nuclei. More open structure. After 6 months Oestrogen therapy. Poor response. Haematoxylin & Eosin x 120.



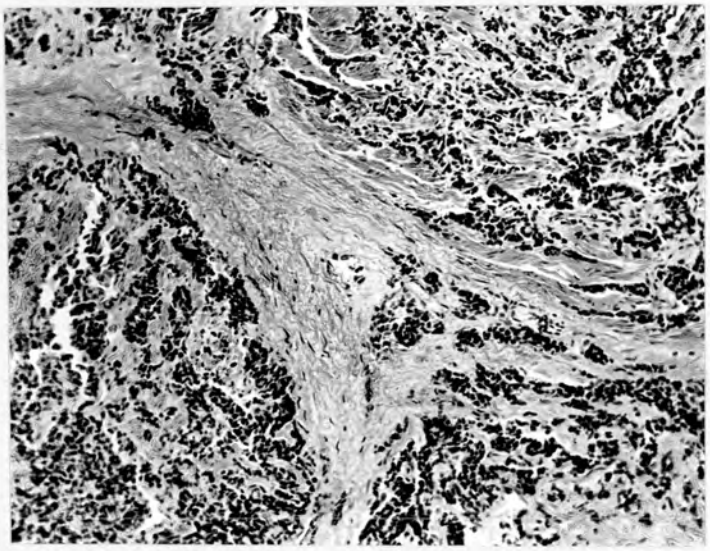
MHA. 3621. Lung. Metastatic nodule undergoing regression. Note pyknotic nuclei. Haematoxylin & Eosin x 120.



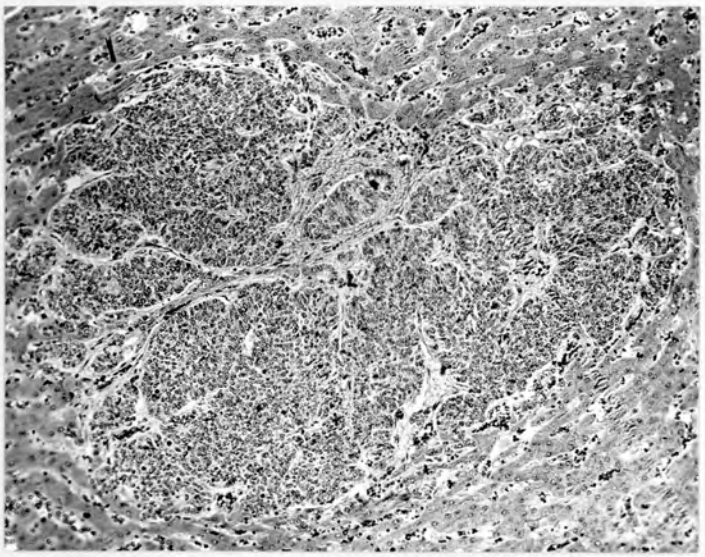
MHA. 3621. Rib. Metastatic deposit undergoing regression. Haematoxylin & Eosin x 170.



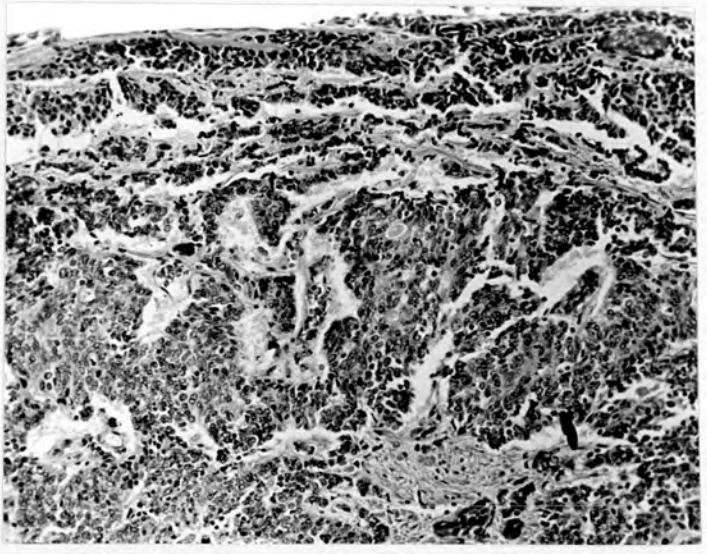
B. 1857. Prostate. Biopsy taken on 10.2.47. Note nuclei pushed to one side. Vacuolated cytoplasm. Cell walls seen. Haematoxylin & Eosin x 150.



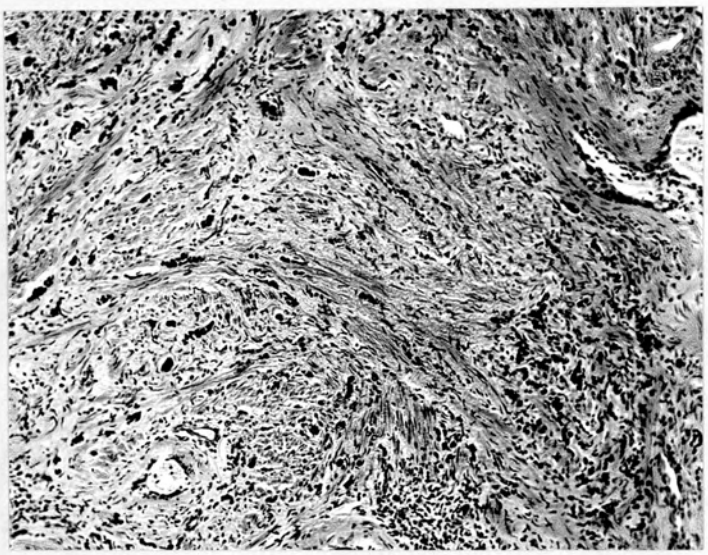
A. 2711. Prostate. Spheroidal-cell type of adenocarcinoma. Nuclei pyknotic. No acinar formation. Haematoxylin & Eosin x 120.



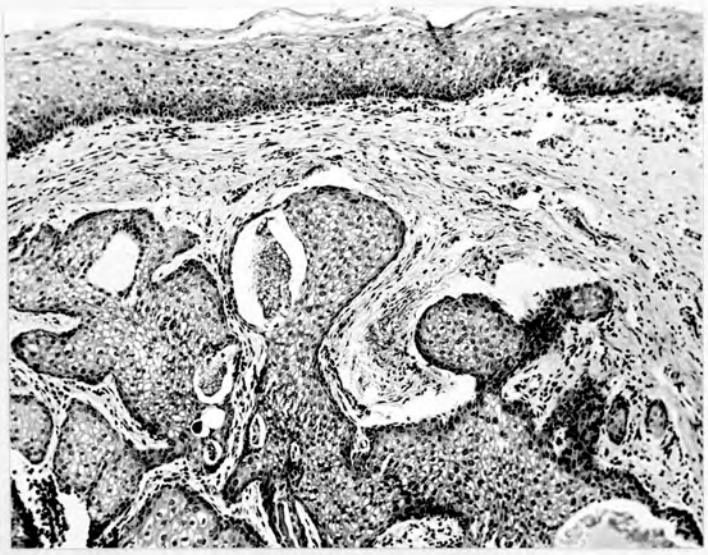
A.2711. Liver. Anaplastic type of adenocarcinomatous nodule. Note numerous mitotic figures. Haematoxylin & Eosin x 90.



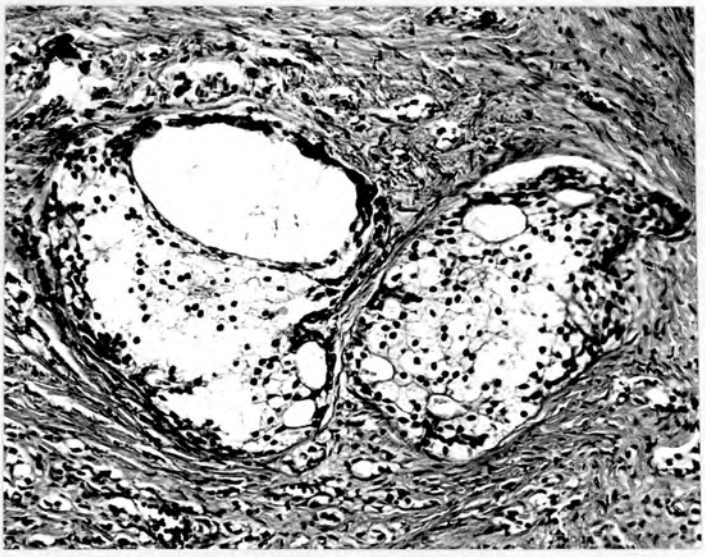
A. 2711. Lung. Highly anaplastic sub-pleural tumour deposit. Numerous mitotic figures. Poor response to oestrogen therapy. Haematoxylin & Eosin x 150.



P.B. 59. Prostate. Remnants of glandular tissue. Increase of fibrous tissue in stroma. Extremely good response to Oestrogen therapy. Haematoxylin & Eosin x 90.



L. 1309. Squamous metaplasia of trans-urethral epithelium following Oestrogen therapy. Haematoxylin & Eosin x 90.



B. 1857. Prostate. Marked vacuolation of cells. Nuclei pushed to one side. Increase of fibrous tissue in stroma. Oestrogenic effect. Haematoxylin & Eosin x 150.

A. 2711. Breast. Gynecomastia. Dilatation of duct with slight round cell infiltration in periphery. Haematoxylin & Eosin x 90.

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and in height of epithelium.

2) Vacuolisation of cytoplasm : displacement of nucleus.

3) Decrease in size of acini.

4) Progressive condensation of chromatin material.

5) Loss of nucleoli and of mitotic figures, pyknosis.

6) Squamous metaplasia.

B. Metastases.

1) Disappearance of nuclear membrane.

2) Loss of staining qualities of cytoplasm and clumping of nuclei.

In general those tumours showing the least cell differentiation show the poorest response to therapy.

Side effects were :

1) Pigmentation of nipples.

2) Gynecomastia.

3) Oedema of extremities.

4) Diminution in size of testes.

(14) CONSIDERATION OF THE MODE OF ACTION.

Having previously discussed the endocrine background of the prostate and also the changes brought about by the use of oestrogens, it is only logical to consider for a moment the manner in which these effects are produced.

A study of the literature shows that there are very few observations on this important and extremely fascinating problem. Nicol (1952) puts forward/

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forward a rather ingenious theory to the effect that oestrogens stimulate the reticulo-endothelial macrophages in the spleen, liver and lymph nodes. Prolonged oestrogens leads to mobilization of the macrophages in these organs and to their accumulation in the secondary sex organs. In orchidectomised animals, oestrogen therapy produced marked fibrosis in the prostate, and the findings suggest that this is probably the result of transformation of the macrophages into fibroblasts, and later into fibrous tissue.

However, Dodds (1946) seems to think that " it is still doubtful, whether, in addition to inhibition of androgens, the synthetic oestrogens exert some definite controlling influence on the malignant cells themselves. " Gutmann (1946) believes that oestrogens such as Stilboestrol act by inhibiting the secretion of pituitary gonadotrophin, thus reducing the secretion of androgens by the testis and suprarenals. This belief is based upon the theory propounded by Huggins and Hodges (1941) that human prostatic cancers fall into two groups, androgen dependent and androgen independent. In the laboratory it has been found that the testes are not the only source of androgen; the adrenals also secrete this type of hormone, though of a kind and quantity that are relatively ineffective. After castration, the adrenal glands enlarge and their secretion of androgen is amplified. This increased androgen production by the/

the adrenals might conceivably account for recurrence of an androgen sensitive prostatic cancer some time after its growth has been checked by castration. In the experimental field of cancer production Horning (1946) puts forward the suggestion that atrophy of prostatic tumours after oestrogen therapy is possibly due to failure of optimum androgen secretion due to a drop in gonadotrophin production. Those tumours which fail to regress are possibly receiving sufficient androgen stimulation from the adrenal cortex.

Inhibition of secretion and degeneration of the epithelium in these tumours are so similar to the changes induced in the normal prostate following castration or oestrogen administration that any more complicated mechanism operating in the case of tumour bearing mice seems unnecessary. Dean, Woodward and Twombley (1947), however, have critized the theory of Huggins and Hodges (1941) that castration and Stilboestrol both exert their effects on human prostatic cancer by inhibiting androgen output, since they claim that castration raises the 17 ketosteroid excretion, whereas stilboestrol depresses it.

Dodds (1946) sums up the situation when he states in a British-Swiss Medical Conference on Oestrogens and Cancer - " the exact mode of action of oestrogens in cancer of the prostate has still to be worked out. The changes in the serum level of acid phosphatase indicate that the metabolism of the malignant cells is interfered with. A

60.

possible explanation for the occasional failure of oestrogen therapy is that these tumours may be due to the malignant development of other cells over which androgens have no control. Again, the question arises whether the improvement arising from oestrogen therapy is due to a change in the endocrine balance or to the specific action of the drug on a certain type of cell. He closes his remarks by stating that a committee has been set up by the Royal Society of Medicine and British Empire Cancer Campaign to investigate a large number of cases of carcinoma treated with synthetic oestrogens and to follow them up over a long period. The reports from this Committee should be helpful in stimulating further research and perhaps offer clues to a solution of the problem of cancer of the prostate gland. "

(15) Symptomatology.

The following features will be considered :-

(i) Duration of symptoms (a) at time of admission;
(b) prior to admission.

(ii) Frequency.

(iii) Variety of symptoms.

(iv) Early symptoms.

(v) Late symptoms.

(vi) Comparison of symptoms in cancer and simple enlargement of prostate.

(vii) Observations from the literature.

1. (a) Duration of Symptoms At time of admission.

To facilitate this study I have prepared tables showing the duration of symptoms in both the/

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the biopsy and autopsy series. The first observation that strikes one is the varying periods of the different symptoms. They extend from a few days to over ten years. There were thirty five cases (22%) with symptoms ranging from one to five days. These were acute retention, overflow incontinence, oedema of legs and sacrum. The symptoms of long duration were frequency and difficulty with micturition - there were only 3 cases (1.9%).

(b) Prior to admission to hospital.

This estimation was made from a study of 369 cancer cases which had been seen at the Radio-therapy Department of the Royal Infirmary from 1936-1952. There were no less than 228 cases (16.7%) with symptoms under one year. The largest % (27) of cases delayed 6 - 12 months before seeking medical aid. There was 1% of cases with symptoms extending over 10 years.

ii. Frequency of symptoms.

The commonest symptoms amongst Royal Infirmary biopsy cases were frequency of micturition (40%) and difficulty with micturition (27%). Acute retention of urine compelled 18% to seek hospital treatment. Haematuria was present in 0.6% of the cases. Pain accounted for 1.3% of the cases. Constant dribbling of urine or overflow incontinence was sufficiently compelling to make 3.2% of the cases to enter hospital at an early date.

iii. Variety of symptoms.

It is the protean nature of the symptoms of prostatic/

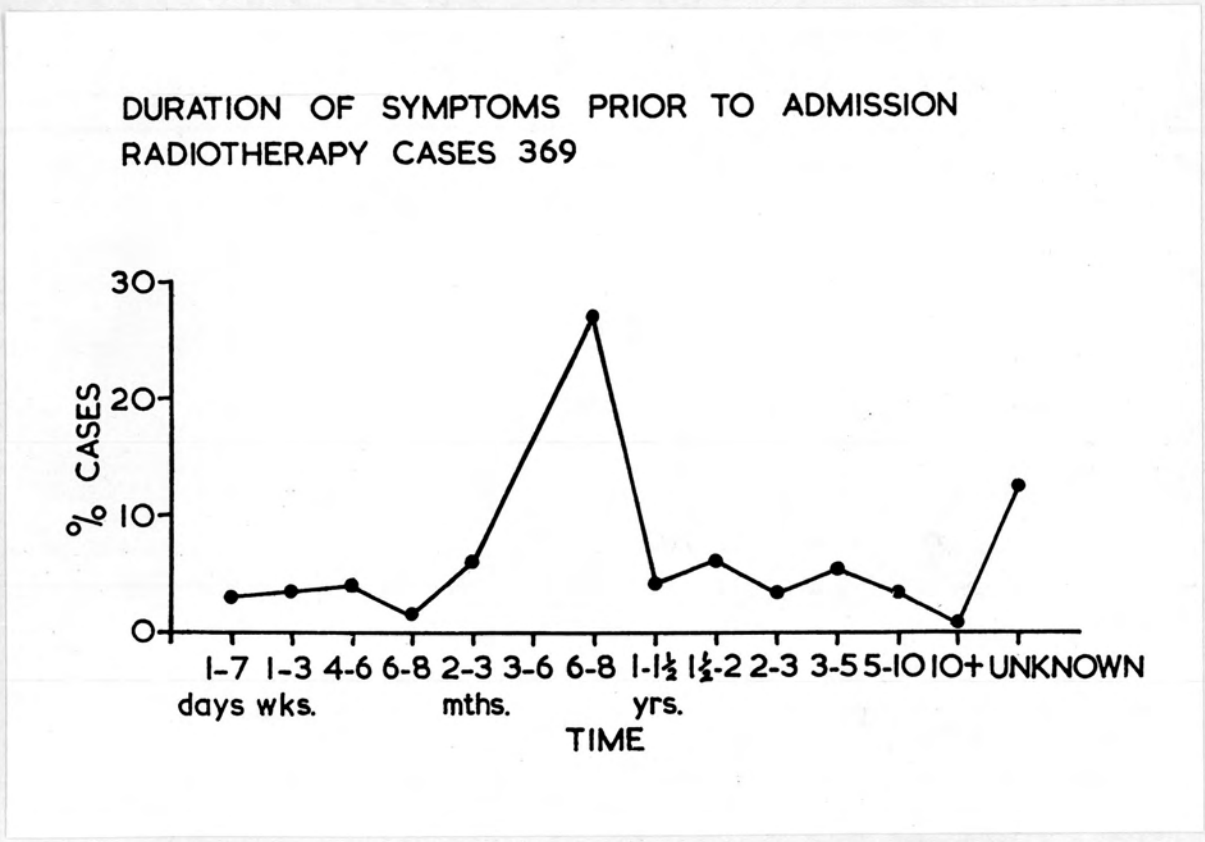
DURATION OF SYMPTOMS PRIOR TO ADMISSION
RADIOTHERAPY CASES 369
% CASES
30
20
10
0
1-7 days
1-3 wks.
4-6
6-8
2-3 mths.
3-6
6-8
1-1½ yrs.
1½-2
2-3
3-5
5-10
10+
UNKNOWN
TIME

Figure 24.

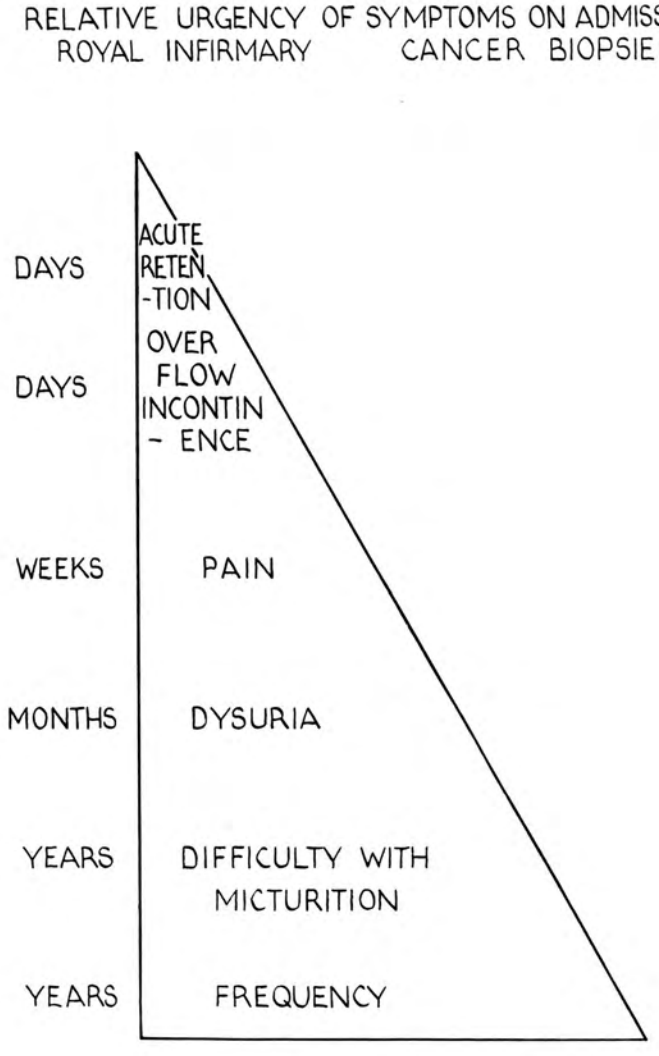
RELATIVE URGENCY OF SYMPTOMS ON ADMISSION
ROYAL INFIRMARY CANCER BIOPSIES
DAYS
ACUTE RETEN -TION
DAYS
OVER FLOW INCONTIN - ENCE
WEEKS
PAIN
MONTHS
DYSURIA
YEARS
DIFFICULTY WITH MICTURITION
YEARS
FREQUENCY

Figure 25.

62.

prostatic carcinoma that make it interesting, not only to the Surgeon, but also to Pathologist and General Practitioner. Frequency of micturition and difficulty with micturition are common symptoms associated with simple enlargement of the prostate. They are symptoms complained of by patients with carcinoma of the prostate too. However, this condition may manifest itself in a far more subtle manner as for instance a sudden fracture of a leg bone, shooting pains down the leg, unexplained macrocytic anaemia, pleural effusion, chronic constipation, etc. and these generally occur without any previous history of genito-urinary disturbances. It is not uncommon to come across cases of carcinoma of the prostate being treated for arthritis, " lumbago", or chronic rheumatism for months and even years until a rectal examination reveals the features of an advanced carcinoma of the prostate.

iv. Early symptoms.

The analysis of the biopsy series of cancer cases reveal the nature of " early " symptoms. In point of fact the so-called " early " symptoms are essentially the same as those observed in simple enlargement of the prostate - see diagram. This fact stresses the need for a careful examination of every elderly male complaining of symptoms of urinary obstruction.

v. Late symptoms.

The autopsy series of cancer cases reveal the nature of symptoms produced by the malignant growth when (1) it has grown rapidly or when it has/

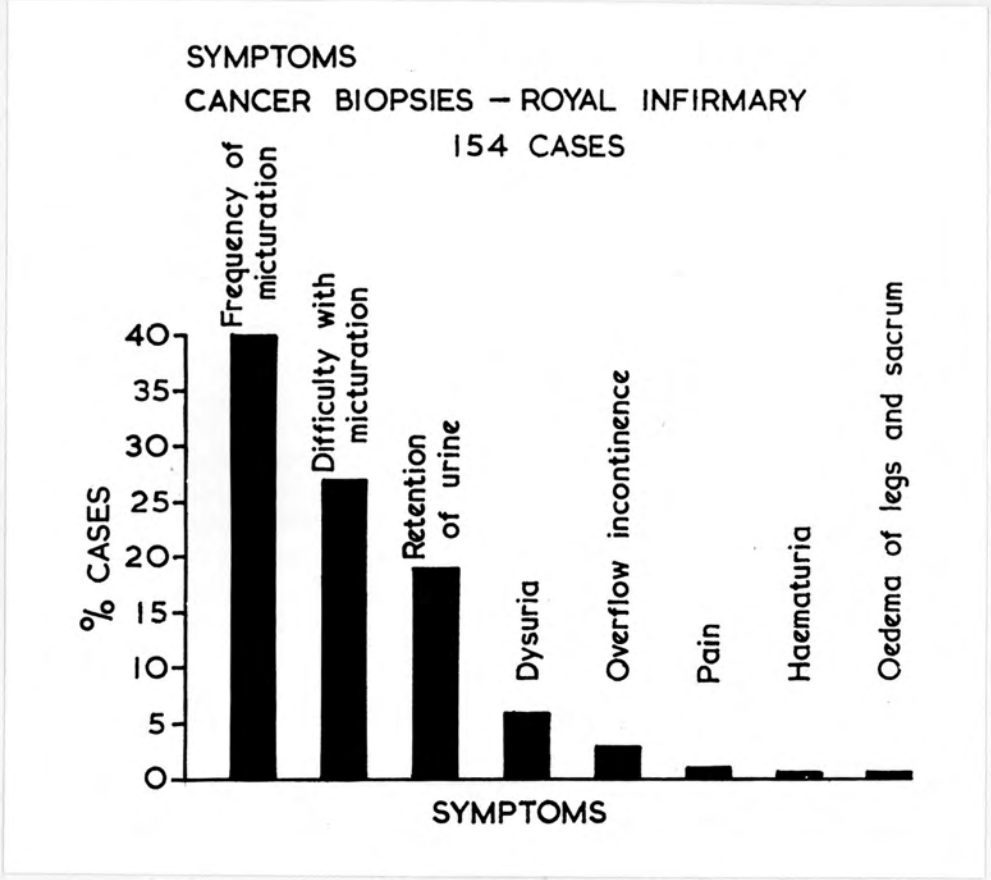

Figure 26.

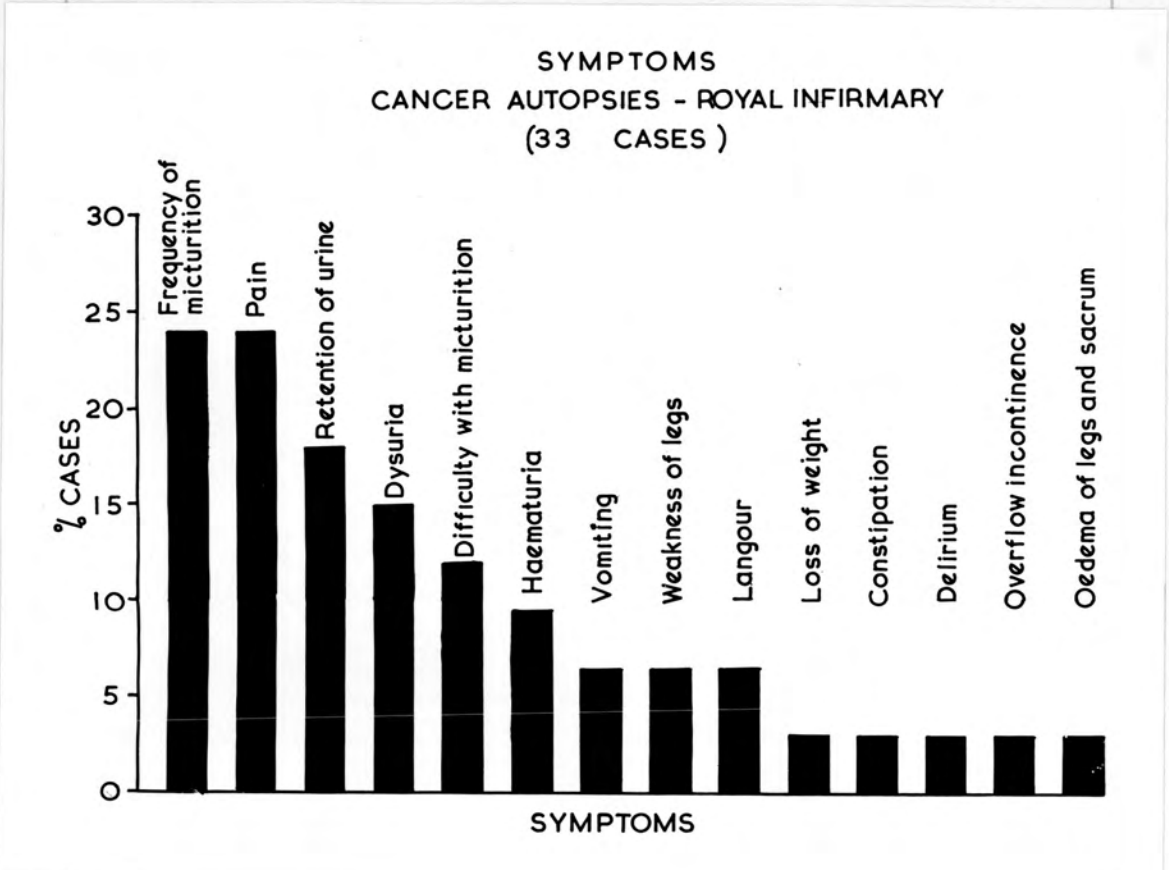

Figure 27.

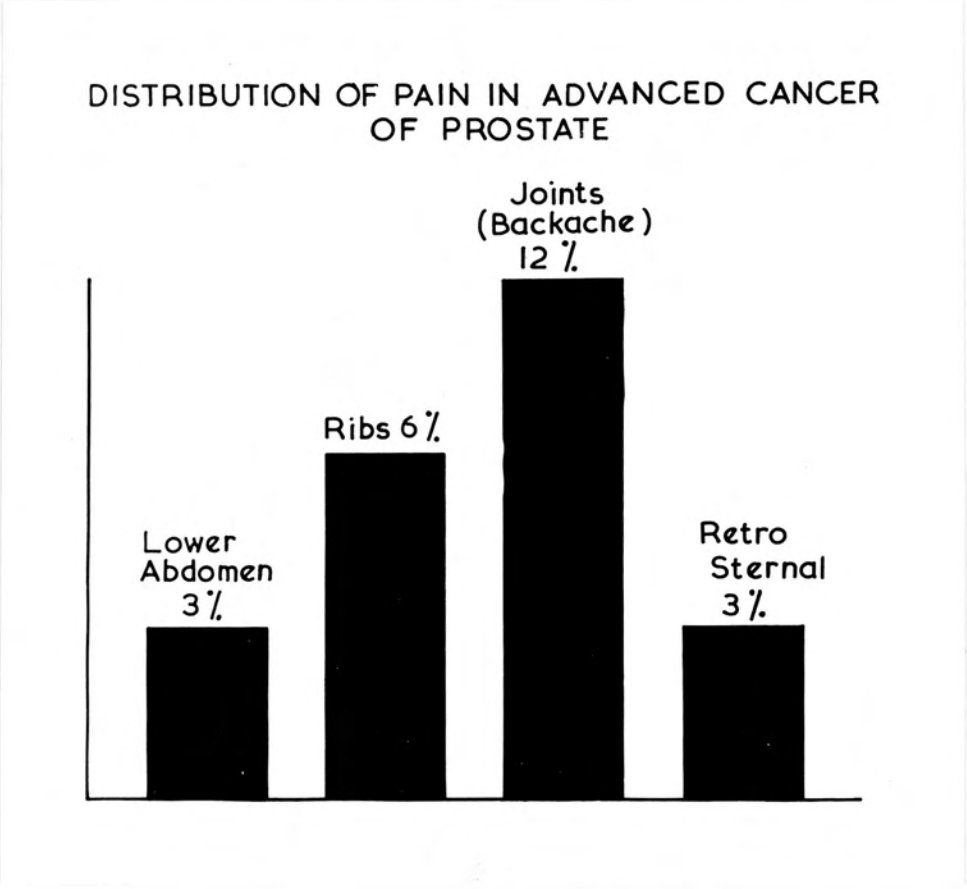
DISTRIBUTION OF PAIN IN ADVANCED CANCER OF PROSTATE
Joints (Backache) 12 %
Ribs 6 %
Lower Abdomen 3 %
Retro Sternal 3 %

Figure 28.

63.

has grown for a long period ; (2) when it has failed to respond to oestrogen therapy ; (3) when the patient has failed to continue taking oestrogen tablets after the initial good response.
These symptoms are, in the main, due to the widespread dissemination of malignant cells to distant tissues and organs. The growth has gone beyond the confines of the prostatic capsule. In the Royal Infirmary series of 33 cases (see diagram Appendix) and in the Municipal Hospital series of 25 cases, the relative frequencies of the different symptoms are very similar. Thus, pain, which appears to be a feature of advanced metastatic growth accounts for 24% and 28% of cases respectively ; haematuria in 9.1% and 12% respectively. Then again we see the effects of rather the complications of advanced growth e.g. uraemia and delirium due to either cancer affecting lower end of ureters causing obstruction here and the eventual destruction of renal tissue from back pressure and the final production of uraemia. Loss of weight, weakness of legs, langour, chronic constipation are also symptoms of advanced carcinoma of the prostate.
It is certainly too late to wait till these symptoms appear to make a diagnosis of carcinoma of the prostate.

6. Comparison of symptoms in Carcinoma and Simple Enlargement of Prostate.

In general, as mentioned earlier the symptoms are essentially the same. However, the fact that we find a greater number of cases complaining of

frequency/

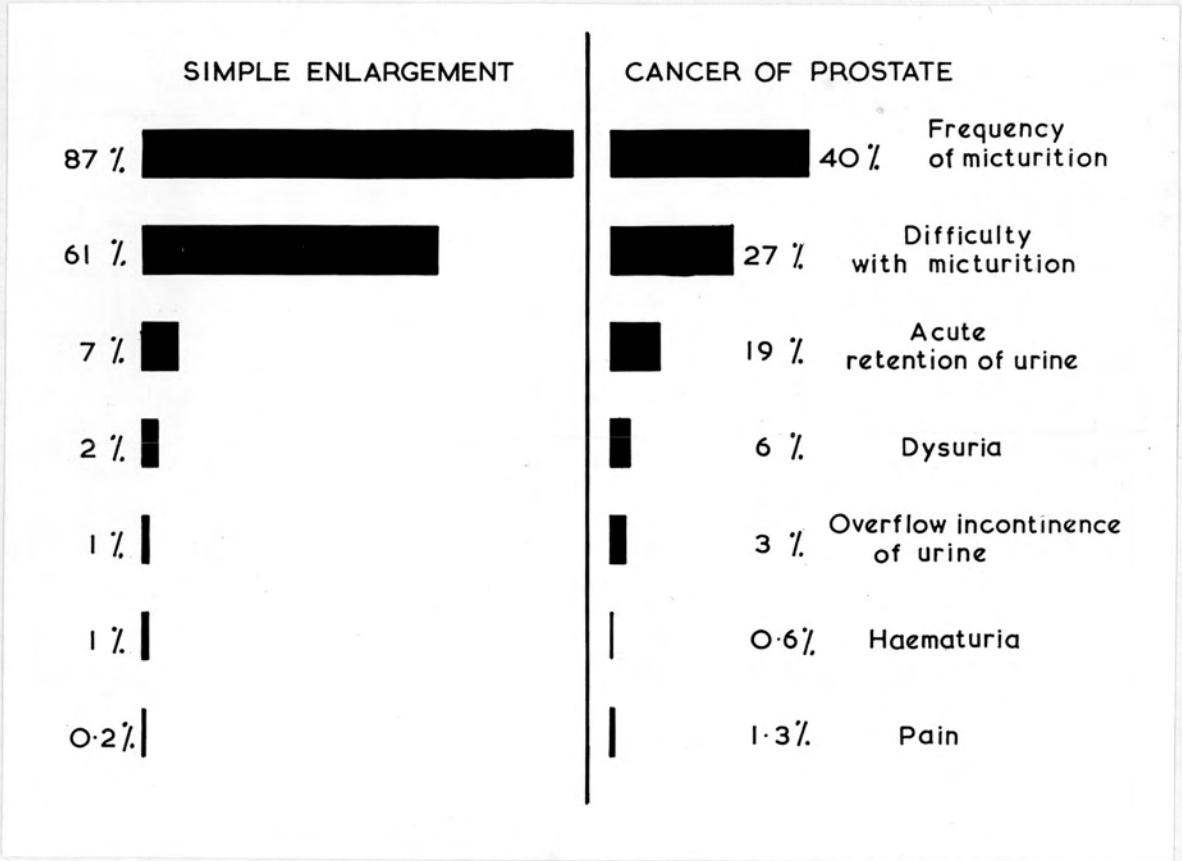
SIMPLE ENLARGEMENT
CANCER OF PROSTATE
87 %
40 %
Frequency of micturition
61 %
27 %
Difficulty with micturition
7 %
19 %
Acute retention of urine
2 %
6 %
Dysuria
1 %
3 %
Overflow incontinence of urine
1 %
0·6%
Haematuria
0·2%
1·3%
Pain

Figure 29.

64.

frequency and difficulty of micturition for a longer period (see diagram 29) amongst the cases of simple enlargement of the prostate as opposed to carcinoma of prostate, is significant. In other words, the duration of symptoms in carcinoma of prostate is much shorter. This being the case it is essential that every case of prostatic enlargement in an elderly male needs to be thoroughly investigated initially and this is not all. He should be examined carefully at regular intervals.

Dysuria is seen more often in cases of carcinoma of prostate (5.8%) than in simple enlargement.

Haematuria occurs more frequently (1.1%) in simple enlargement than in carcinoma (0.6%).

Acute Retention - A greater proportion (18.8%) of cases of carcinoma of prostate seek medical aid early owing to this complaint than simple enlargement (6.8%).

Overflow Incontinence is seen more often in cancer of the prostate (3.2%) than in simple enlargement (1.9%).

Pain is more frequently complained of by cancer patients.

7. Observations from the literature.

Young (1909) in a study of 145 cases of carcinoma of the Prostate gland confirms the fact that an increase of frequency and difficulty in micturition are often slowly progressive in character. The observations as regards pain are not in agreement with my findings - Young states that/

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that pain alone is a much more common symptom and frequently remains for a long time the only symptom.

Willam (1913) analysing the clinical features of 33 cases of Cancer of the Prostate gland states that increased frequency of micturition is the most prominent symptom as a rule and pain in carcinoma of the prostate is variable and not characteristic. Barringer (1931) stresses the importance of frequency of micturition (47.8%) and difficulty of micturition (34.2%) as initial symptoms in the early diagnosis of Carcinoma of the prostate gland in a series of 280 cases. He states that many patients waited until retention (16%) or haematuria (8.5%) compelled them to seek advice.

There are no symptoms or signs that are pathognomonic of carcinoma of the prostate. Generally, as mentioned earlier, when weight loss, haematuria, oedema of legs and pain in the back do occur, the disease has spread beyond the confines of the prostate gland and it is too late for an effective attack to made upon the disease (Crowell, 1940).

Strohm (1941) in reviewing the symptomatology of 429 cases of cancer of prostate gland agrees with the observation that the two most common symptoms of carcinoma of the prostate gland are frequency and nocturia (88%), and difficulty in micturition (62%).

Finally, I cannot help quoting, in full, Birdsall's (1948) account of the symptomatology for he paints a very true picture.

" Carcinoma/

66.

" Carcinoma of the prostate gland in its incipiency masquerades under such a seemingly innocent mask and so insidious in its onset and so uncharacteristic is the symptomatology that the subjective complaints are quite indistinguishable from those of benign hypertrophy.

In striking contrast the clinical picture of advanced carcinoma of the prostate gland is one of extreme hopelessness with its cachectic and septic pallor, profound anaemia, loss in weight, obstructive urinary sequence of frequency, urgency, retention, and infection with the surmounting complaint of constant or increasingly intermittent pain due to metastases. Such is the picture and great is the pity that the patient is reluctant to seek advice in the early stage, or the rectal examination withheld because of the commonly accepted impression that the presented mild complaints are those of only another case of beginning benign enlargement of the prostate gland concomitant with advancing years. "

My observations are in agreement with those of all the other workers.

(16) PATHOLOGICAL BASIS OF SYMPTOMS OF PROSTATIC CARCINOMA.

(i) Frequency of micturition and (ii) difficulty with micturition, and (iii) dysuria.

These are all probably due to congestion from either acute or chronic inflammation following infection of the mucosae of the bladder and prostatic urethra. In the late stages of the malignant/

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malignant growth these symptoms may be due to secondary spread of the growth to involve the prostatic urethra.

If simple hypertrophic changes are present in the gland, then there might be enlargement of the middle lobe which projects into the bladder cavity and so obstructs the outflow of urine via the prostatic urethra and thereby being responsible for the difficulty in micturition.

(iv) Haematuria.

When it occurs in the early stages it is probably due to either (a) acute congestion of the capillaries of the bladder mucosa with consequent rupture of the vessel walls resulting in haemorrhage into the bladder cavity; (b) invasion of the prostatic urethra by the malignant process and eventual ulceration of the tissues.

(v) Acute retention.

This is mainly due to the acute infection of the prostatic urethra which results from a stagnant urine together with a partial obstruction caused by prostatic enlargement of the middle lobe.

(vi) Pain.

(a) Suprapubic ; (b) Rectal pain ;
(c) Lumbago ; (d) Rib pain and pain in retro-sternal region.

(a) <u>Pain in the suprapubic region</u> is probably due to a twofold mechanism - firstly due to distended bladder causing irritation of nerve endings in the wall of the bladder, and secondly to the contraction of the bladder musculature trying/

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trying to expel the urine contained within its distended cavity.

(b) Rectal pain : This was a feature in one case. It is probably due to direct extension of the growth to the rectum. The malignant cells infiltrate the muscle coat and the pain will be felt when there is distension and relaxation of the rectum. The severity of the pain will vary, probably, with the degree of infiltration of the rectal wall. The pain so produced is sufficient to cause constipation - a similar state of affairs is seen when there are haemorrhoids.

(c) Lumbago - Fibrositis - Backache : This pain which is frequently interpreted as being due to chronic rheumatism or " Sciatica " is often the cause of delay in proper treatment. It is certainly not unusual to come across many unfortunate individuals (see appendix containing case histories) who have been treated by their medical advisers for " a touch of the rheumatics " or for that matter for everything else but cancer of the prostate. This has gone on until the disease has advanced beyond the hope of effective treatment. The pain which is complained of is usually backache or at times a sharp pain running down the back of the thigh - in the distribution of the sciatic nerve. The backache is sometimes attributed to a disc lesion. It is probably due to irritation following perineural lymphatic involvement.

(d) Rib pain and retrosternal pain : The first site of pain is probably due to involvement of the periosteum/

69.

periosteum by the neoplastic process and consequent irritation of the nerve endings in the periosteal layer. The pain of a retrosternal nature might be due to associated disease of coronary arteries - producing an ischaemic type of pain.

(vii) Vomiting and Delirium : These two symptoms are hardly ever seen in the early stages of the disease. It is commonly met with as the presenting symptom which compelled the individual to obtain medical attention. These two manifestations of prostatic carcinoma are in point of fact the result of advanced renal damage resulting from hydrostatic pressure following urinary obstruction at the level of the prostatic urethra. This renal damage has resulted in an accumulation of the products of nitrogenous excretion in the blood : This in turn causing an alteration in the pH of the blood. This alteration in pH is most certainly bound to affect the most sensitive tissue of the body namely the brain, hence the delirium. The vomiting too is probably another manifestation of central origin. The two symptoms might be described as being " toxic" in nature - a mere cloak to hide our ignorance or lack of knowledge of the true nature of URAEMIA.

(viii) Weakness : Langour.

These two subjective symptoms are probably due to a general feeling of being ill. The organism reacts as a whole to a change, be it small or great, in any organ or tissue. If I may use a familiar analogy it is as if a mother is stricken to the heart when her offspring is ill - the child being/

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being a unit of the family. They are manifestations of the systemic disturbance caused by carcinoma of the prostate.

(ix) Loss of weight.

This was a symptom in four of the autopsy series of the Municipal hospitals. Loss of weight is an extremely late manifestation of carcinoma of the prostate. These cases complained of it for from 5 months to 7 years. In this connection I thought it might be interesting to analyse the nutritional state of the body of all the cases of carcinoma of the prostate that came to autopsy to the Royal Infirmary of Edinburgh. My findings are summarised below :-

Table 19.

Nutritional State in Carcinoma of Prostate.

		No. of Cases.	%
Loss of Weight	Well nourished	8	24.1
	Moderately well nourished	4	12.1
	Poorly nourished	5	15.1
	Emaciated	6	18.2
	Very emaciated	2	6.1
	Unknown	8	24.1
		33	

Loss of weight was noticed in 17 cases (i.e. in at least 50%). Of course, one cannot be absolutely accurate in saying that loss of weight was seen in 50% of the autopsy series for the simple reason/

71.

reason that the autopsies were not performed by a single individual. There is the personal factor as a serious drawback - a fact which no critic will fail to detect. Perhaps, the recording of the weights in addition to taking the height (a practice which is being done now in the Autopsy Department of the Edinburgh Royal Infirmary) of all bodies coming to post mortem will throw light on this aspect of carcinoma of the prostate gland. One might be able to draw conclusions as to whether the cancerous process is of such a nature as to cause a marked loss of weight ; or whether obese individuals are more likely to develop prostatic carcinoma.

(x) Anaemia.

This was a symptom in three cases. It would appear as if the neoplastic deposit in bone exerted some inhibitory influence on blood formation in the bone marrow. Whether it is a combined direct action or whether it is due to pressure atrophy by the cancerous growth on the bone marrow is not certain.

(xi) Overflow incontinence.

This is probably due to the overflow of urine resulting when the action of the sphincter mechanism at the prostatic urethra is overcome by the hydrostatic pressure of the urine in the bladder.

(17) /

72.

(17) PRESENT TRENDS IN PROSTATIC CARCINOMA.

When the number of prostates received annually is noted from the graph from 1936 till the year 1952 one is impressed by the general trend of the graph, namely a steady rise through the years except for the year 1938 when there was a very slight fall in the number of biopsies. The most striking change observed is a rise which commences on the completion of World War II in 1945. The graph for the number of simple enlargement of the prostate cases closely follows graph (1). The third graph shows the number of cancer biopsies received at the Royal Infirmary. This shows a fairly gradual increase in the numbers with an occasional drop as in 1948, 1950 and 1951. It is difficult to correlate the sudden rise of the Cancer cases in 1949 with the coincident fall in the total number of simple enlargement of the prostate biopsies. However, the upward trend in all prostate biopsies is indeed a most encouraging indication that :-

i. More patients with prostate disease are being operated upon.

ii. More prostate glands which have been removed surgically are being examined histologically.

iii. Surgeons and Physicians are alive to the seriousness of the problem and Surgeons remove the offending organ.

iv. Physicians are sending in more cases for Surgical treatment.

It is only by removing increasing numbers of enlarged prostate glands and submitting them to histological/

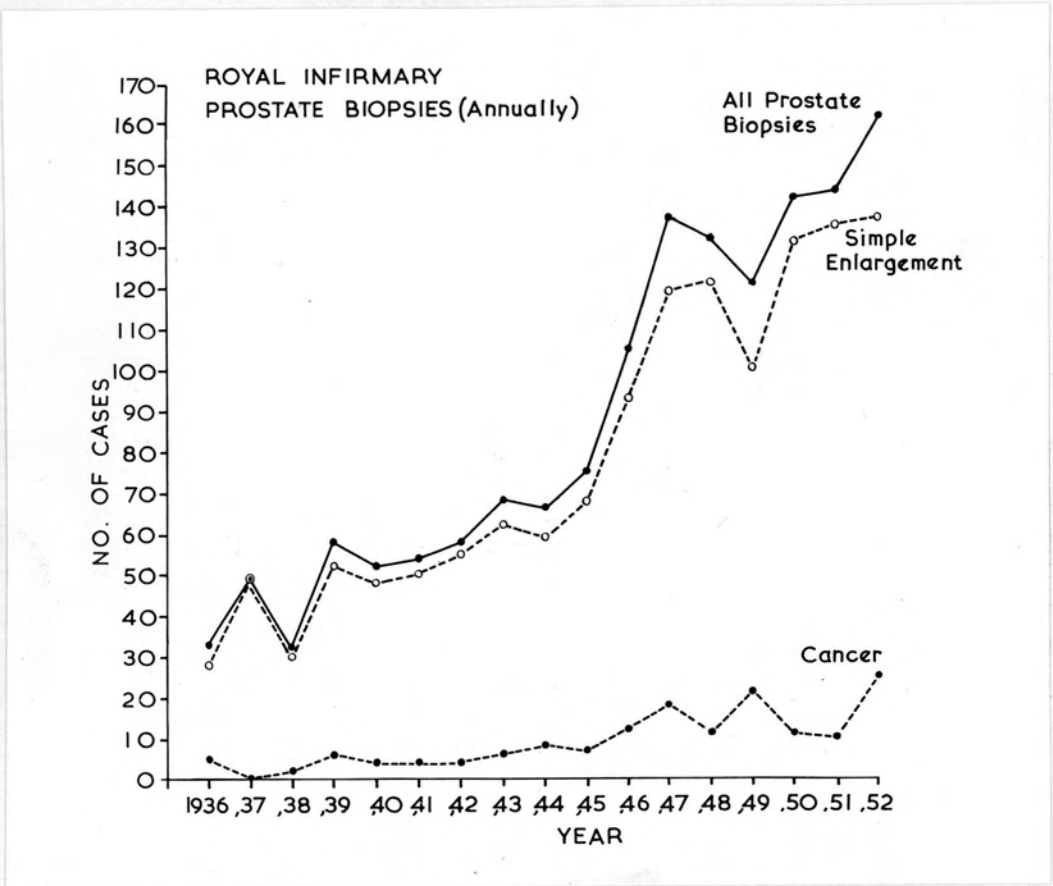
ROYAL INFIRMARY
PROSTATE BIOPSIES (Annually)
All Prostate Biopsies
Simple Enlargement
Cancer
NO. OF CASES
YEAR
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
1936
,37
,38
,39
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Figure 30.

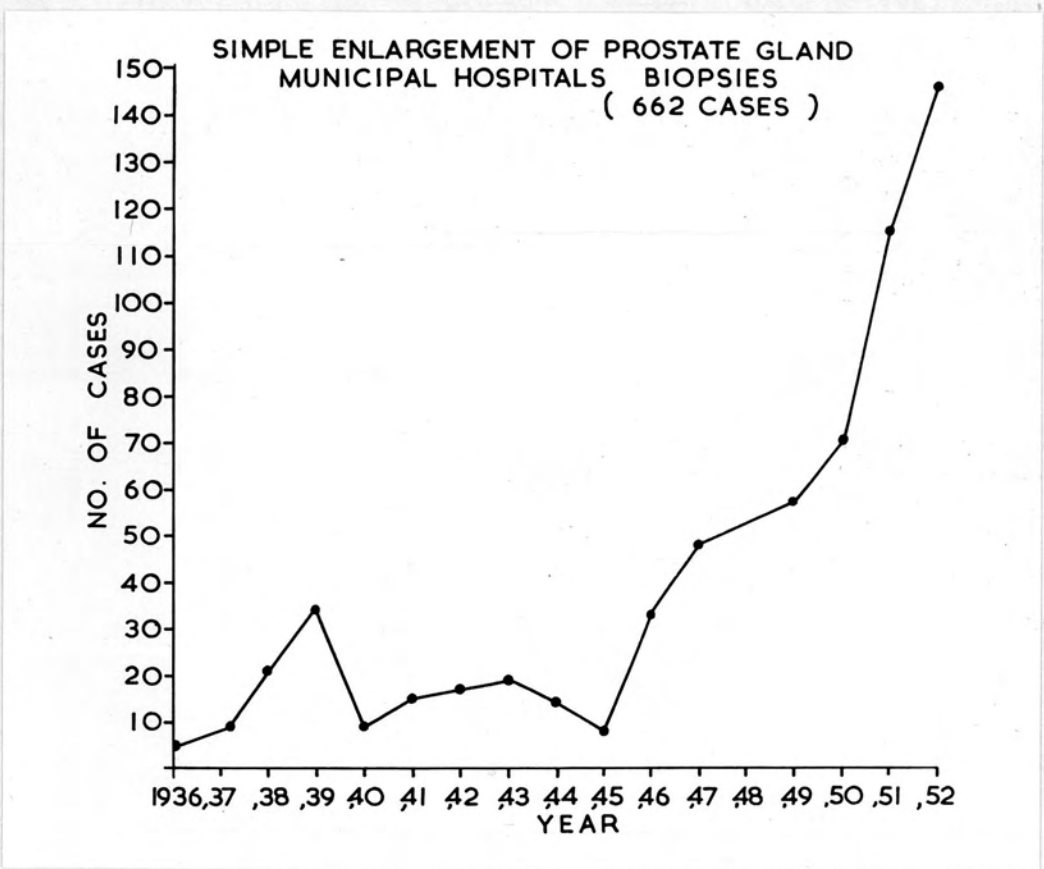
SIMPLE ENLARGEMENT OF PROSTATE GLAND
MUNICIPAL HOSPITALS BIOPSIES
(662 CASES)
NO. OF CASES
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
1936,37 ,38 ,39 ,40 ,41 ,42 ,43 ,44 ,45 ,46 ,47 ,48 ,49 ,50 ,51 ,52
YEAR

Figure 31.

73.

histological examination can we control the potentially malignant cases. This is demonstrated very strikingly in Fig. (31). In this graph significant increases in the number of cancer cases only after 1945 are seen. Before this year the number of cancer cases has been relatively few.

(18) FUTURE PROGRESS.

" The circumstances attending the onset, and in fact, a great deal about the progress of early cancer as distinguished from the advanced cancer which first comes to medical attention are obscure and not likely soon to be made clear by chance observations such as have this far contributed most of the information which exists on the subject. " (Soper 1930). This is only one of the many reasons for establishing a Research Centre - to study amongst other organs the early features of Carcinoma of the prostate. This central organisation will be responsible for co-ordinating all research on neoplasms - Carcinoma of the prostate being investigated by the Genito-Urinary Unit. This Unit will receive all cases sent in by General Practitioners and by other Units. The layout is illustrated schematically in the diagram. Every stage of the case will be recorded - from the clinical history to diagnosis, progress in hospital, operation details - naked eye appearances as seen by the Surgeon will be recorded by Stenographers in the Operating theatre in the course of the operation, treatment given, duration of stay in hospital, etc.

will/

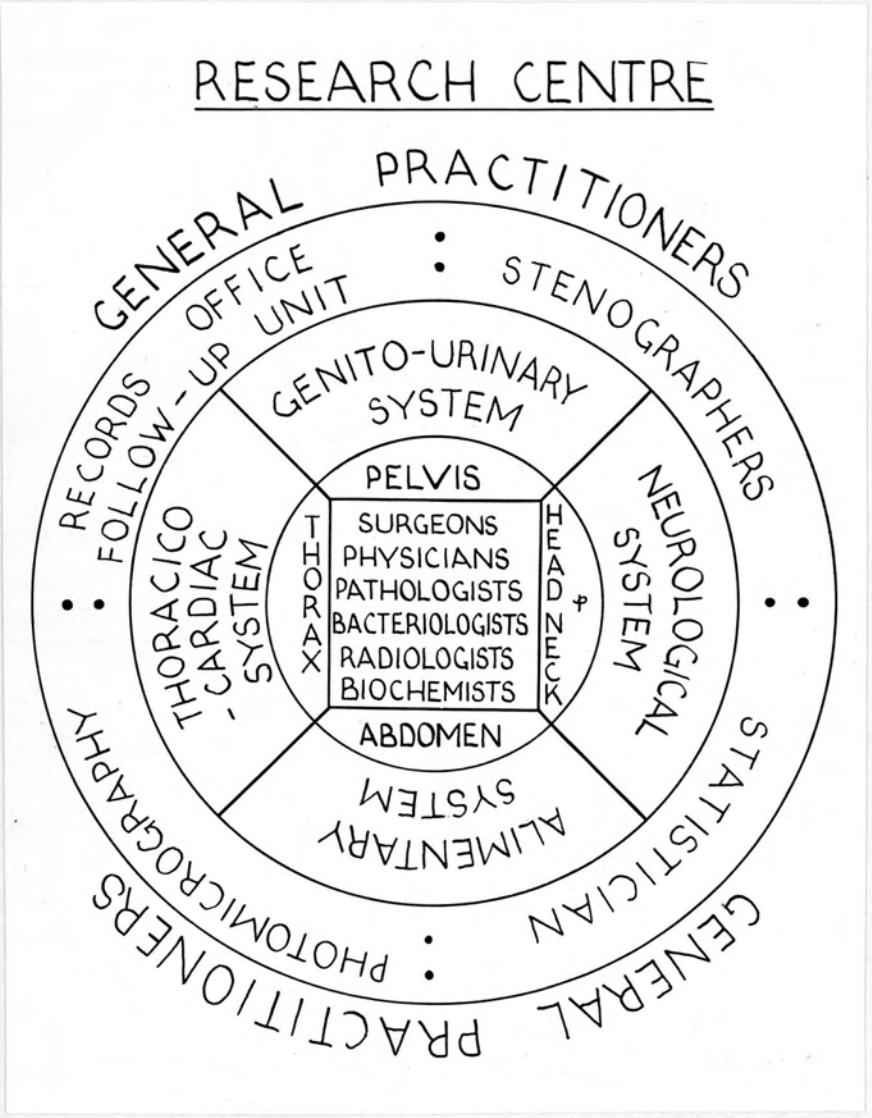
RESEARCH CENTRE
GENERAL PRACTITIONERS
STENOGRAPHERS
STATISTICIAN
GENERAL PRACTITIONERS
PHOTOMICROGRAPHY
RECORDS
FOLLOW-UP
OFFICE
UNIT
GENITO-URINARY SYSTEM
NEUROLOGICAL SYSTEM
THORACICO-CARDIAC SYSTEM
ALIMENTARY SYSTEM
PELVIS
THORAX
HEAD & NECK
ABDOMEN
SURGEONS
PHYSICIANS
PATHOLOGISTS
BACTERIOLOGISTS
RADIOLOGISTS
BIOCHEMISTS

Figure 32.

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will be recorded. The information so obtained will be file indexed and carefully stored in the Records office. It will be the responsibility of the Research Centre to diagnose the condition of the patient. The onus rests with the Staff of this Centre. All the information so obtained could be analysed by the team. It will form valuable data for future research.

Instruction to Medical students and Refresher Courses to General Practitioners could also be carried out here. Medical students should have a thorough knowledge of the early features of Carcinoma of the prostate and also appreciate the very real difficulties of diagnosing Carcinoma of the prostate even with all auxilliary methods.

" To the physicians in general practice the Cancer problem presents itself as perhaps the most difficult, the most distressing, and the most hopeless of all of the many baffling problems with which he has to deal in his daily rounds. The diagnosis of cancer at its early stages is of vital importance. Therefore a more accurate knowledge of the essential facts in regard to Cancer, a greater alertness to obscure suspicious symptoms and a disposition to avoid delay and to procure immediate settlement of the question of diagnosis by reference to the patient to a Specialised Genito-Urinary Unit is most essential " (Greenough, 1931).

Careful investigations could be carried out with a view to (i) estimating the excretion products of steroid metabolism in the following :-

((a) /

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CORRELATED WITH LIVER FUNCTION TESTS.

(a) Males of different age groups - to obtain normal values.

(b) Cases with simple enlargement of the prostate gland.

(c) Cases with carcinoma of the prostate gland.

(d) Cases with carcinoma of prostate gland receiving hormone treatment.

(e) Carcinoma cases that have failed to respond to oestrogen therapy.

II. Investigate the mode of action of hormonal preparations in the prostate gland.

III. Study the histological change produced in the prostate gland by different hormonal preparations and at varying dosage levels.

IV. Reasons for failure of oestrogen therapy.

V. Relation of response of oestrogen therapy to histological type of cancer.

The education of the lay public with regard to Cancer of prostate will now be discussed as follows :-

Firstly the general practitioners role

Secondly the Research Centre and its part in this sphere.

(1) The general practitioner is in a very privileged position which not even a specialist could hold. For it is a general practitioner who really " knows " his patients. He knows their moods and temperaments. He it is who could earn their confidence and as such encourage them to seek medical advice no sooner there is a slight departure from their usual self - even the slight urinary discomfort. He should inquire as a routine, as/

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as to state of health of elderly males and ask them to visit the surgery as soon as possible for a careful examination and if necessary be referred to the Research Centre. This state of affairs finds a parellel in the dyspepsia and its relation to gastric carcinoma. The medical practitioner is the one best able to explain to his patients the dangers of delay in seeking medical advice early. He could do this quite easily without using the word CANCER in his talks and so developing a cancer phobia in his patients.

(2) The Research Centre and the lay education of the public.

The British Empire Cancer Campaign has on several occasions considered the question of lay education in cancer as a means of earlier diagnosis of the disease. Those who favour a campaign of intensive lay education in Cancer argue that even at the worst it must bring to light some cases in the earlier and potentially curable stage, and that in any case a policy of diffusing knowledge is more likely to abolish, than to create fear, which they feel is largely born of ignorance.

Those who take the opposite view argue that the early diagnosis of cancer is unlikely to be appreciably affected by a campaign of lay education. The risk attached to this campaign is the danger of producing cancer neurosis in the population might render the family doctor's task more difficult. This might happen in two ways : first by fear engendered by the propoganda keeping some genuine cases/

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cases away and secondly by overloading the doctor with cases of cancer phobia (Horder, 1953). Also vexatious demands on the part of querulous patients for full complete investigation for every minor symptom. If this is not done to their satisfaction it may lead to an increase in the incidence of litigation neurosis. Errors either in diagnosis or in treatment may be followed by actual litigation against doctor and hospitals. Donaldson (1953) who has had considerable experience of " lay education in Cancer " made as assessment of the value of such education. He found that in an audience of 896 individuals no less than 883 expressed approval to questions as to whether lectures on Cancer relieved their mind, was helpful and whether more such lectures should be given. It is interesting to record the observations of one who has written a book upon the subject for the lay public. Berenblum's (1953) -"Science against Cancer." In his preface he justly claims that though his approach to his subject is scientific, his treatment has been as far as possible nontechnical. He explains the present stage of cancer research fully and fairly, in words which everybody can follow because, as he says, the ordinary reader still has but a hazy idea of what it is all about. Much of the fear which Cancer inspires springs from the belief that it is a complete mystery, against which patient and doctor are helpless. His book reduces this disease to the level of others which lack its terrifying aura./

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aura. In a nutshell the laymen should be so enlightened as to talk about the subject quite freely just as he discussed any other disease, e.g. Tuberculosis. In a word - " KNOWLEDGE IS THE ANTIDOTE TO FEAR. " The Central Health Service Council's standing Cancer and Radio-Therapy Advisory Committee decided that it was undesirable at the present time (1953) for any Cancer publicity to be carried out by a Central government organisation direct to the general public. It believes that the education of doctors themselves in the early diagnosis of cancer was a very important part in the fight against cancer. Donaldson (1953, b) points out that local authorities could certainly help by launching a series of Classes illustrating Cancer to the laymen. The information obtained from these pilot experiments could be analysed, co-ordinated, and carefully studied by this Central Research body and in this way turn out to be really effective.

Another method of attempting to detect Carcinoma in the early stages was suggested by Abrahams (1953). He advocated periodic medical overhaul when well. In this way future illness may be avoided or early evidence of trouble already present, discovered and arrested. He concludes by asking a rather pointed question namely, " are doctors the best teachers of health routine ?" for he says doctors are constantly thinking of the individual in terms of ill health and are thus not best/

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best fitted for this task. Capel (1953) believes in periodic medical overhaul at appropriate intervals and that the examination should be thorough. He states further, that the presence or absence of symptoms is immaterial.

These are only a few of the tremendous potentialities of such a Research Centre as I have planned. The building of one will no doubt take time. However, long term planning for such a project will be amply rewarded.

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(21) SUMMARY.

(1) In this section I. of my thesis I have attempted to describe the clinico-pathological features of prostatic carcinoma. This study is based upon an examination of 2,458 prostate glands : it is supplemented by a careful study of the case records of 369 cancer cases referred to the Radiotherapy department of the Royal Infirmary.

(2) The anatomy and physiology of the prostate gland together with their applications in Surgical pathology are described.

(3) The historical aspects of prostatic carcinoma are brifly outlined.

(4) The difficulties of ascertaining, with any degree of accuracy, the incidence of prostatic carcinoma in a teaching hospital such as the Royal Infirmary, are briefly discussed.

(5) The maximum age incidence of this cancer occurs in the decade 61-70 years. This is in agreement with the observations of other workers.

(6) There was no way of ascertaining the frequency of lobe involvement by the carcinomatous growth owing to failure to record such important details. A method to overcome this difficulty has been suggested.

(7) Carcinoma of the prostate is met with in all societies.

(8) It is a disease which occurs more commonly in/

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in the married male.

(9) No transition from simple enlargement to carcinoma was detected.

(10) The problem of diagnosis of prostatic carcinoma is discussed. The difficulties of early diagnosis are stressed.

(11) The pathological features of this cancer are dealt with in great detail.

(12) The mode of spread of prostatic carcinoma is described and the distribution of metastatic deposits stated.

(13) The oestrogenic effects on the primary growth and on metastases are outlined and illustrated.

(14) The probable mode of action of the oestrogens on the cancer is briefly discussed.

(15) The symptomatology is discussed in detail.

(16) The pathological basis of the symptoms are suggested.

(17) The problem of carcinoma of the prostate as seen to day is described.

(18) The future progress in the field of cancer in general and cancer of the prostate in particular is discussed.

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(21) APPENDIX.

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Contents. Page.

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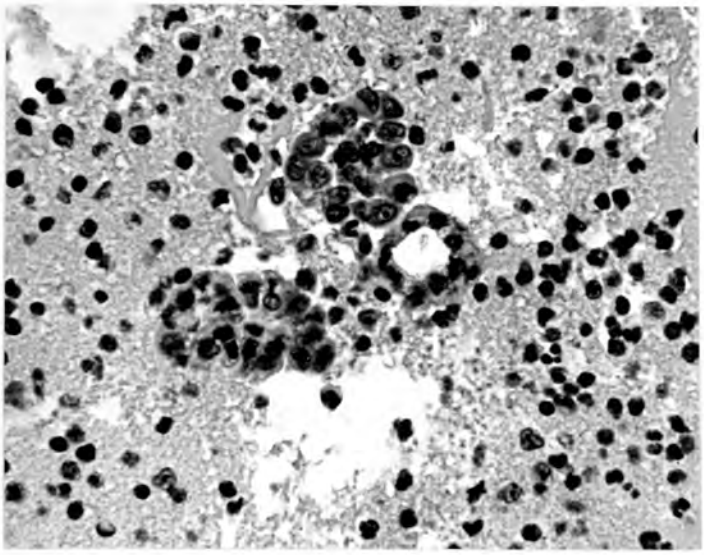
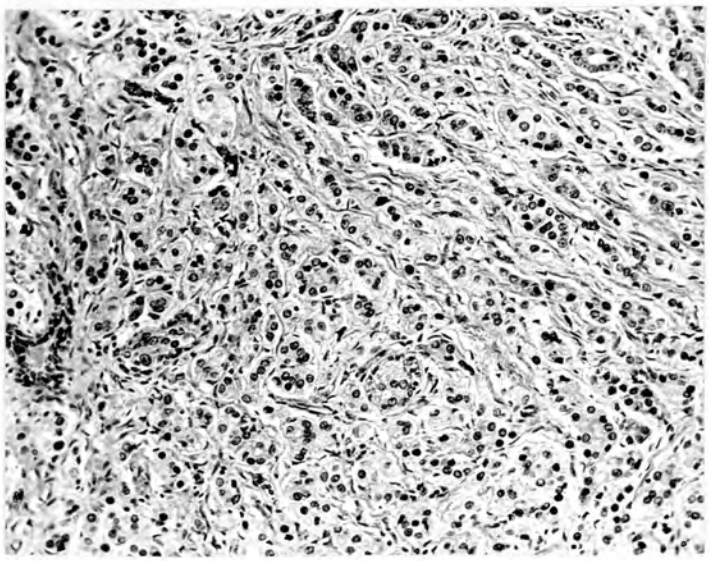


B.13253. Pleural aspiration. Cluster of cells suggesting a malignant growth arising from glandular structure. Haematoxylin & Eosin x 460.



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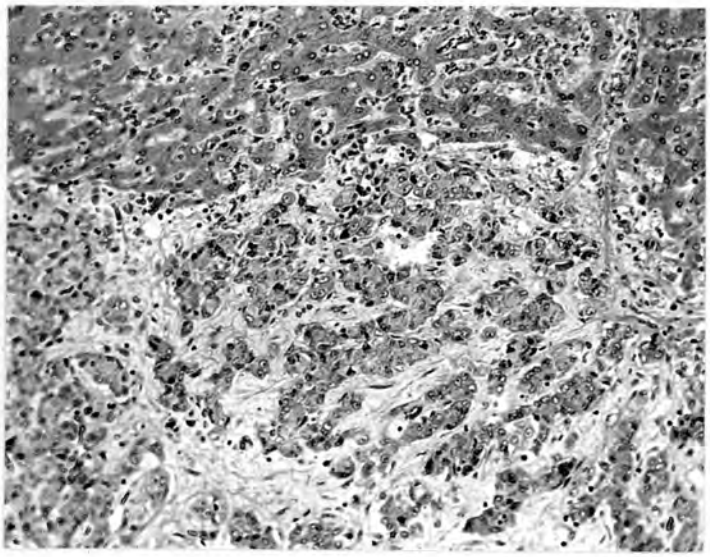

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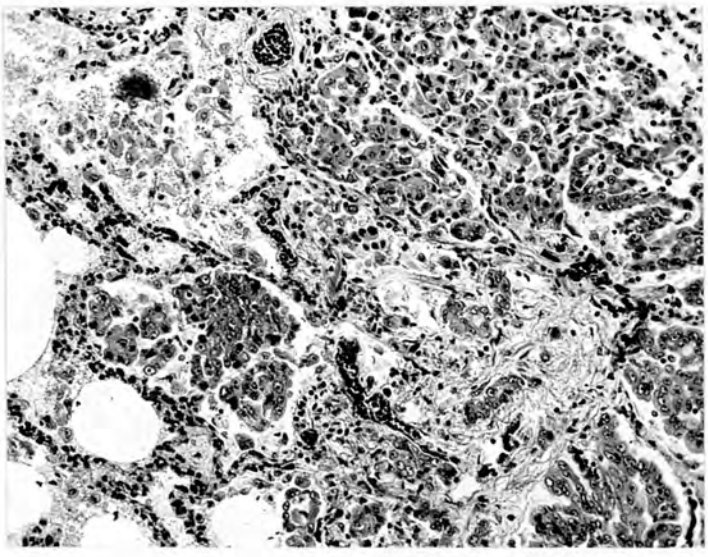


P.M. A. 5281. Lung. Moderately well differentiated carcinomatous deposit. Some nuclei hyperchromatic. Haematoxylin & Eosin x 150.

Case Reports.

Case 1. - 60 yrs.

Admitted to Eastern General Hospital under Mr. Logan in January 1953 with a history of breathlessness of 6 months duration. While in hospital developed bilateral pleural effusion. Bronchial carcinoma was suspected. On examination of aspirated fluid peculiar acinar forms were seen. The pathologist reported " in addition to red blood cells and leucocytes there are large, polyhedral and columnar cells arranged in a definite acinar pattern. This finding is suggestive of adeno-carcinomatous involvement of the pleural space. " The patient was then transferred to the Western General Hospital where Carcinoma of the prostate was diagnosed. It was interesting to note that the patient never complained of obstructive symptoms of urinary dysfunction such as frequency of micturition, dysuria, or retention. While in the Western General Hospital six months later the patient died suddenly.

On post mortem examination widespread secondary deposits were discovered.

Case 2.

P.M. 55/49. 60 yrs. Wd. 23. RIE No. 14816.
Died 28th January 1949.
Provisional diagnosis - Secondary carcinoma of liver from primary in stomach.

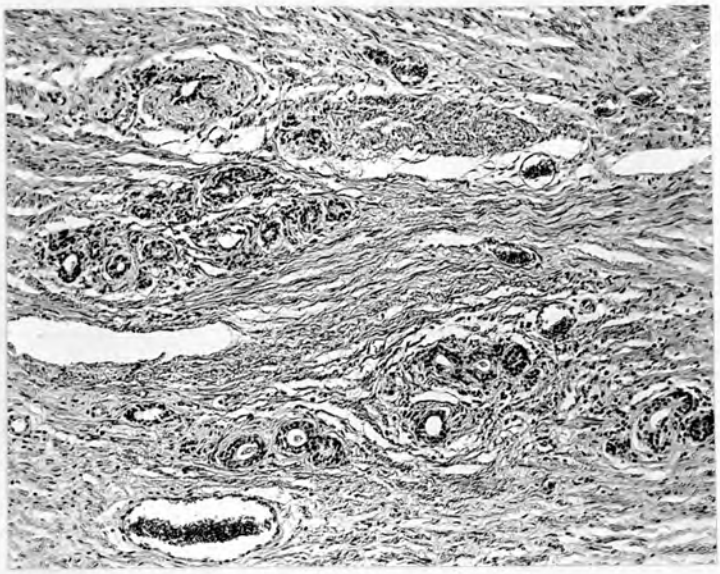
Gradual loss of weight for some years - worse during the last six months. Pain in left sacro-iliac joint developed about Dec. 1947. Spread of pain down left leg and of a typical sciatic distribution. The pain was continually present at time of admission. Since then progress had been uniformly downhill. The pain was controlled by increasing doses of morphia. NO URINARY SYMPTOMS.

On examination - General nutrition poor. Abdomen - generalised distension with enlargement of liver about 8 cms. below costal margin, edge hard and smooth.

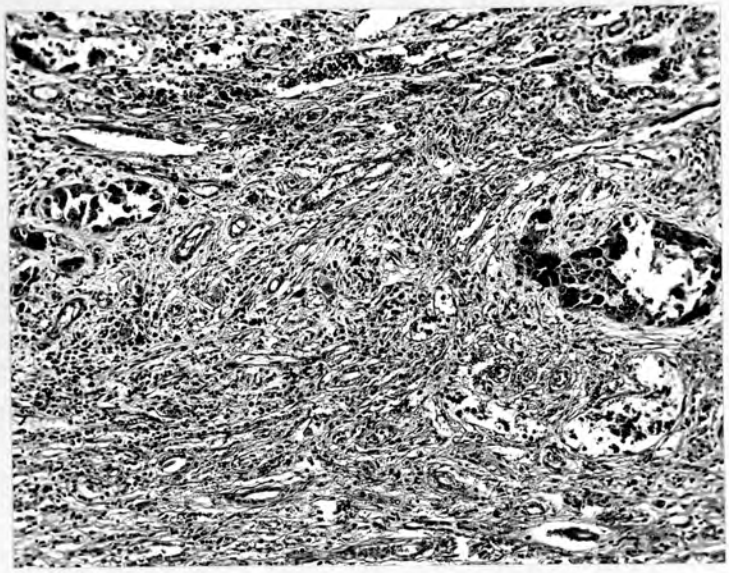
Peritoneal sac - A large mass of dense scirrhous neoplastic tissue occupied the coeliac region. Similar tissue encased the aorta from the level of coeliac axis to the bifurcation and beyond this level on the left side along the course of the common iliac artery into the pelvis. The coeliac mass had invested and severely compressed the splenic vein. The pelvic mass had invested and obliterated the left ureter as well as the iliac vein, and the lumbo-sacral roots were compressed.

Individual lymph nodes could not be identified in the neoplastic tissue.

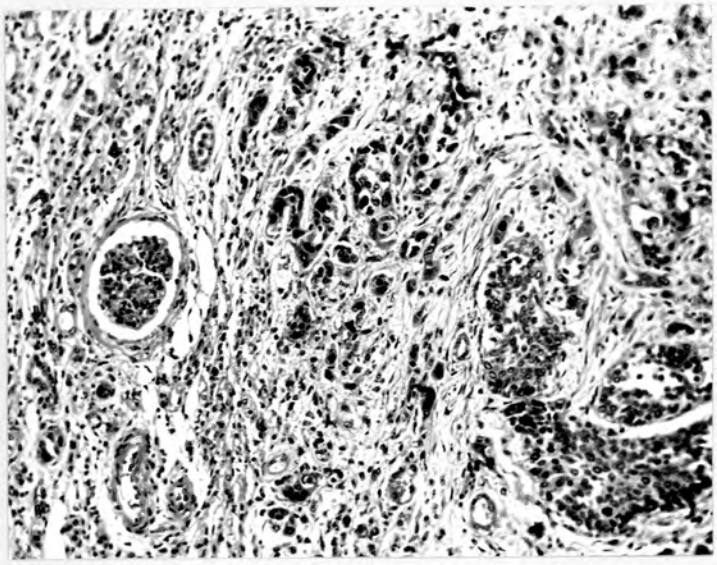
Left kidney. As a result of occlusion of the left ureter by its incorporation in the neoplastic tissue which invested it the left kidney was hydro-nephrotic./



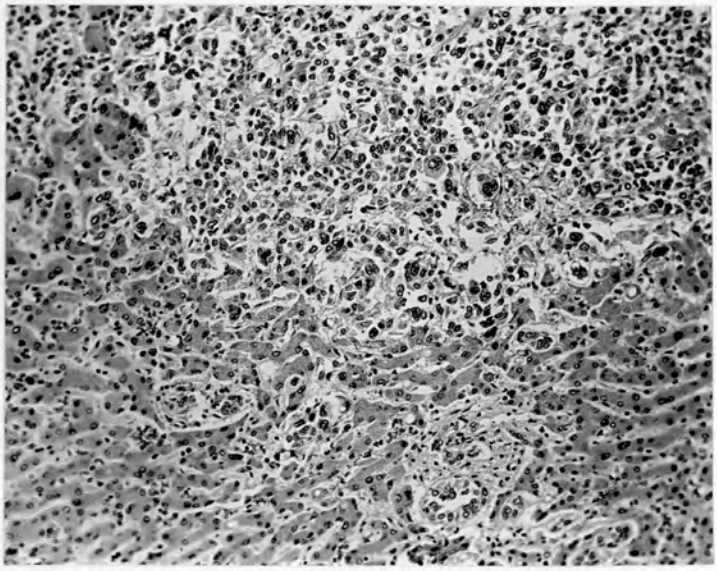
P.M. 55/49. (1) Prostate. Acini are small, lining epithelium poorly formed. Marked scirrhous reaction around them. Suspicious - No definite evidence of malignancy. Haematoxylin & Eosin x 90.



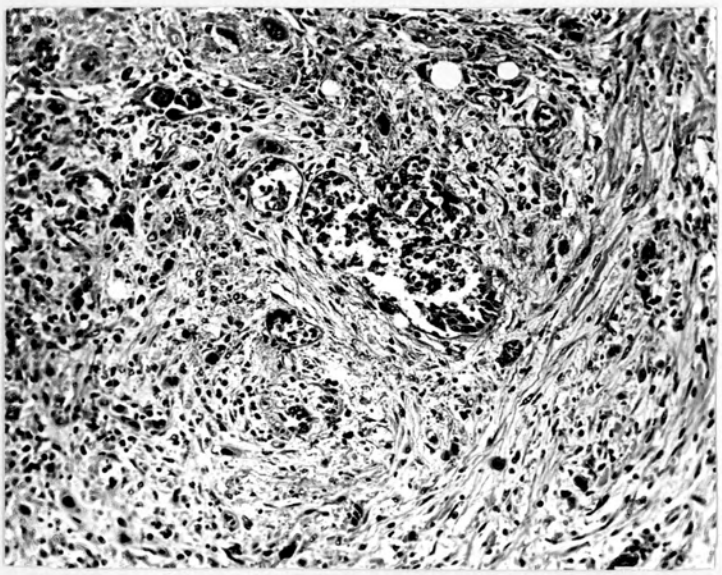
P.M. 55/49. (2) Prostate. Another block from same gland. Showing intra-acinar proliferation of cells with rupture of basement membrane. Moderately well differentiated adenocarcinoma. Haematoxylin & Eosin x 90.



P.M. 55/49. Kidney. Moderately well differentiated adenocarcinoma. Mitotic figures seen. Haematoxylin & Eosin x 120.



P.M. 55/49. Liver. Moderately well differentiated adenocarcinomatous deposit. Highly cellular. Haematoxylin & Eosin x 120.



P.M. 55/49. Suprarenal. Infiltrated by moderately well differentiated adenocarcinoma. Haematoxylin & Eosin x 120.

nephrotic. The calyces were greatly dilated and the parenchyma reduced to a thin shell. The renal pelvis was largely obliterated by tumour tissue which extended into the kidney.

Prostate. Was small and fibrous.

Liver. Swollen and projected three fingers below costal margin. Only a few tumour nodules in its substance. These lay in relation to some of the larger portal tracts. A nodule of tumour tissue was situated at the lower margin of the right lobe.

Pancreas. Was distorted by the coeliac mass of tumour tissue. It appeared to be quite separate from the mass and could be dissected from it with ease.

Spleen. Considerably enlarged. Pulp dark and firm.

Suprarenals. Both were surrounded by tumour tissue which in the case of the left gland had partly replaced its substance.

Lungs. Emphysematous bullae were present at both apices and along the anterior margins. On section the parenchyma showed congestion and oedema. A localised area of bronchiectasis was present deep in the upper lobe of right lung. This was about 3 cms. in diameter.

Microscopic appearances.

Prostate. The majority of the acini are lined by two and sometimes more layers of epithelial cells. Most of them show a moderate degree of dilatation with some irregularity in shape. In some of the acini pronounced epithelial proliferation has resulted in papilliferous processes projecting into the lumen. At other points the acini are completely occluded by masses of epithelial cells which show only slight irregularity in size and in nature, though suspicious of malignancy. In some areas of the sections examined the basement membrane of the acini has ruptured and epithelial cells are seen still coming out into the surrounding stroma. There is however very little irregularity in these cells and mitotic figures are very scanty. The stroma shows an active proliferation of plump fusiform fibroblasts with scattered foci of lymphocytic infiltration.

Left kidney. Moderately well differentiated adenocarcinoma infiltrates kidney tissue. Mitotes very numerous.

Liver. Tumour nodules consist of moderately well differentiated adenocarcinoma similar to that found in the left kidney and also with a well marked scirrhous reaction.

Coeliac and para-aortic glands. These show almost complete replacement by tumour tissue, though in one section, lymph gland structure can be made out with tumour emboli lying in the sinuses. The scirrhous reaction is more marked and degeneration has occurred in some areas.

Left suprarenal. Deposits as in liver and kidney.

Right lung. Section through the area of bronchiectasis in the upper lobe shows it to be a metastatic tumour nodule, spheroidal cell, but attempted acinar formation seen.

Commentary/

Commentary.

This case is of more than ordinary interest in that the neoplastic changes in the prostate gland are of an extremely early character, whereas the malignant deposits in the other organs are extremely well differentiated and of a more advanced stage. The proliferative nature of the growth is demonstrated by the presence of mitotic figures. Another very significant fact is the manner in which carcinoma of the prostate has manifested itself. This is just another illustration of the excellent mimicry of Carcinoma of the prostate.

Further it proves quite conclusively the false sense of security that develops in the mind of the surgeon following a report from the pathologist that the cancerous process is seen at a very early stage. The surgeon may feel - and quite naturally too - that he has treated the patient satisfactorily simply because he has removed the malignant prostate in toto.

Finally, this case illustrates the fact that even the pathologist who handled the tissues at post mortem was unable to suspect cancer of prostate and thus the difficulty of diagnosing cases of cancer of the prostate by naked eye examination. The diagnosis became known only after careful microscopic examination.

The lessons learnt from this case are
(1) ALWAYS EXAMINE THE PROSTATE GLAND AT POST MORTEM.
(2) NEVER FAIL TO STUDY THE MICROSCOPIC APPEARANCE of the prostate gland regardless of the diagnosis.

Case 3.

P.M. 92/48. 55 yrs. Ward 15/16. RIE No. 8281.
Died 15.2.48.
Provisional diagnosis : Carcinoma of rectum.
? Cerebral thrombosis.

In November 1945 he injured his left foot in an accident in the pit. This was followed by swelling of the leg which took months to resolve. Further injuries were sustained to left leg in May and December 1947. On each occasion there was pain and swelling of his leg.

In January 1948, he had elephantiasis of left leg, oedema of penis : severe pains in thighs and left back.

Rectal examination revealed a hard mass, also a hard mass in prostate.

Several inguinal glands on left side and two hard glands on right side.

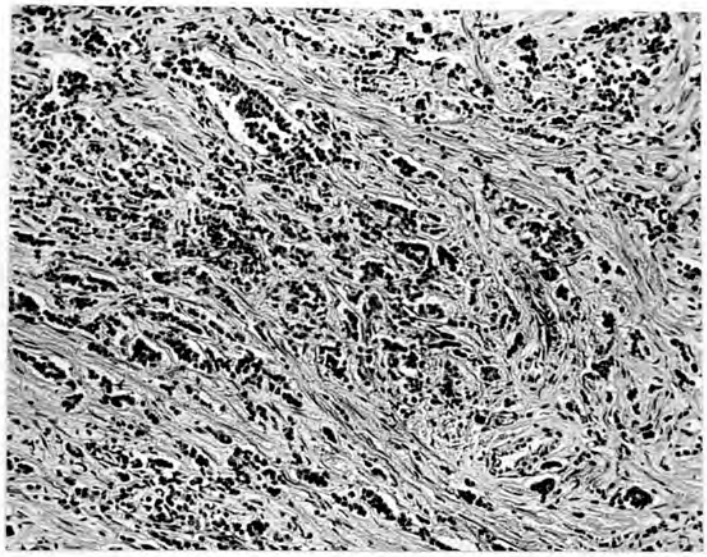
Wassermann reaction negative.

4.2.48. Sudden left sided hemiplegia : the patient was highly irrational. there was a progressive disorientation.

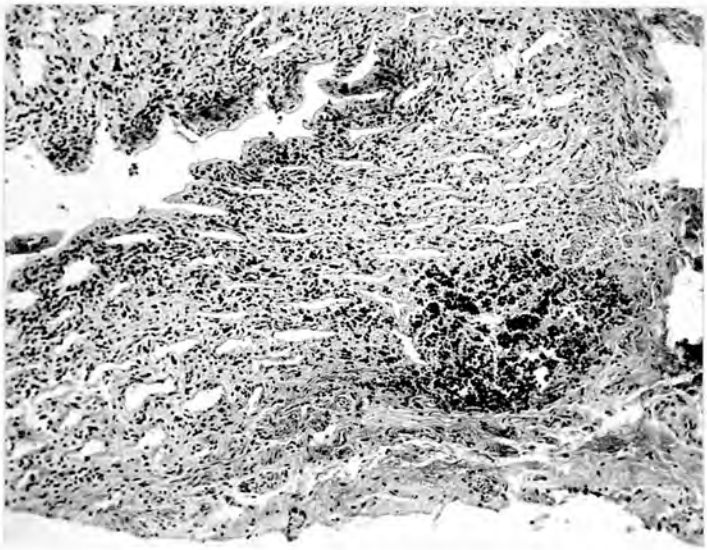
15.2.48. Died.

Abstract.

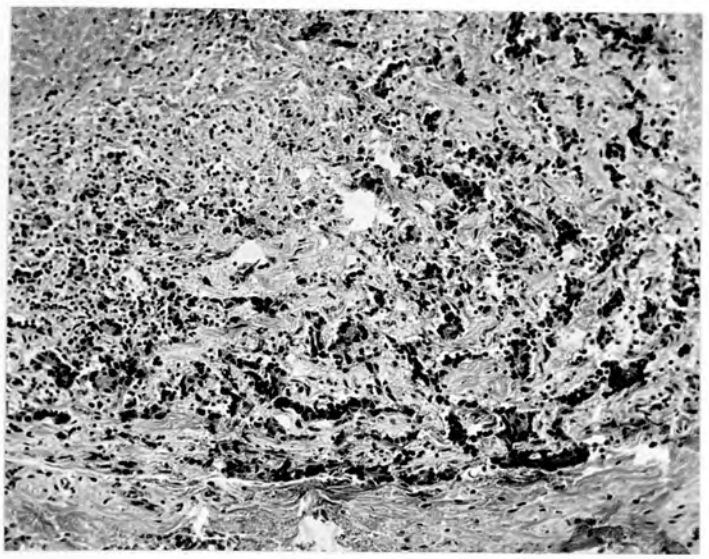
Carcinoma of prostate with infiltration of pelvic wall./



P.M. 92/48. Prostate. Scirrhous carcinoma. Haematoxylin & Eosin x 120.



P.M. 92/48. Rectum. Scirrhous carcinoma in submucosal layer. Haematoxylin & Eosin x 90.



P.M. 92/48. Liver. Well differentiated adenocarcinomatous deposit. Haematoxylin & Eosin x 120.

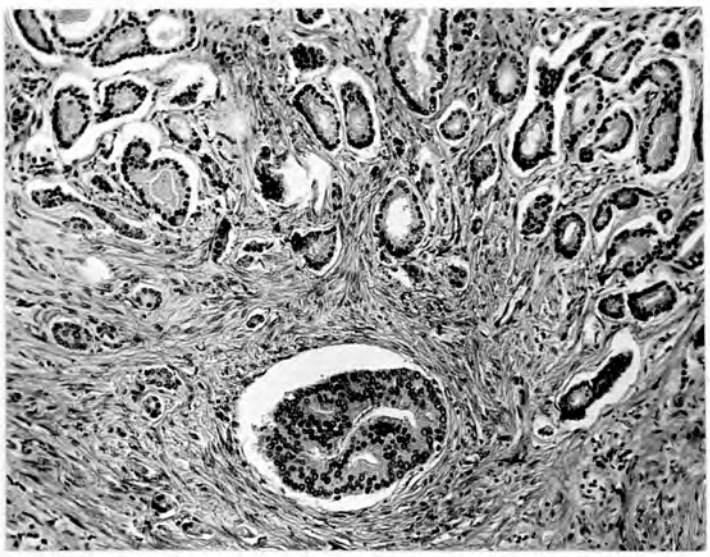
wall surroundings and into outer coats of rectum.
Metastatic deposits in liver.
Para-aortic glands were enlarged, firm and matted.
At the pelvic brim the ureters were involuted in a mass of glands on either side and showed great dilatation.
The pelvis was narrowed by an encircling mass of tumour tissue and was filled almost completely by a full and distended bladder.
Bladder : dilated and wall hypertrophied. Middle lobe of prostate enlarged.
Prostate. Enlarged, but lower posterior part of left lobe was very firm and nodular and from this the tumour tissue had spread posteriorly and laterally to infiltrate round the rectum and into its muscular coats and round the walls of the pelvis. One large mass of lymphatic deposits lay in the wall of the femoral canal and had obstructed the vessels therein.
Rectum. Mucosa raised up into many little nodules by tumour growth invading from without.
Liver. Larger than the average though general shape unchanged : through the capsule many small rounded, white nodules of tumour deposit could be seen against the pale soft tumour tissue and on section nodules of varying size (1 - 4 cm.) in diameter were clearly seen, many with reddish necrotic centres.

Microscopic features.

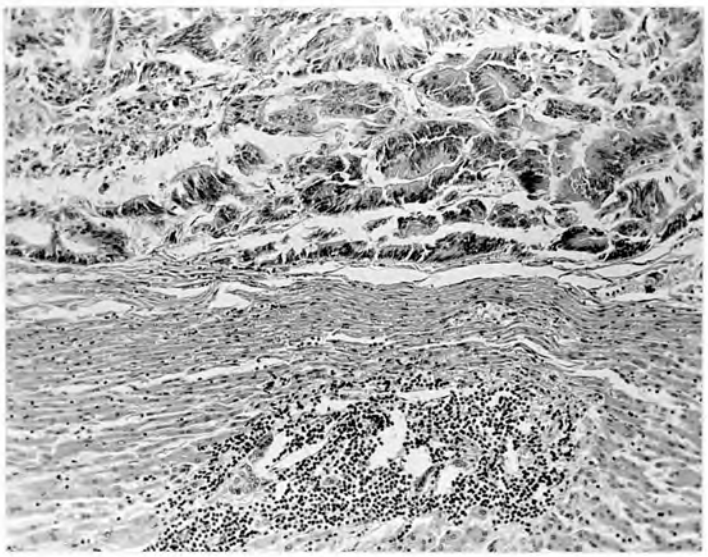
Prostate. Extensive invasion by a SCIRRHOUS adenocarcinoma and also a fairly marked round cell infiltration.
Rectum. Mucosa complete. In submucosa are deposits of adenocarcinoma lying within and outside lymphatics. Tumour deposits also seen in subserous layer. One or two large areas could also be seen amongst the tumour tissue.
Liver. Well differentiated adenocarcinomatous deposits present.

Commentary.

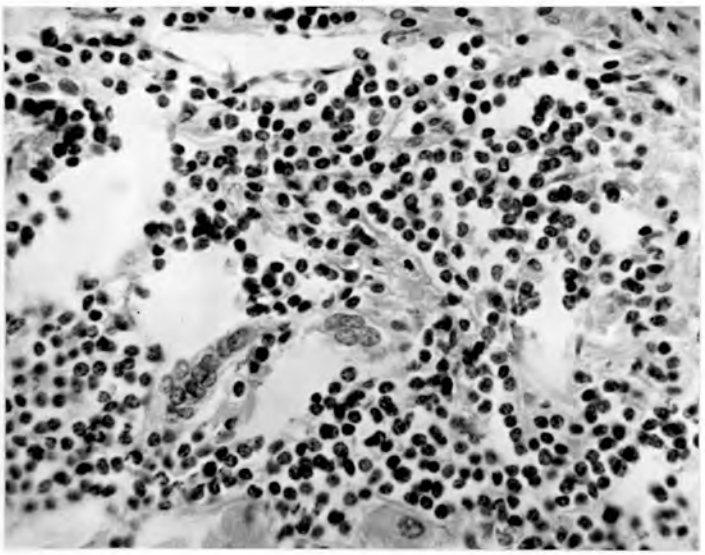
There are many features which make this case worth recording.
In the first place the history may suggest some cardiac or renal pathology to cause oedema of leg, oedema of penis. However there is one very significant clue which unravels the mystery - namely Elephantiasis of left leg. This signifies lymph stasis. There is no history of this patient having lived abroad : no history of fever at night to suggest Filariasis. The only other possibility to account for the oedema is some mechanical obstruction to the flow of the lymph. There is a feature in favour of this possibility, namely a large mass of lymphatic glands in the femoral canal of the left leg.
The fact that a hard mass was felt in the rectum on rectal examination and a hard mass in the prostate/



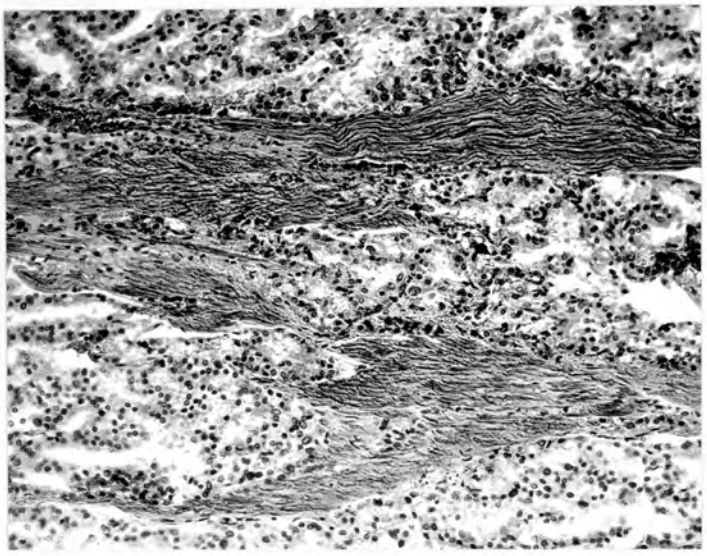
P.M. 194/41. Prostate. Well differentiated adenocarcinoma. Haematoxylin & Eosin x 120.



P.M. 194/41. Liver. Well differentiated adenocarcinoma together with a collection of round cells. Note compression atrophy of liver cells. Haematoxylin & Eosin x 120.



P.M. 194/41. Leukaemic deposit. Same field as in Liver. Lymphatic leukaemia. Haematoxylin & Eosin x 460.



P.M. 194/41. Bladder wall. Well differentiated adenocarcinoma invading muscle. Haematoxylin & Eosin x 120.

prostate suggests one of two things, either a carcinoma of the prostate involving the rectum or carcinoma of the rectum involving the prostate. In this connection Woodward (1947) makes some interesting observations concerning the differential diagnosis of Carcinoma of the prostate. He estimated the acid phosphatase content of portions of tissue removed from the area involved. A high reading is obtained when it is carcinoma of the prostate.

The last interesting feature in this case is the degree of differentiation of the primary as compared with the secondary deposits in liver and rectum on histological examination. It is still a mystery why this should be so.

Case 4.

Aged 65 yrs. P.M. 194 /41.
Prof. Davidson - Ward 26.

Began to complain of weakness and listlessness following an attack of influenza in January 1940. Had some vague backache after this. In July 1940 complained of frequency of micturition and difficulty in passing water. At about this time he developed a prostatic abscess. These urinary disturbances were treated conservatively.

18.10.40. On examination of his peripheral blood the following features were noticed.

W.B.C.	67,000.	R.B.C.	3,370,000.
Hb.	65%	C.I.	0.95.

Differential cell count.

Polymorphs		5 %
Lymphocytes	(Small	84 %
	(Large	90 %
Lymphoblasts		0.8 %
Eosinophils		0.4 %
Basophils		0.4 %
Monocytes		0.4 %.

On clinical examination.

Numerous glandular swellings were seen. They were mainly in the region of the groins, axillae and lower part of left side of neck.

Deep ray therapy was given.

Two months later (12.12.40) blood examination revealed the following :-

White blood cells 21,000 per cu. mm.
Red blood cells 280,000 per cu. mm.
Hb 70%.

23.3.41.

Approximately three months later the blood count was :

WBC	9,400.	RBC	4,050.
Hb	70%.	CI.	0.87.

At this date the liver was found to be enlarged.

Below/

Below the liver there was an irregular palpable mass in the mid line just above the umbilicus. It was noticed that frequency of micturition was very much more severe. Consequently this patient was referred to the Genito-Urinary Clinic.

The frequency of micturition was treated conservatively by prostatic massage and catheterisation. This relieved his urinary symptoms but his general health was poor and consequently was referred back to Ward 26 (26.4.41). However he did not respond and died on 2.5.41.

At post mortem (P.M. 194/41).

Peritoneal cavity. The great omentum was extensively infiltrated by malignant tissue and was in consequence, rolled up into a broad thick layer placed immediately beneath the stomach. The malignant tissue was in the form of multiple confluent nodules of firm pale yellow tissue. Further neoplastic nodules of small size were present in the parietal peritoneum both on the under surface of the anterior abdominal wall and on the inferior aspect of the diaphragm - A few nodules were also present in the cavity.

Bladder. definitely dilated : muscular trabeculae definitely hypertrophied. Mucous membrane lining bladder normal, except for a limited area of submucus malignant infiltration in the neighbourhood of the urethral outlet.

Prostate. Enlarged to a spherical mass about three times the normal size. Moderately firm in consistence. On section, diffuse infiltration by pale yellow malignant tissue.

Liver. Definitely enlarged and rendered irregular on the surface by many projecting carcinomatous nodules, some of which were umbilicated. Section revealed carcinomatous nodules with central necrosis, scattered throughout the surface.

Para-aortic lymph nodes. Markedly enlarged and of unusually firm consistence owing to infiltration by pale yellow malignant tissue.

Microscopic appearances.

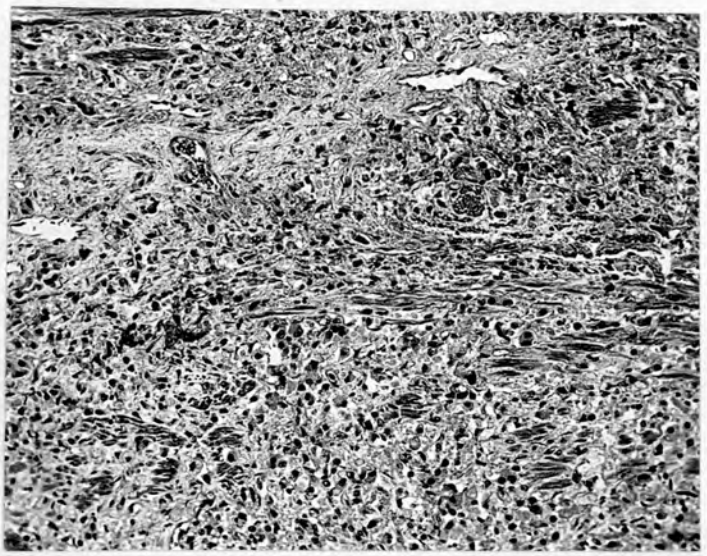
Prostate. The neoplasm infiltrating the prostate gland has the structure of a well differentiated adenocarcinoma.

Liver. The portal tracts in the liver are markedly infiltrated with lymphocytes as in lymphatic leukaemia. There is a nodule of well developed adenocarcinomatous tissue.

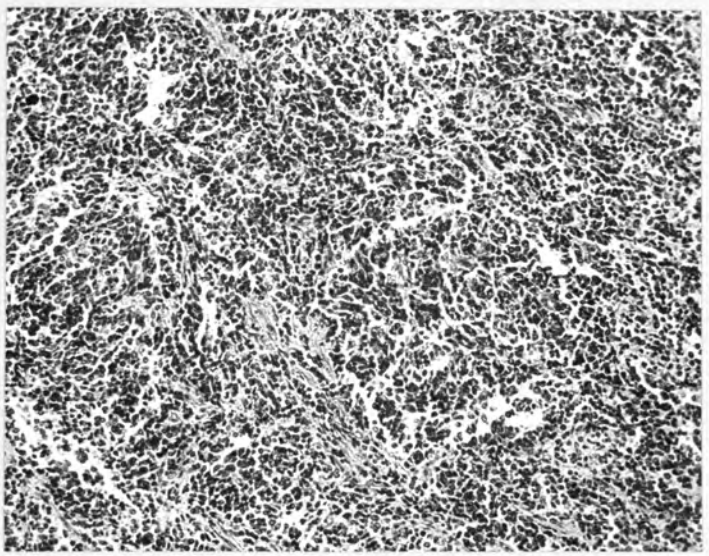
Case 5.

64 yrs. Died 20th. July, 1949.
Provisional diagnosis - Pneumoconiosis.

Chronic cough with increasing breathlessness for years. Symptoms much worse since accident to back in April. Has had stubborn constipation since and was therefore admitted to Wards 7/8 on several occasions. Has been very breathless since. Xray of/



P.M. 361/49. Prostate. Poorly differentiated adenocarcinoma. Nuclei rather pyknotic. Haematoxylin & Eosin x 120.



P.M. 361/49. Lung. Typical bronchogenic carcinoma. Haematoxylin & Eosin x 120.

of chest shows changes of Pneumoconiosis. Admitted to ward 29 for breathlessness. Condition deteriorated.

Pleural sacs.(left) Contained about one pint of clear fluid. The pleural surface of the left lower lobe was studded with numerous deposits of secondary tumour growth. (Right). No excess of fluid and pleura was smooth and shining.

Lungs. Both were very voluminous. Numerous pale nodules seen on section. Dependent parts congested. Large nodular mass in hilum of right lung. Left lung substance not infiltrated.

Mass of enlarged glands at bifurcation of trachea.

Pericardial sac. Contained about 5 ozs. of clear fluid.

Pericardium over the anterior surface of heart was roughened by a layer of tumour infiltration.

Prostate. Moderately enlarged. Uppermost portion felt tough and stringy, one or two small lumps were present beneath the mucous membrane of the bladder at a distance of about 1" from prostate itself.

Histologically, the malignant deposits all over the body had the same features.

1) Bronchial carcinoma.
2) Carcinoma of prostate.

Case 6.

61 years. Brewery worker.

Patient first began to have vague back and abdominal pains with frequency of micturition in October 1949 and consulted his doctor at this time but was reassured after examination. On 13th. December 1949 he fell, felt dizzy and unsteady and was unable to micturate. On 15th. December he consulted his own doctor and was referred to Western General Hospital with urinary retention and paralysis of both legs. Bladder was distended to umbilicus.

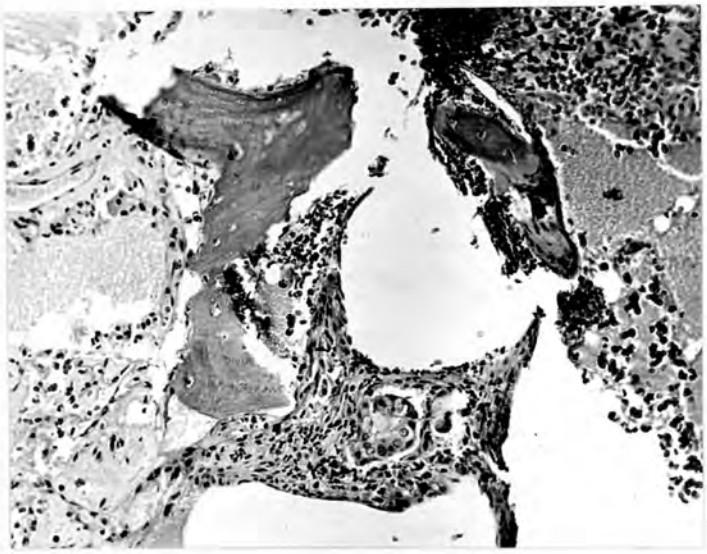
On rectal examination prostate was small, flat and regular.

Was transferred to Ward 20 with a provisional diagnosis of Spinal cord tumour. This diagnosis was made in view of the fact that the patient complained of backache, girdle pains and spastic paraplegia which on 29th. December 1949 had an upper sensory level (Thoracic and with sacral sparing).

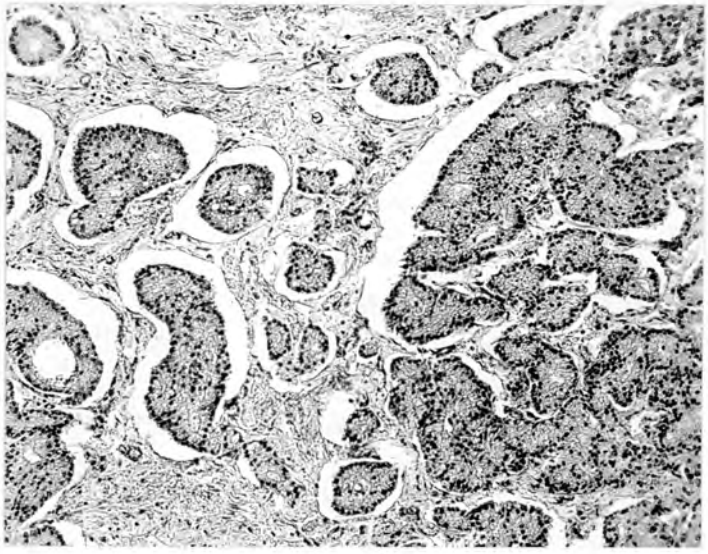
Lumbar puncture showed complete block with xanthrochromatic fluid.

30th. December 1949. Myelography showed a complete arrest at lower border of thoracic 7.

31st. December 1949. Laminectomy initially and through Thoracic 6, 7, 8 but owing to evidence of block at level of Thoracic 4, Thoracic 4 and 5 were removed. The bone at operation was thought to be involved by tumour and what was thought to be an infiltrating epidermal tumour at level of Thoracic 4 and/



MHA.3621. " Spinal cord tumour " - well differentiated adenocarcinomatous deposit. Haematoxylin & Eosin x 150.



MHA. 3621. Prostate. Well differentiated adenocarcinoma. Haematoxylin & Eosin x 90.

and Thoracic 5 partially removed. After operation patient developed a urethritis.

5th. January 1950. On lumbar puncture - yellow fluid at a pressure of 90 mm. was obtained.

4th. January 195 0. Serum acid phosphatase 26 King Armstrong Units.

7th. January 1950. Stilboestrol 5 mgm. t.i.d.

Rectal examination : Prostate not enlarged but left lobe is hard especially in its upper part which is irregular. The findings are suggestive of a typical carcinoma.

Histological examination :

EHB 2882) 31.12.49. Operation specimens of tumour
NP 4422) which were removed at the level of Thoracic 5, 6, 7, 8.

X-ray 11.1.50. Chest and pelvis.

Diffuse metastatic involvement by osteoplastic metastases of lumbar side of pelvis and of all the ribs.

17.1.50. Serum acid phosphatase 32 Units.
1.2.50. Serum acid phosphatase 14 Units.
19.2.50. Serum acid phosphatase over 60 Units.

The patient was a test case for Prof. McWhirter. The pituitary gland was irradiated.

On readmission to Western General Hospital one day before death, the patient developed anuria, was very dehydrated and died suddenly.

At post mortem. (MHA 3621.)

Primary in prostate.

Metastatic deposits were present in left iliac glands, ribs, left ileum, ischium, thoracic vertebra, lungs.

The prostate gland was enlarged and of irregular shape. On section it was found to be replaced by very firm, white homogeneous tumour tissue. The tumour extended laterally on the left side and was adherent to the fascia over the ischium and had spread up over the iliacus muscle.

The left iliac group of glands were considerably enlarged and replaced by tumour similar to that in the primary growth.

Lungs. Subpleural white nodules varying from a few millimetres to one centimetre in diameter. Both lungs contained tumour deposits. They were firm to the touch. On section they appeared as white homogeneous deposits.

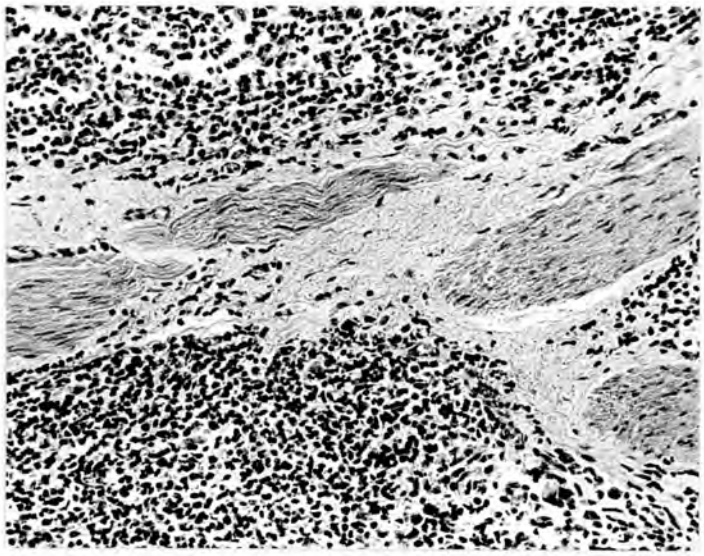
Bones. Deposits in ribs, ilium with evidence of osteoblastic activity.

Case 7.

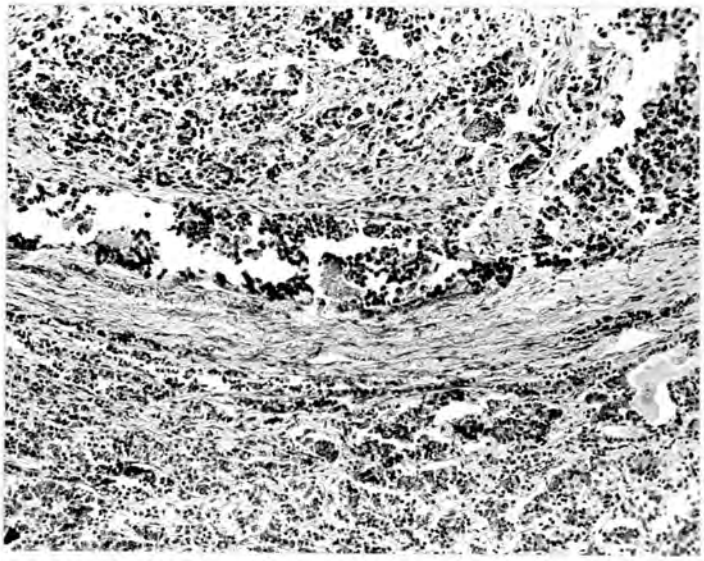
16 yrs. Mr. Jeffreys. Chalmers Hospital.
Farm labourer.

At beginning of August 1947 noticed some discomfort in lower abdomen. He was able to continue work as farm labourer. On 1.9.47 right leg began to swell and left leg felt weak. Was referred to Chalmers Hospital by his medical attendant. On 4.9.47 admitted to Chalmers.

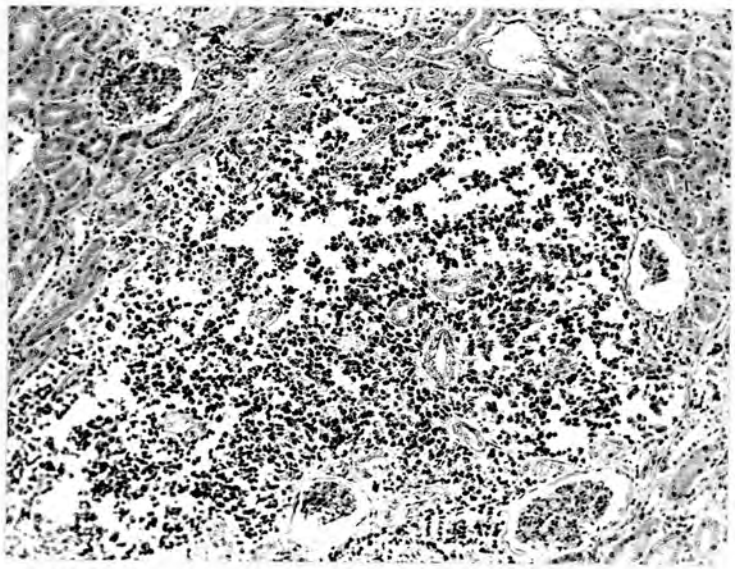
On/



CHA. 64. Psoas muscle. Invaded by lymphosarcoma of prostate. Haematoxylin & Eosin x 120.



CHA.64. Suprarenal. Invaded by lymphosarcoma of prostate. Haematoxylin & Eosin x 90.



CHA.64. Kidney. Invaded by lymphosarcoma of prostate. Haematoxylin & Eosin x 90.

On examination there was oedema of the whole of right leg.

Rectal examination revealed an enlarged prostate.

While in hospital developed acute retention which was not relieved by catheterisation, hot baths, etc.

On 15.9.47 a cystoscopy was performed. It was then considered malignant.

There was an enlarged lymph node just deep to left sterno-mastoid.

On Stilboestrol.

22.12.47. Readmitted owing to pain in right temporal region and numbness in supraorbital region.

16.1.48. Died. P.M. ChA. 64.

Abstract :

1. Widespread involvement of lymph nodes with neoplastic tissue. ? primary or secondary.
2. ? Secondary involvement of kidneys and pituitary.
3. Neoplastic involvement of ribs on left side.

Genito-Urinary System.

Both kidneys were considerably swollen, of the usual shape and fairly firm, consistence. Section revealed very pale surfaces in which cortex was poorly differentiated from medulla. Vessels healthy. Capsules stripped off readily revealing smooth, very pale surfaces which showed a number of spheroidal deposits approximately 2 mm. in diameter, which were suggestive of secondary neoplastic involvement.

Pelves, ureters, bladder and prostate. Pelves and ureter showed no abnormalities. The posterior aspect of the outer part of the bladder wall showed a number of scattered, ovoid, whitish deposits highly suggestive of neoplastic tissue. The bladder, apart from that, showed no abnormalities.

The prostate did not reveal any departure from the normal on macroscopic examination.

Brain. Doubtful evidence of secondary involvement of the pituitary (posterior part) was present. In addition, the bone comprising the sella turcica appeared to be somewhat disintegrated, suggesting neoplastic infiltration of its substance.

Microscopic examination.

Prostate. Several blocks taken from the prostate show the same appearances, viz., the greater part of the gland is of normal structure apart from localised areas which show malignant tissue. In these areas the neoplasm is completely undifferentiated, consisting of closely-packed masses of round or polyhedral cells. The majority of the cells are degenerated in appearance, no doubt due to the effects of irradiation, and hence detailed description will be found in the various secondary deposits (vide infra). However, it can be stated at this stage that after examination of all areas of neoplasia, this neoplasm is not a carcinoma, but is an undifferentiated, highly anaplastic sarcoma taking origin from the prostate. Such lesions, though exceedingly rare, are well known entities in young people.

Lymph/

Lymph Nodes. Lymph nodes taken from the various involved regional groups (see autopsy report) reveal a similar structure. In all cases the nodes are replaced by a completely undifferentiated anaplastic sarcoma. The majority of the cells are round or polyhedral in shape and fairly closely packed. In addition, large bizarre giant cells are scattered throughout, containing multiple nuclei. In the smaller cells the nuclei are large, very active in appearance, and fill the greater part of the cell body, only a scanty rim of cytoplasm remaining. Mitotic figures are scattered throughout but are not excessive. Areas of necrosis are not present in any size, but in some situations a polymorph infiltration indicates secondary infection. A fairly delicate fibrous stroma, containing thin-walled vessels, supports the neoplastic tissue. Many vessels contain masses of tumour cells.

Postero-Superior wall of Bladder. The outer part of the muscle coat contains well defined nodules of similar neoplastic tissue which project slightly above the free surface just below a narrow layer of fibrous tissue.

Kidneys. The small foci seen at autopsy are small collections of tumour cells lying in the cortex.

Pituitary Gland. The entire posterior lobe is replaced by neoplastic tissue of similar character.

Mass of tissue on Left 6th. Rib : Entirely composed of neoplastic tissue of similar character.

Case 8.

MHA 2316. 60 yrs.
Admitted 28.3.47. Died 12.5.47.

Haematuria since June 1946, also sciatic pain along left leg. Pain was partially relieved by Stilboestrol within 1 week and very considerably within three months. Steady loss of weight since 1939.

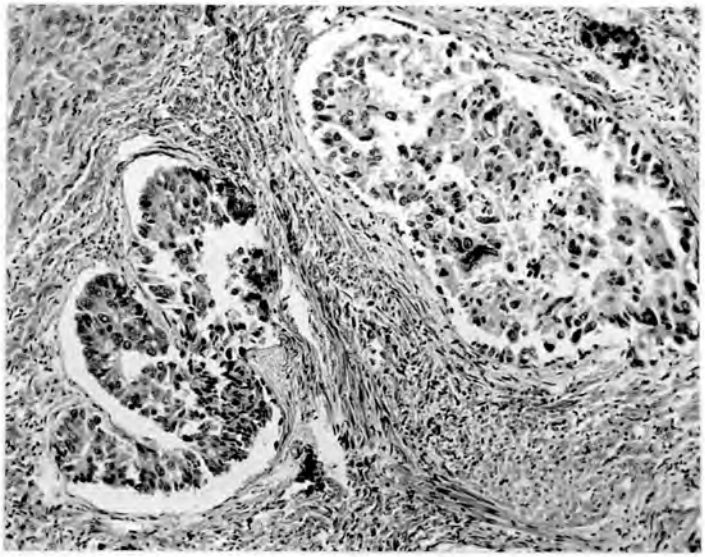
On admission pain on pressure over sciatic notch. Enlarged supra clavicular gland on left side.

Prostate. Both lateral lobes slightly enlarged. Right lobe having a firmer consistence.

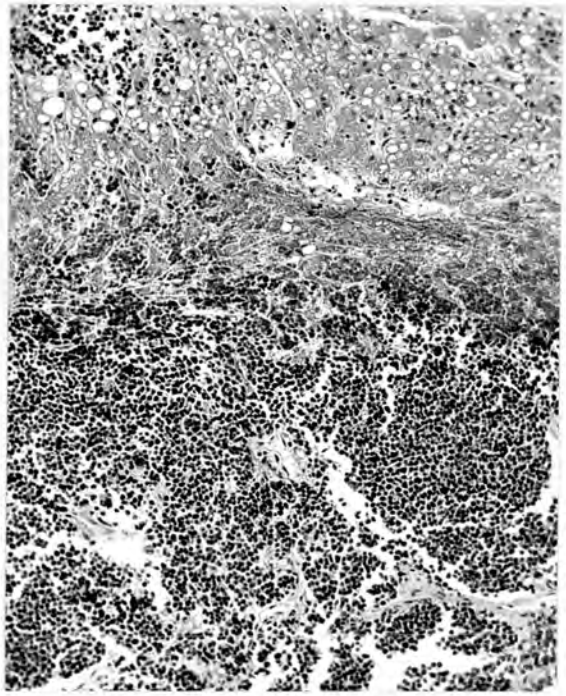
Liver. Contained two small nodules of metastatic growth. One at the right lower pole of liver and the other at a point on the posterior surface and upper border in the same vertical axis as the first.

Lungs. There was a mass of firm tumour tissue at root of right lung extending diffusely into substance of upper lobe, and appearing as a smooth diffuse nodularity in the mucosal surface of the wall of the right epiarterial bronchus. There were numerous haemorrhagic spots in the adjacent lung tissue. At several points the tumour tissue was found growing within the lumen of the pulmonary venules.

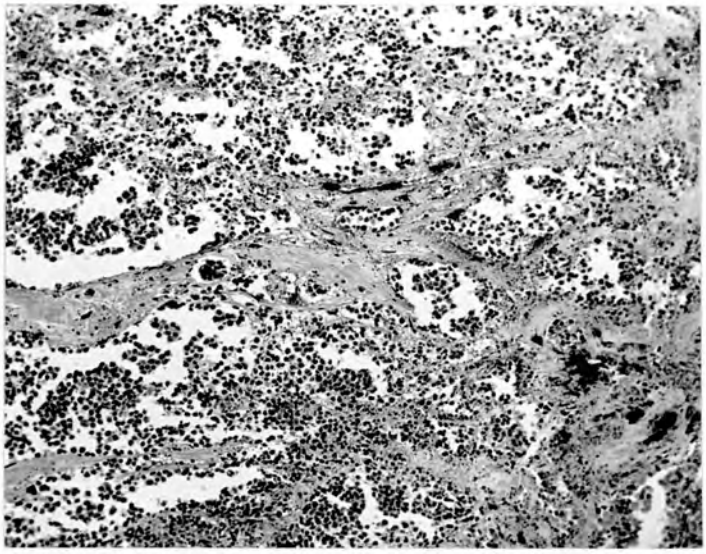
The upper anterior mediastinal glands were involved in tumour tissue which formed a massive block/



MHA. 2316. Liver (1). Well differentiated adenocarcinomatous deposit undergoing retrogressive change. Note fragmentation of glandular epithelium. Haematoxylin & Eosin x 120.



MHA. 2316. Liver (2). Deposit from Bronchogenic carcinoma. Haematoxylin & Eosin x 120.



MHA. 2316. Prostate. Note pyknotic nuclei. Loss of glandular structure. Fair response to oestrogen therapy. Haematoxylin & Eosin x 120.

block at the thoracic ribs and extending up to the neck on the left side.

Abstract.

Carcinoma of the prostate with signs of regression.
Bronchogenic carcinoma with secondary deposits in liver and lymph nodes.
No bone involvement.

Case 9.

475/49. 78 yrs.
Admitted 3.10.49. Died 10.10.49.

Admitted with a history of frequency and thirst having been on DINOESTROL 15 mgm. since 22.9.49.
On rectal examination the prostate was enlarged, hard, irregular and diagnosis of Carcinoma of prostate was made.
Since admission has been weaker and shows signs of early uraemia. Intensive DINOESTROL therapy (15 mgm. 4 hrly.) was given together with frequent catheterisation to decompress the bladder. Though disorientated he remained fairly well till this morning when he suddenly collapsed. Nothing could be made out on examination to account for this collapse and though stimulants were given he died at 10.45 a.m.

Abstract.

Carcinoma of prostate.
Secondary deposits in lungs.
Hydronephrosis.
Uraemia.

Lungs (left) had a nodular sensation : whitish grey fibrous markings on surface. Small nodules scattered in lung substance.
(Right) Oedema at base of lung.
Prostate. Twice its normal size. Nodular. Lateral lobe mainly enlarged.

Microscopic appearance.

Prostate. Hypertrophy of acini. The acini show increase in number. Some of them show marked hyperplasia of lining epithelium which is thrown into villous processes and fill acinar cavity. Others are dilated and contain hyaline and acidophil substances - corpora amylacea. In other sinuses the epithelium is so active as to break the basement membrane, fill the acinar cavity and infiltrates the surrounding parenchyma. There is therefore a malignant transformation.
Lungs. Well differentiated adenocarcinoma.

Case 10.

370/ 50. 66 yrs.

Has been treated with DINOESTROL for Carcinoma of prostate with pelvic metastases during last two years/

years. Recently developed considerable urinary difficulty. Suprapubic cystostomy was done despite patency of urethra. Became very lethargic with considerable personality change. ? cerebral metastases. He has been having very severe hypertension for years but no history of a cerebrovascular accident.

Abstract.

Carcinoma of prostate with secondaries in lumbar vertebrae.
Hypertrophy and dilatation of bladder.
Mild hydronephrosis and hydroureter.
Left ventricular hypertrophy and dilatation.
Old myocardial infarct.
Severe coronary, cerebral and aortic atheroma.
Oedema and haemorrhage of lungs.

Prostate. Slightly enlarged. It was of firm consistence, but not stony hard. On section white homogeneous tissue was present with here and there a few small more firm nodules suggestive of neoplastic change. The capsule was intact and there was no evidence of tumour infiltration into the peri-prostatic tissue. The membranous urethra admitted a probe with ease.

Bladder. Moderately dilated : well hypertrophied with prominent trabeculae. Mucosa oedematous with occasional areas of haemorrhage.

Kidney. No evidence of pyelonephritis or metastatic deposits. Renal pelvis dilated on each side.

Heart. Moderately enlarged. Globular in shape.

Lungs. Emphysema; slight oedema at bases of lungs.

Brain. Two old infarcts were found in the lentiform nucleus.

Lumbar vertebrae. All extensively replaced by firm white tumour metastases ; increasing a few milimetres to 1 cm. There were no collapsed vertebrae.

Microscopic features.

Prostate. Glandular elements scanty. Those present show hyperplastic changes, dilatation and desquamation of the epithelial cells into the lumina. In several areas are found foci of poorly differentiated adenocarcinoma the component cells being small with poorly staining cytoplasm and circular densely staining nuclei. Mitoses are scanty and the general picture of these neoplastic areas is one of quiescence.

Lumbar vertebrae. Spheroidal cells with large nuclei and showing no glandular differentiation. Mitoses scanty. Well marked osteoblastic reaction in the vicinity of these secondaries.

Case 11./

Case 11.

MHA 3308. 64 yrs.
Western General Hospital. DI.
Admitted 11.3.49. Died 26.6.49.

In 1946 patient complained of delay in micturition, no pain, difficulty in commencing the act. Now passes urine every hour with polyuria. No retention.

Twelve months ago complained of pains in upper part of right thigh.

11.3.49. Fell, breaking upper third of right femur. Since admission has been treated with STILBOESTROL for prostatic carcinoma.

Has been Xrayed.

Carcinoma of prostate with local infiltration of pelvic fascia and pelvic bone on right side.

Lymph glands along right internal iliacs affected.

Blood metastases to pelvis, ribs, femur, vertebral column, lower and upper lobe of left lung.

Gynecomastia of breast.

Prostate. Very slightly enlarged, especially right lobe which is replaced by scirrhous carcinoma. A small infiltrating zone of carcinoma is present in left lobe. The carcinoma of right lobe has infiltrated pelvic fascia in its neighbourhood forming a vague but continuous band of tumour tissue between prostate and a mass of tumour in acetabular region of the right pelvic bone.

Ribs. Tiny metastases in middle of 5th. and 6th. ribs on right side.

Vertebral column. One solitary metastatic deposit two cm. in diameter in body of first lumbar vertebra.

Pelvis. One metastatic nodule 2.5 cm. in diameter just lateral to left sacro-iliac joint. The right hemi pelvis is largely replaced by firm white neoplasm. The main mass is in the acetabular region and has grown through the pelvis downwards around and infiltrating the neck of upper third of the femur where there is a pathological fracture which is surrounded by a mass of tumour 10 cms. in diameter, infiltrating the muscles as well as the bone.

Liver. Slightly enlarged and contains numerous metastatic deposits of varying size. The largest in the right lobe is 6 cm. in diameter.

Microscopic features.

Prostate. Is infiltrated and largely replaced by moderately well differentiated adenocarcinoma showing some areas of anaplasia.

Right iliac node. A small zone of infiltration by carcinoma identical with the anaplastic areas of the primary.

Breasts. Slight increase and suggestive of proliferation of small ductules.

Case 12./

Case 12.

MHA 4336. 83 yrs.
Admitted 10.2.51. Died 20.5.51.

Carcinoma of prostate 3-4 years.
Nocturia, frequency and urgency.
Has been treated with oestrogens - DINOESTROL.
Bi weekly tests of gastric secretion.
Has been Xrayed.

Prostate. Enlarged slightly. On section widespread nodularity. No naked eye evidence of malignancy.
No metastases in lymph nodes : even on microscopic examination.

Microscopic examination of prostate.

Simple enlargement of prostate + in some areas large hyperchromatic cells with prominent nucleoli, are seen in stroma, often having the appearance of collapsed acini. These are the malignant areas which have regressed and become greatly atrophic under Dinoestrol treatment.

Case 13.

MHA 2711. 63 yrs. Western General Hospital.

Had a transurethral resection for prostatic carcinoma two years ago in Leith Hospital. Was given Stilboestrol for a short time. 2nd. January, 1947 - Developed acute retention following an attack of flu and was catheterised.
2nd. February 1947. Second transurethral resection done.
7th. April 1948. Admitted with anuria passing blood per urethra and in an increasing state of uraemia.

Abstract.

Carcinoma of prostate with spread to bladder wall.
Metastasis in iliac nodes, para-aortic nodes, liver, hepatic nodes, right psoas muscle, lymphatic spread in lungs.
Gynecomastia.

Both breasts were enlarged and the nipples were enlarged to about 3 times normal. Very hard in consistence and gave a gritty sensation on cutting with a knife. On section the cut surface appeared as a firm, white tissue with no evidence of nodularity, flecked here and there with small yellow areas. The tumour tissue appeared to be confined in the prostate gland to the lateral lobes for on the posterior aspect of the prostatic urethra no undue thickening could be felt.

Both ureteric orifices were surrounded by tumour growth which was heaped up to give a small round/

round swelling about one centimetre in diameter.

Testis. Found to be very much smaller than normal especially left side.

Liver. Grossly enlarged : on external examination there were very numerous tumour deposits throughout both lobes. They showed central umbilication.

Lymph glands. Metastatic deposits were present in lymph glands along internal iliac arteries : common iliacs and para-aortic gland. Early involvement of glands in porta hepatis.

Lumbar vertebrae. Body of 4th. lumbar vertebrae showing a small round nodule of pale tissue.

Right psoas muscle. in relation to the large internal iliac glands showed extensive haemorrhage into muscle fibres. This involved practically the whole of the body of the muscle.

Microscopic features.

Spheroidal cell carcinoma with no evidence of acinar formation, the cells lying in clumps. The cells have a small quantity of clear cytoplasm with rather vacuolated nuclei : moderate numbers of mitotic figures are seen. Many pyknotic and fragmentary nuclei are scattered among the tumour cells with here and there clumps of such material. Both lymphatic and vascular embolism are present, the former frequently perineural. The stroma is abundant consisting mainly of plain muscle and is there has been hyperplasia of the muscle tissue of the gland.

The biopsy taken on 10.2.47 (MHB 1857) shows much more glandular differentiation into glandular structures and though pyknosis is present it is less marked. The cells have more abundant cytoplasm which is markedly vacuolated and the cell walls which are often difficult to see in the autopsy material are easily distinguishable in the biopsy. Mitosis is less frequent.

Secondary deposits.

Metastatic deposits in para-aortic and omental glands, liver and lung. In all these areas the tumour had basically similar appearances, though in the para-aortic and lung : it is much more pleomorphic and mitosis is more frequent. Degenerative changes in the cells are less marked and the stroma is much more fibrous.

In the lung metastases had occurred not only in the subpleural region, but in lymphatics and veins well within the lung substance.

Case 14.

730/ 50. 75 yrs.

Apparently a diagnosis of Carcinoma of the prostate with bony secondaries was made two months ago at the Western General hospital. He was referred to the Radiotherapy department and given a course of Pituitary irradiation. He suddenly collapsed yesterday and was admitted moribund and died within a few hours.

Abstract.

Carcinoma of the prostate with gross local spread.
Metastatic deposits in para-aortic glands, 3rd. and 4th. lumbar vertebrae and liver.
Obstruction of ureters.
Bilateral hydronephrosis and hydroureter.
Uraemia.
Oedema of lungs.
Hypertensive hypertrophy of heart.
General cardiac dilatation.

Liver. Average size and shape : pale and soft : through its external surface could be seen numerous rounded yellowish-white metastatic tumour deposits. On section many tumour nodules were seen with central necrosis.

Bladder. Arising from the posterior part of the prostate and spreading across the recto-vesical space into the wall of the rectum, penetrating this until it lay just under the rectal mucosa and spreading laterally more markedly on left side than on the right, to invade the muscles of the wall of the pelvis, and stretching superiorly to involve the lower para-aortic glands there was a large, whitish mass of firm tissue - a carcinoma of the prostate. It had also ulcerated into the trigone of the bladder, and had surrounded the mouths of either ureter.

Lumbar vertebrae. The bodies of the 3rd. and 4th. lumbar vertebrae had been largely replaced by whitish tumour tissue.

STATISTICAL DATA.

Table I.
Pathological Material Examined.

Total no. of simple enlargement of prostate biopsies	=	1998
Total no. of cancer of prostate biopsies	=	226
Total no. of simple enlargement of prostate autopsies	=	176
Total no. of cancer of prostate autopsies	=	58
Grand total	=	2458.

Table II.

Pathological Material Classified.

Biopsies	Royal Infirmary	Municipal Hospitals
Simple enlargement of prostate	1336 (90%)	662 (90%)
Carcinoma of prostate gland	154 (10%)	72 (10%)
Autopsies		
Simple enlargement of prostate	80 (70%)	96 (81%)
Carcinoma of prostate gland	33 (30%)	25 (19%)
	113	121

Table III.

Number of Biopsies (Annually) - Royal Infirmary.

Year	Simple Enlargement	Cancer	Total Prostate Biopsies.
1936	28	5	33
1937	49	0	49
1938	30	2	32
1939	52	6	58
1940	48	4	52
1941	50	4	54
1942	55	4	59
1943	62	6	68
1944	59	8	67
1945	68	7	75
1946	93	12	105
1947	119	18	137
1948	121	11	132
1949	100	21	121
1950	131	11	142
1951	134	10	144
1952	137	25	162
Total	1336	154	1490
Percentages	89.65%	10.35%	4.66%

Table IV.

Number of Biopsies (Annually) - Municipal Hospitals.

Year	Simple Enlargement	Cancer	Total Prostate Biopsies
1936	5	0	5
1937	9	1	10
1938	21	13	34
1939	33	2	35
1940	9	1	10
1941	15	1	16
1942	17	2	19
1943	19	2	22
1944	14	1	15
1945	8	0	8
1946	33	3	36
1947	48	6	54
1948	32	11	43
1949	67	9	76
1950	70	8	78
1951	115	4	119
1952	147	8	155
Total	662	72	734
Percentages	90.06 %	9.94 %	

Table V.

Number of Biopsies (Annually) - Royal Infirmary.

Year	All Biopsies	Simple Enlargement	Cancer	Total Prostate Biopsies
1936	950	28	5	33
1937	855	49	0	49
1938	883	30	2	32
1939	991	52	6	58
1940	1232	48	4	52
1941	1190	50	4	54
1942	1304	55	4	59
1943	1406	62	6	68
1944	1299	59	8	67
1945	1369	68	7	75
1946	1601	93	12	105
1947	2118	119	18	137
1948	2368	121	11	132
1949	3819	100	21	121
1950	4369	131	11	142
1951	3086	134	10	144
1952	3099	137	25	162
Total	31939	1336	154	1490
%		89.65%	10.33%	4.66%

Table VI.

Number of Biopsies (Annually) - Municipal Hospitals.

Year	Simple Enlargement	Cancer	Total Prostate Biopsies
1936	5	0	5
1937	9	1	10
1938	21	13	34
1939	33	2	35
1940	9	1	10
1941	15	1	16
1942	17	2	19
1943	19	3	22
1944	14	1	15
1945	8	0	8
1946	33	3	36
1947	48	6	54
1948	32	11	43
1949	67	9	76
1950	70	8	78
1951	115	4	119
1952	147	8	155
Total	662	73	735
%	90.06%	9.94%	

Total number of all Biopsies 17947 4.096%
Total number of Prostate Biopsies 735

Table VII.

Number of Autopsies (Annually) - Royal Infirmary.

Year	Simple Enlargement	Cancer
1936	3	0
1937	2	1
1938	4	1
1939	6	0
1940	8	1
1941	2	2
1942	3	2
1943	1	1
1944	4	0
1945	1	0
1946	4	3
1947	1	4
1948	1	3
1949	3	7
1950	6	3
1951	27	2
1952	4	3
Total	80	33

Table VIII.

Reference Numbers. Simple Enlargement of Prostate.

(Autopsies). M.H.A.

1936. Nil.

1937. MHA/181, MHA/256.

1938. MHA/277, MHA/295, MHA/346.

1939. MHA/484, MHA/520, MHA/554.

1940. MHA/665, MHA/684.

1941. MHA/780, MHA/971.

1942. MHA/1059, MHA/1111.

1943. MHA/1224, MHA/1363.

1944. MHA/1519, MHA/1558, MHA/1660.

1945. MHA/1863.

1946. MHA/1967, MHA/2008, MHA/2111, MHA/2135.

1947. MHA/2215, MHA/2278, MHA/2313, MHA/2402, MHA/2427, MHA/2474, MHA/2476, MHA/2483.

1948. MHA/2596, MHA/2657, MHA/2740, MHA/2821, MHA/2848, MHA/2886, MHA/2916, MHA/2924, MHA/2933, MHA/3049.

1949. MHA/3131, MHA/3142, MHA/3158, MHA/3328, MHA/3405, MHA/3413, MHA/3415, MHA/3482, MHA/3504.

1950. MHA/3350, MHA/3592, MHA/3859, MHA/3864, MHA/3979, MHA/4006.

1951. MHA/4205, MHA/4268, MHA/4436, MHA/4504, MHA/4505, MHA/4506, MHA/4512, MHA/4572, MHA/ 4584.

1952. MHA/4762, MHA/4935, MHA/4936.

1952. EHA/1574, EHA/1606, EHA/1619, EHA/1692, EHA/1754, EHA/1759.

1940. CHA/9, CHA/28.

1939. DHA/3, DHA/23, DHA/29, DHA/175.

1940. LHA/38, LHA/118.

1943. LHA/120, LHA/136, LHA/177.

1945/

1945. LHA/218.

1946. LHA/270.

1947. LHA/305.

1948. LHA/357, LHA/374.

1950. LHA/457, LHA/462, LHA/469.

1951. LHA/1289.

1952. LHA/586.

Table IX.

Reference Numbers of Simple enlargement - Autopsies - Royal Infirmary Series.

1936. 521, 541, 549.

1937. 513, 536.

1938. 214, 288, 340, 462.

1939. 15, 86, 284, 375, 446, 485.

1940. 10, 16, 128, 179, 234, 317, 396, 419.

1941. 21, 203.

1942. 341, 405, 444.

1943. 171.

1944. 8, 69, 211, 415.

1945. 172.

1946. 21, 107, 270, 257.

1947. 458.

1948. 608.

1949. 80, 332, 500.

1950. 52, 144, 147, 503, 649, 720.

1951. 97, 145, 241, 281, 283, 298, 313, 330, 338, 348, 370, 453, 492, 556, 584, 587, 606, 607, 608, 612, 634, 669, 737, 752, 764, 767, 809.

1952. 80, 142, 356, 577.

Total number of autopsies = 80.

Table X.

Reference Numbers. Cancer of Prostate (Autopsies)

Municipal Hospitals.

1936. Nil.

1937. MHA/214.

1938. Nil.

1939. MHA/484, DHA/10, LHA/8.

1940. Nil.

1941. MHA/835, MHA/889.

1942. Nil.

1943. MHA/1294.

1944. Nil.

1945. MHA/1754, MHA/1766.

1946. MHA/1948, MHA/2133.

1947. MHA/2316, MHA/ 2497, MHA/3567.

1948. MHA/2711, MHA/2832, MHA/2936, CHA/64.

1949. MHA/3308, MHA/3342.

1950. MHA/3621, MHA/3939.

1951. MHA/4336.

1952. MHA/4621, EHA/1788.

Total Number of Cancer Autopsies = 25.

Table XI.

Reference Numbers. Cancer of Prostate - Biopsies.

Municipal Hospital Series.

1936. Nil.

1937. MHB/154.

1938. MHB/237, MHB/238, MHB/242, MHB/246, MHB/261, MHB/277, MHB/298, MHB/329, MHB/345, MHB/357, MHB/358, MHB/366.

1939. MHB/466, MHB/467.

1940. MHB/483.

1941. MHB/576.

1942. MHB/741, MHB/793.

1943. MHB/1057, MHB/1108.

1944. MHB/1144.

1945. Nil.

1946. MHB/1518, MHB/1587, MHB/1666.

1947. MHB/1857, MHB/1963, MHB/2 010, MHB/2039, MHB/2311, MHB/2331, MHB/2389.

1948. MHB/2416, MHB/2658, MHB/2680, MHB/2798, MHB/2807, MHB/2964, MHB/3181, MHB/3373, MHB/3443, MHB/3580, MHB/3727.

1949. MHB/4171, MHB/4289, MHB/4349, MHB/4554, MHB/4806, MHB/4943, MHB/5277, MHB/5393.

1950. MHB/5681, MHB/6003, MHB/6106, MHB/6674, MHB/7203, MHB/7231, MHB/7520, MHB/7925.

1951. MHB/8157, MHB/8863, MHB/9726, MHB/10119.

1952. MHB/11939, EHB/4739, EHB/4346, EHB/4576, EHB/12761, EHB/12910, EHB/12709, EHB/12979.

Total number of MHB and EHB Cancer Biopsies = 72.

Table XII.

Rreference Numbers of Biopsy material -

Royal Infirmary Series.

Simple Enlargement of the Prostate.

Volume 40. 1936.

46, 54, 106, 125, 232, 266, 273, 275, 279, 387, 421, 472, 486, 545, 558, 575, 600, 656, 686, 694, 712, 724, 735, 784, 892, 900, 919, 927.

Total Biopsies = 28.

Volume 41. 1937.

3, 18, 56, 60, 62, 84, 104, 107, 138, 142, 147, 153, 225, 253, 255, 257, 307, 330, 339, 354, 375, 381, 385, 400, 418, 420, 421, 458, 464, 475, 485, 486, 488, 492, 507, 596, 609, 615, 644, 651, 703, 704, 712, 713, 717, 756, 801, 830.

Total Biopsies = 49.

Volume 42. 1938.

25, 36, 37, 42, 59, 68, 73, 82, 135, 190, 191, 262, 322, 323, 355, 385, 424, 508, 509, 528, 585, 583, 591, 592, 650, 669, 725, 839, 870, 881.

Total Biopsies = 30.

Volume 43. 1939.

17, 18, 23, 37, 69, 105, 106, 121, 138, 168, 195, 215, 259, 263, 339, 357, 377, 426, 443, 448, 493, 494, 504, 526, 530, 543, 556, 577, 582, 590, 603, 616, 624, 639, 657, 665, 687, 699, 707, 708, 721, 739, 746, 747, 757, 801, 806, 812, 877, 910, 912, 962.

Total Biopsies = 52.

Volume 44. 1940.

32, 62, 63, 77, 111, 138, 302, 337, 392, 413, 439, 460, 483, 505, 615, 620, 621, 644, 690, 691, 742, 730, 783, 819, 823, 875, 907, 945, 948, 994, 1001, 1004, 1012, 1017, 1051, 1091, 1125, 1132, 1148, 1161, 1163, 1168, 1175, 1176, 1178, 1220.

Total Biopsies = 48.

Volume 45./

Volume 45. 1941.

20, 42, 47, 124, 144, 176, 178, 183, 200, 224, 231, 310, 312, 320, 322, 324, 356, 384, 390, 392, 403, 436, 452, 481, 482, 497, 520, 545, 567, 568, 576, 578, 623, 634, 697, 724, 801, 849, 851, 889, 901, 913, 932, 1006, 1041, 1043, 1044, 1136, 1138, 1151.

Total Biopsies = 50.

Volume 46. 1942.

29, 48, 110, 125, 165, 185, 186, 188, 263, 271, 286, 295, 340, 358, 379, 381, 382, 385, 394, 395, 415, 457, 468, 536, 542, 591, 628, 637, 682, 704, 739, 752, 772, 782, 793, 797, 823, 898, 899, 902, 923, 942, 950, 954, 983, 1009, 1032, 1063, 1098, 1140, 1144, 1145, 1234, 1259, 1295.

Total Biopsies = 55.

Volume 47. 1943.

9, 27, 44, 67, 76, 118, 124, 138, 193, 209, 307, 309, 329, 346, 379, 396, 424, 481, 490, 510, 518, 533, 534, 537, 551, 603, 631, 667, 677, 725, 753, 763, 787, 804, 851, 896, 932, 972, 1002, 1005, 1009, 1020, 1075, 1081, 1100, 1123, 1124, 1130, 1155, 1183, 1185, 1197, 1201, 1207, 1240, 1267, 1274, 1283, 1355, 1388, 1396.

Total Biopsies = 62.

Volume 48. 1944.

49, 64, 67, 111, 119, 136, 137, 163, 168, 184, 192, 209, 211, 243, 283, 331, 370, 371, 420, 455, 476, 517, 533, 535, 559, 574, 591, 640, 676, 699, 728, 749, 785, 789, 791, 831, 833, 845, 896, 968, 984, 992, 993, 994, 996, 1007, 1027, 1043, 1071, 1104, 1167, 1168, 1178, 1216, 1240, 1254, 1257, 1284.

Total Biopsies = 59.

Volume 49. 1945.

21, 54, 60, 72, 83, 120, 129, 167, 197, 202, 236, 263, 271, 273, 275, 291, 294, 298, 305, 329, 332, 368, 371, 384, 432, 484, 526, 563, 564, 591, 621, 628, 672, 682, 683, 686, 829, 900, 926, 930, 949, 963, 1000, 1010, 1021, 1037, 1037, 1086, 1087, 1092, 1109, 1140, 1147, 1159, 1186, 1200, 1232, 1254, 1255, 1265, 1304, 1317, 1339, 1357, 1363, 1364, 1368, 1369.

Total Biopsies = 68.

Volume 50. 1946.

14, 26, 27, 45, 46, 57, 62, 73, 85, 86, 87, 88, 112, 113, 155, 174, 177, 180, 181, 184, 185, 192, 205, 208, 225, 250, 263, 264, 270, 327, 364, 374, 391, 398, 439, 446, 472, 486, 491, 494, 513, 522, 535, 587, 601, 652, 654, 658, 680, 685, 740, 777, 780, 783, 813, 815, 820, 858, 890, 902, 903, 920, 927, 930, 945, 955, 964, 994, 1054, 1056, 1068,1112, 1158, 1194, 1196, 1232, 1282, 1310, 1325, 1345, 1363, 1373, 1394, 1406, 1412, 1413, 1461, 1407, 1513, 1533, 1541, 1552, 1554.

Total Biopsies = 93.

Volume 51. 1947.

36, 40, 41, 43, 80, 98, 101, 143, 144, 149, 163, 166, 219, 221, 243, 251, 258, 274, 278, 284, 334, 338, 372, 376, 470, 481, 492, 493, 494, 538, 541, 561, 575, 743, 677, 732, 767, 771, 785, 814, 837, 840, 844, 866, 878, 886, 921, 922, 947, 948, 956, 989, 1037, 1038, 1072, 1082, 1091, 1104, 1125, 1127, 1134, 1155, 1219, 1236, 1239, 1244, 1246, 1258, 1281, 1286, 1318, 1347, 1348, 1352, 1361, 1367, 1383, 1421, 1438, 1439, 1449, 1453, 1464, 1467, 1468, 1487, 1497, 1502, 1505, 1506, 1507, 1513, 1570, 1606, 1630, 1677, 1683, 1700, 1764, 1791, 1792, 1849, 1855, 1859, 1879, 1904, 1918, 1919, 1923, 1930, 1950, 1955, 2026, 2032, 2056, 2063, 2065, 2106, 2119.

Total Biopsies = 119.

Volume 52. 1948.

1, 11, 12, 13, 47, 72, 77, 97, 105, 164, 189, 238, 251, 260, 265, 273, 288, 289, 309, 321, 324, 379, 438, 465, 476, 490, 503, 600, 646, 659, 711, 720, 725, 754, 765, 795, 799, 816, 830, 848, 858, 862, 865, 960, 986, 960, 993, 1005, 1009, 1021, 1028, 1041, 1062, 1077, 1112, 1117, 1133, 1151, 1158, 1240, 1268, 1275, 1298, 1317, 1336, 1363, 1367, 1393, 1407, 1430, 1432, 1440, 1460, 1472, 1473, 1483, 1488, 1497, 1514, 1517, 1521, 1543, 1545, 1570, 1590, 1598, 1600, 1608, 1616, 1657,1664, 1684, 1720, 1735, 1779, 1784, 1807, 1837, 1871, 1897, 1909, 1915, 1940, 1941, 1942, 1950, 1952, 1953, 1967, 1986, 2024, 2037, 2056, 2073, 2085, 2107, 2138, 1249, 2226, 2279, 2305, 2368.

Total Biopsies = 121.

Volume 53. 1949.

12, 47, 65, 92, 100, 134, 137, 14 0, 154, 166, 195, 204, 224, 232, 321, 343, 344, 358, 381, 385, 427, 465, 491, 502, 517, 531, 545, 639, 704,741, 750 , 802, 805, 832, 872, 920, 923, 926, 928, 929, 933/

933, 976, 992, 1004, 1039, 1051, 1085, 1128, 1136,
1140, 1156, 1173, 1235, 1261, 1265, 1268, 1361,
1460, 1477, 1549, 1580 , 1606, 1767, 1823, 1864, 1869,
1880, 1916, 1921, 1939, 1962, 1969, 1977, 1981,
2007, 2010, 2089, 2106, 2116, 2125, 1232, 2149,
2196, 2263, 2293, 2296, 2297, 2311, 2317, 2329,
2331, 2340, 2372, 2393, 2433, 2496, 2505, 2574,
2576, 2607.

Total Biopsies = 100.

Volume 54. 1950.

18, 52, 60, 128, 139, 141, 155, 215, 229,
230, 234, 254, 352, 378, 415, 469, 494, 502, 506,
543, 557, 582, 647, 655, 676, 679, 684, 702, 738,
778,783, 784, 806, 881, 926, 953, 974, 1004,
1025, 1053, 1093, 1099, 1134, 1141, 1180, 1214,
1222, 1236, 1247, 1304, 1308, 1315, 1329, 1331,
1368, 1435, 1440, 1478, 1522, 1593, 1621, 1624,
1650,1667, 1716, 1782, 1785, 1796, 1817, 1825,
1831,1842, 1844, 1847, 1849, 1853, 1 892, 1897,
1899, 1914, 1940, 1942, 1952, 1956, 1966, 1986,
1994, 2002, 2060, 2061, 2062, 2088, 2092, 2131,
2142, 2157, 2176, 2182, 2187, 2210, 2245, 2301,
2309, 2334, 2375, 2413, 2453, 2480, 2482, 2511,
2603, 2635, 2658, 2659, 2660, 2661, 2688, 2714,
2732, 2747, 2771, 2785, 2787, 2819, 2821, 2835,
2840, 2850, 2853, 2859, 2862.

Total Biopsies = 131.

Volume 55. 1951.

26, 31, 46, 49, 82, 171, 172, 198, 217, 248,
330, 419, 449, 465, 471, 476, 485, 539, 609, 621,
624, 661, 694, 695, 699, 730, 74 0, 756, 767, 777,
811, 841, 901, 947, 948, 965, 977, 1049, 1050,
1064, 1076, 1077, 1165, 1185, 1241, 1272, 1286,
1348, 1363, 1428, 1430, 1452, 1454, 1468, 1469,
1478, 1486, 1505, 1517, 1528, 1542, 1547, 1558,
1618, 1619, 1637, 1665, 1675, 1701, 1715, 1750,
1775, 1785, 1822, 1824, 1911, 1940, 1942, 1944,
1969, 1987, 1989, 2002, 2023, 2035, 2036, 2043,
2065, 2094, 2105, 2144, 2156, 2157, 2239, 2279,
2295, 2307, 2311, 2325, 2357, 2407, 2443, 2451,
2453, 2457, 2461, 2495, 2496, 2497, 2524, 2535, 2536,
2561, 2619, 2635, 2651, 2654, 2724, 2732, 2751,
2757, 2758, 2774, 2807, 2827, 2842, 2853, 2869,
2889, 2894, 2900, 2997, 3059, 3065.

Total Biopsies = 134.

Volume 56, 1952.

22, 40, 41, 64, 75, 91, 92, 99, 101, 102, 125,
163, 173, 189, 193, 194, 292, 317, 359, 416, 417,
458, 474, 612, 615, 625, 640, 652, 671, 679, 699,
790, 847, 961, 993, 1016, 1017, 1043, 1078, 1119,
1152/

1152, 1174, 1179, 1181, 1226, 1239, 1256, 1277,
1299, 1318, 1336, 1341, 1342, 1400, 1407, 1431,
1449, 1476, 1477, 1486, 1493, 1506, 1570, 1582,
1588, 1650, 1695, 1734, 1735, 1745, 1789, 1797,
1810, 1812, 1815, 1823,,18 51,1860, 1877, 1880,
1934, 1948, 1950, 2021, 2034, 2043, 2066, 2064,
2065, 2118, 2125, 2127, 2161, 2163, 2170, 2172,
2177, 2200, 2273, 2287, 2298, 2300, 2309, 2335,
2336, 2347, 2365, 2400, 2416, 2462, 2489, 2501,
2532, 2546, 2605, 2606, 2608, 2622, 2652, 2656,
2660, 2708, 2709, 2790, 2798, 2802, 2858, 2923,
2933, 3000, 3001, 3019, 3030, 3032, 3046, 3095,
3096.

Total Biopsies = 137.

Total Simple Enlargement Biopsies 1336.

Table XIII.

Reference Numbers of Cancer of Prostate - Biopsies -

Royal Infirmary Series.

1936. Vol: 40. (Total No: of Biopsies - 950 ; Cancer - 5). 468, 473, 775, 852, 950.

1937. Nil. (Total No: of Biopsies - 855 ; Cancer - Nil.)

1938. Vol: 42. (Total No: of Bopsies - 883 ; Cancer - 2). 272, 700.

1939. Vol: 43. (Total No: of Biopsies - 991 ; Cancer - 6). 16, 43, 264, 634, 660, 670.

1940. Vol: 44. (Total No: of Biopsies - 1232 ; Cancer - 4). 92, 389, 401, 866.

1941. Vol: 45. (Total No: of Biopsies - 1190 ; Cancer - 4). 431, 753, 856, 929.

1942. Vol: 46. (Total No: of Hopsies - 1304 ; Cancer 4). 266, 294, 815, 1239.

1943. Vol: 47. (Total No: of Biopsies - 1406 ; Cancer - 6). 126, 279, 583, 617, 926, 1090.

1944. Vol: 48. (Total No: of Biopsies - 1299; Cancer - 8). 282, 347, 467, 581, 589, 762, 788, 959.

1945. Vol: 49. (Total No: of Biopsies - 1369 ; Cancer - 7). 140, 161, 272, 494, 605, 896, 1125.

1946. Vol: 50. (Total No: of Biopsies -1601 ; Cancer - 12). 44, 45, 426, 473, 928, 1024, 1148, 1179, 1309, 1332, 1559, 1578.

1947. Vol: 51. (Total No: of Biopsies - 2118; Cancer - 18). 48, 168, 170, 172, 346, 450, 540, 615, 716, 805, 952, 998, 1131, 1488, 1537, 1789, 2062.

1948. Vol: 52. (Total No: of Biopsies - 2368; Cancer - 11). 392, 406, 524, 877, 940, 1137, 1236, 1985, 2138, 2289, 2334.

1949. Vol. 53. (Total No. of Biopsies - 4019 ; Cancer - 21. 4, 51, 141, 308, 378, 634, 708, 740, 924, 1012, 1240, 1294, 1461, 1560, 1573, 1909, 2126, 2154, 2283, 2532, 2606.

1950/

1950. Vol: 54. (Total No. of Biopsies - 4369 ; Cancer - 11.) 8, 208, 540, 907, 1701, 1749, 1786, 2004, 2254, 2269, 2616.

1951. Vol : 55. (Total No. of Biopsies - 3086 ; Cancer - 10). 82, 217, 233, 623, 916, 1390, 1703, 1807, 1830, 3086.

1952. Vol : 56. (Total No: of Biopsies - 3099 ; Cancer - 25.) 78, 358, 570, 814, 836, 866, 936, 942, 1082, 1162, 1676, 1714, 1747, 1768, 2124, 2210, 2234, 2348, 2462, 2525, 2530, 2661, 2965, 2991, 3058.

Total - 154.

Table XIV.

Macroscopic appearance of Autopsy Material.

Carcinoma of Prostate.

Macroscopic Appearances.	Royal Infirmary.	Municipal Hospitals.
Enlarged	28	14
Small	2	-
Normal	1	1
Hard	22	4
Soft	1	2
White (cut surface)....	11	-
Yellow (cut surface)...	6	-
Grey (cut surface).....	3	-

Table XV.

Incidence of Mitoses.

Autopsies.

Incidence of Mitoses.	Royal Infirmary.	Municipal Hospitals.
Scanty Mitoses (+)	5	4
Numerous Mitoses (++)	4	1
Total number showing Mitoses	9 (27.2%).	4 (16%)
No Mitoses	24 (72.8%)	21 (84%)

Biopsies.

Incidence of Mitoses.	Royal Infirmary.	Municipal Hospitals.
Scanty Mitoses (+)	8	11
Numerous Mitoses (++)	6	6
Total number showing Mitoses	14 (9%)	17 (23.6%)
No Mitoses	140(91%)	55 (76.4%)
Total	154	72

Table XVI.

Distribution of Metastases.

Autopsies. (a) Lymph gland involvement.	Number of cases. Royal Infirmary.	Municipal Hospitals.
Para aortic	20	8
Pelvic	15	5
Iliac	6	4
Mediastinal	6	3
Pancreatic	2	-
Mesenteric	2	1
Deep Cervical	2	2
Infraclavicular	1	1
Hepatic	1	1
Inguinal	1	1
Supraclavicular	-	2
	56	28

Table XVI.

Autopsies. (b) Visceral	Royal Infirmary.	Municipal Hospitals.
Lungs	14	3
Bladder	12	4
Liver	10	2
Rectum	7	1
Ureters	7	1
Kidneys	4	-
Adrenals	4	1
Heart	1	-
Pituitary	1	-
Spleen	1	-
	61	12

Table XVI (Concluded)

Autopsies.

(c) Skeletal	Royal Infirmary.	Municipal Hospitals.
Lumbar Vertebrae	9	2
Ribs	3	-
Sternum	1	-
Cervical Vertebra	1	-
Thoracic Vertebra	1	-
Femur	1	-
Sacrum	1	-
Tibia	1	-
Ischium	1	-
Psoas muscle	3	2
Pelvic Tissues	1	1
	24	5

Table XVII.

Nutritional State - Cancer Autopsies.

Royal Infirmary.

Year.	P.M.No:	
1936.	Nil.	
1937.	82.	Well developed elderly male; marked jaundice.
1938.	301.	Well developed, poorly nourished elderly male.
1939.	Nil	
1940.	57.	Not described.
1941.	133.	Emaciated old man.
	194.	Well developed, moderately well nourished.
1942.	62.	Well developed, well nourished.
	260.	Emaciated elderly male.
1943.	383.	Normally developed, very emaciated elderly male.
1944.	Nil	
1945.	Nil	
1946.	199	Poorly nourished elderly male.
	433.	Well developed adult male.
	456.	Well built, well nourished elderly male.
1947.	288.	Well developed, but somewhat emaciated middle aged man.
	360.	Elderly male who looked his age.
	362.	Small and considerably deformed elderly man.
	603.	Poorly nourished but not emaciated.
1948.	92.	Slight, rather poorly nourished middle aged man.
	146.	Well developed, moderately well nourished elderly male.
	362.	Well built, well nourished elderly.

1949/

1949.	55.	Emaciated elderly male of large stature.
	77.	Well nourished male, above average build.
	85.	Elderly male.
	343.	Thin elderly male.
	361.	Well nourished.
	475.	Well built old man.
	553.	Moderately well nourished elderly male.
1950.	370.	Moderately well covered elderly male.
	730.	Elderly male.
	755.	Elderly poorly nourished male.
1951.	513.	Elderly rather emaciated male.
	346	Well nourished male.
1952.	611.	Not described.
	684.	Very emaciated old man.
	479.	Not described.

Summary.

Nutritional State of Body at Post Mortem (Cancer Autopsies - Royal Infirmary).

Well nourished	8	(24.5%)
Moderately well nourished	4	(12.25%)
Poorly nourished	5	(15.1%)
Emaciated	6	(18.1%)
Very emaciated	2	(6.1 %)
Unknown	8	(25.5%)
Total	33	

Table XVIII.

Occupation and Cancer of Prostate.

Professional.	Skilled workers		Unskilled.		Retired.
Lawyer	1	Baker	3	Caretaker	1	46
Engineers	5	Basket maker	1	Cinema Attendant	2	
Colonel	1	Book keeper	1	Fisherman	2	
Total 7.		Cycle agent	1	Gamekeeper	1	
		Chimney sweep	1	Hammerman	1	
		Clerk	3	Labourer	16	
		Engine driver	1	Stableman	1	
		Farmer	1	Total 24.		
		Forrester	1			
		Grocers	5			
		Horse trainer	1			
		Hairdresser	1			
		Iron founder	1			
		Joiner	1			
		Lorry driver	1			
		Maltsman	1			
		Miners	21			
		Painter	1			
		Porter	1			
		Printer reader	1			
		Post office worker	1			
		Power station attendant	1			
		Rubber worker	1			
		Steelworks manager	1			
		Stenographer	1			
		Seaman	1			
		Skinner	1			
		Stonedyke builder	1			
		Salesman	3			
		Signalman	2			
		Steel worker	1			
		Tram driver	1			
		Tailor	1			
		Undertaker	1			
		Waiter	1			
		Total 66.				

Table XIX.

Duration of Symptoms at time of Admission.

Simple Enlargement of Prostate - RIE Biopsies (1336 cases).

Time	Frequency	Difficulty with Micturition	Dysuria	Overflow Incontinence
2-4 wks.	48	28	4	8
1-3 mths.	198	148	6	3
3-6 mths.	186	134	2	4
6-12 mths.	177	139	2	5
1 -3 yrs.	393	219	7	5
3 -5 yrs.	86	67	2	1
6 -10 yrs.	44	25	8	Nil
Over 10 yrs.	23	21	2	Nil
	1155	811	33	26
%	86.6%	60.7%	2.4%	1.9%

ACUTE RETENTION	91	(6.8%) (1 - 5 days)	
HAEMATURIA	15	(1.1%) (1 - 5 days)	
LUMBAGO	1	- (1 yr)	0.07%
PAIN (SUPRAPUBIC)	2	(1-3 mths: 6-10 yrs)	0.14 %

Table XX.

Duration of Symptoms at Time of Admission.

Cancer of Prostate - R.I.E. Biopsies (154 cases).

Time	Frequency	Difficulty with Micturition	Dysuria	Haematuria	Pain
2-4 wks.	7	3	2	Nil	Nil
1-3 mths.	5	4	Nil	Nil	1
3-6 mths.	16	11	3	Nil	1
6-12 mths.	13	10	1	1	Nil
1-3 yrs.	15	10	3	Nil	Nil
3-5 yrs.	4	2	Nil	Nil	Nil
6-10 yrs.	1	Nil	Nil	Nil	Nil
Over 10 yrs.	1	2	Nil	Nil	Nil
	62	42	9	1	2
%	40.3%	27.3%	5.8%	0.6%	1.3%

Days	Retention	Overflow Incontinence	Oedema of legs and Sacrum.
1	9	1	
2	10	2	
3	4	1 (3-6 mths)	1
4	4	-	
5	2	-	
14	Nil	1	
	29 -	5 -	1 = 35
%	18.8%	3.2%	0.6%

Table XXI.

Duration of Symptoms at Time of Admission.

Cancer of Prostate - R.I.E. Autopsies (33 cases).

Time	Frequency	Difficulty with Micturition	Dysuria	Haematuria
2-4 wks.	2	1	1	3
1-3 mths.	1	Nil	1	Nil
3-6 mths.	Nil	Nil	Nil	Nil
6-12 mths.	2	1	1	Nil
1-3 yrs.	2	1	1	Nil
3-5 yrs.	Nil	Nil	Nil	Nil
6-10 yrs.	1	1	1	Nil
Over 10 yrs.	Nil	Nil	Nil	Nil
Total	8	4	5	3
%	24.2 %	12.1 %	15.2%	9.1%

Time	Weakness of legs	Langour	Loss of Weight	Constip-ation.
2-4 wks.	Nil	Nil	Nil	Nil
1-3 mths.	Nil	1	1	Nil
3-6 mths.	Nil	Nil	Nil	1
6-12 mths.	2	1	Nil	Nil
1-3 yrs.	Nil	Nil	Nil	Nil
3-5 yrs.	Nil	Nil	Nil	Nil
6-10 yrs.	Nil	Nil	Nil	Nil
Over 10 yrs.	Nil	Nil	Nil	Nil
Total	2	2	1	1
%	6%	6%	3%	3%

Table XXI. (Concluded).

Time	Oedema of legs and sacrum	Time	Overflow Incontinence.
Unknown	1	2-4 wks.	1
%	3%		3%

Days	Vomiting	Acute Retention	Delirium.
1	1	1	1
2	Nil	2	Nil
3	1	2	Nil
4	Nil	1	Nil
Total	2	6	1
%	6.10 %	18.2%	3.0 %

PAIN

Time	Lower Abdominal	Retro-sternal	Ribs	Joint Backache Fibrositis
2-4 wks	Nil	1	Nil	2
1-3 mths.	1	Nil	1	Nil
3-6 mths.	Nil	Nil	1	1
6-12mths.	Nil	Nil	Nil	1
1-3 yrs.	Nil	Nil	Nil	Nil
3-5 yrs.	Nil	Nil	Nil	Nil
6-10 yrs.	Nil	Nil	Nil	Nil
Over 10 yrs.	Nil	Nil	Nil	Nil
Total	1	1	2	4
%	3.0%	3.0% = 24.2 %	6.10 %	12.1 %

Table XXII.

Duration of Symptoms at time of Admission.

Cancer of Prostate - M.H.A. - Autopsies (25).

Time	Frequency	Difficulty with Micturition	Haematuria	Loss of Weight
2-4 wks.	Nil	Nil	2	Nil
1-3 mths.	Nil	Nil	Nil	Nil
3-6 mths.	3	1	Nil	1
6-12 mths.	1	1	1	2
1-3 yrs.	1	Nil	Nil	Nil
3-5 yrs.	Nil	Nil	Nil	Nil
6-10 yrs.	Nil	Nil	Nil	1
Over 10 yrs.	Nil	Nil	Nil	Nil
	5	2	3	4
%	20%	8%	12%	16%

Time (Days)	Acute Retention	Pathological Fracture	Uraemia
1	Nil	1	Nil
2	1	Nil	1
3	Nil	Nil	Nil
4	1	Nil	Nil
5	1	Nil	Nil
	3	1	1
%	12%	4%	4%

Table XXII. (Concluded).

PAIN.

Time	Rectal	Backache	Sciatica	Constip-ation.	Anaemia
2-4 wks.	Nil	Nil	Nil	3 yrs. 1	Nil
1-3 mths.	1	Nil	Nil		Nil
3-6 mths.	Nil	2	Nil		2
6-12 mths.	Nil	1	1		Nil
	1	3	1		2
%	4%	12%	4%		8%

Section II.

A Combined Morbid Anatomical and Histological Study of Unsuspected Carcinoma of the Prostate Gland.

Section II.

Section II.

(1) INTRODUCTION.

Teem (1936) examined the prostate gland in a series of 100 consecutive autopsies on males ranging from 20-89 years at time of death. This investigation was concerned with simple enlargement of the prostate. Moore (1936) studied the histological appearances in 50 prostate glands removed from children. He described the normal changes in the gland in the new born and in the prepubertal gland. Swyer (1944), in a very detailed study described the changes in the prostate gland at birth, prior to puberty and in the adult. He does not enter into any discussion on the pathological changes occurring in the gland during these three stages of development. Moore (1952) described the morphological appearances of the prostate gland in adults and also enumerates a few criteria of senile atrophy of the prostate gland. Andrews (1949) made a study based on 142 prostate glands from males between the ages 15-79 years in whom the diagnosis of carcinoma of the prostate had not been made clinically or on gross examination at autopsy. It was undertaken to establish the true incidence of latent carcinoma of the prostate by employing a careful and uniform technique. This study, detailed though it be, fails to describe carefully the/

the morbid anatomical features of latent carcinoma of the prostate. Even other studies on latent carcinoma of the prostate (Muir, 1934 ; Moore, 1935 ; Rich, 1935 , Gaynor 1938 ; McGavin, 1938; Kahler, 1939; Baron and Angrist, 1941 ; Luppi, 1947 ; Labess, 1952 ; and Totten et al, 1953) deal very inadequately with this aspect of latent carcinoma of the prostate. This study was undertaken to describe the morbid anatomical and histological features of Unsuspected carcinoma of the prostate gland.

(2) MATERIALS AND METHODS.

My work is based upon an examination of 142 prostate glands removed from males coming to autopsy to the Royal Infirmary, whose ages range from 9 - 88 years. The gland was carefully dissected out, a cut made through its substance and it was then allowed to remain in a bottle containing Zenker formol solution for a period of 24 hours. The glands were then removed from the fixative and all the excess of fluid removed from the gland with the aid of blotting paper. The remains of surrounding fatty fibrous tissue was carefully snipped off with the aid of a pair of sharp scissors. Next, the prostate glands were weighed on a Butchart balance and measurements taken according to the method of Teem (1936).

The consistence of the gland was estimated in two ways. Firstly by the degree of firmness experienced when the gland was compressed between the thumb and index finger, and secondly the sensation/

sensation experienced when the gland is being cut.

After fixation the cut surface was first examined with the naked eye and a more detailed study made with the aid of a hand lens such as a reading glass : for it was found by experience that more detail could be made out in the gland after fixation. The glands were then sliced coronally and each section examined carefully. Sections were then selected from different areas in the gland in order to get as representative a picture as possible. Care was taken to remove for histological study any suspicious looking portions such as homogeneous white masses, discoloured portions, and nodules. This is the method followed by many of the pathologists attached to the pathology units of the Infirmary and the University. Sections were cut at a thickness of approximately 8 μ and stained with Haematoxylin Eosin, Weigerts elastic tissue stain and Van Gieson fibrous tissue stain. On an average there were 3 sections from each gland.

(3) CRITERIA OF MALIGNANCY.

The glands were then examined microscopically and carcinoma was diagnosed when one or more of the following criteria were seen :-

(a) Deformed acini with basophilic staining cytoplasm invading muscle.

(b) Irregular proliferation of acinar epithelial cells.

(c) Pleomorphic and hyperchromatic nuclei.

(d)/

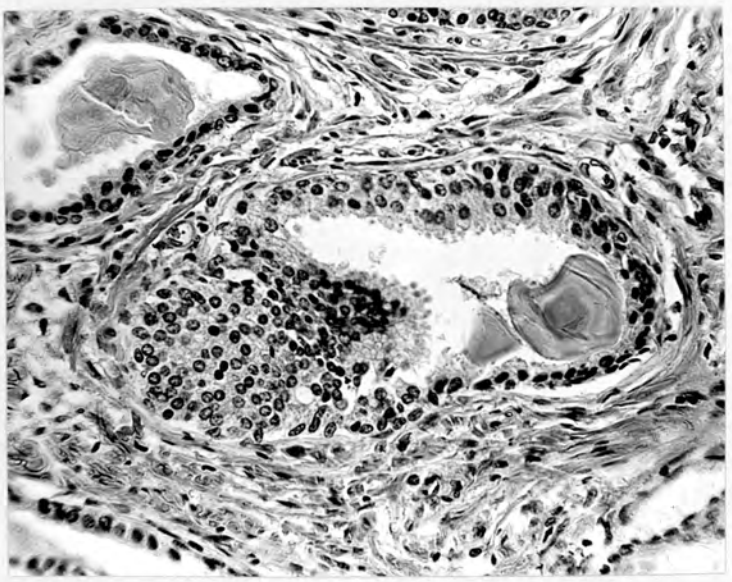


Fig. 1 a. Prostate. Note heaping up of nuclei with rupture of basement membrane. Haematoxylin & Eosin x 275.

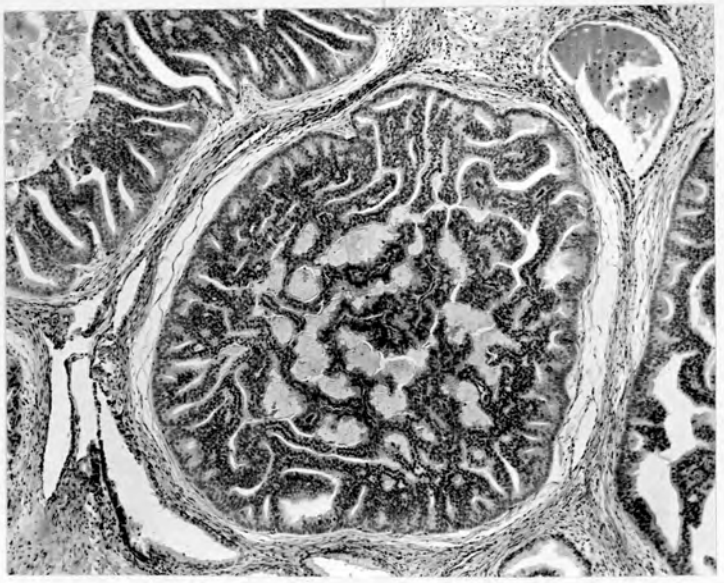


Fig. 2 a. Prostate. Irregular proliferation of acinar epithelial cells. Appearance similar to an intraduct carcinoma of breast. Haematoxylin & Eosin x 65.

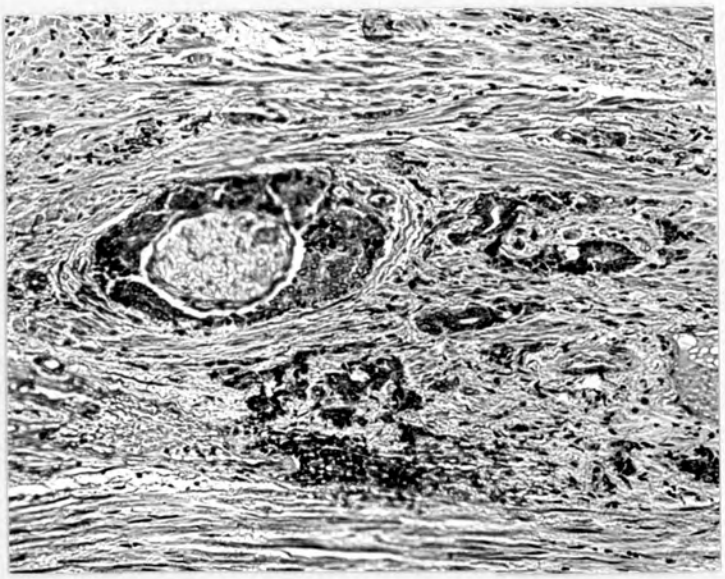


Fig. 3 a. Prostate. Perineural lymphatic involvement by malignant cells. Haematoxylin & Eosin x 150.

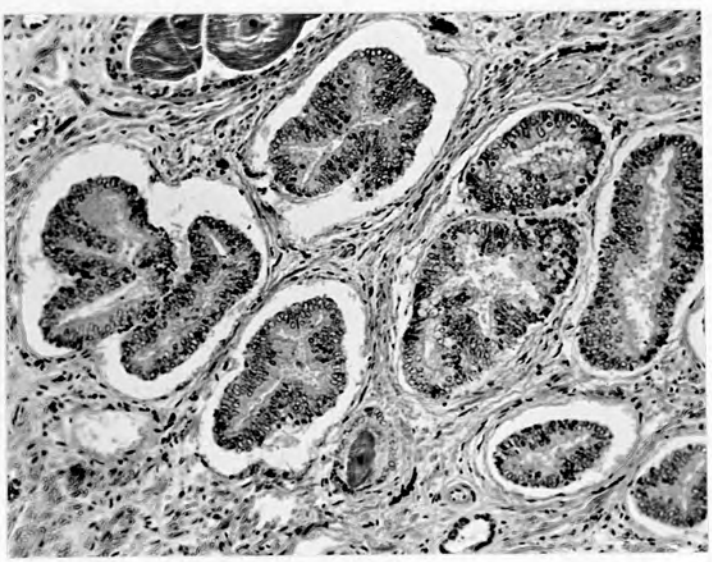


Fig. 4 a. Prostate. Basophil staining cytoplasm. Haematoxylin & Eosin x 120.

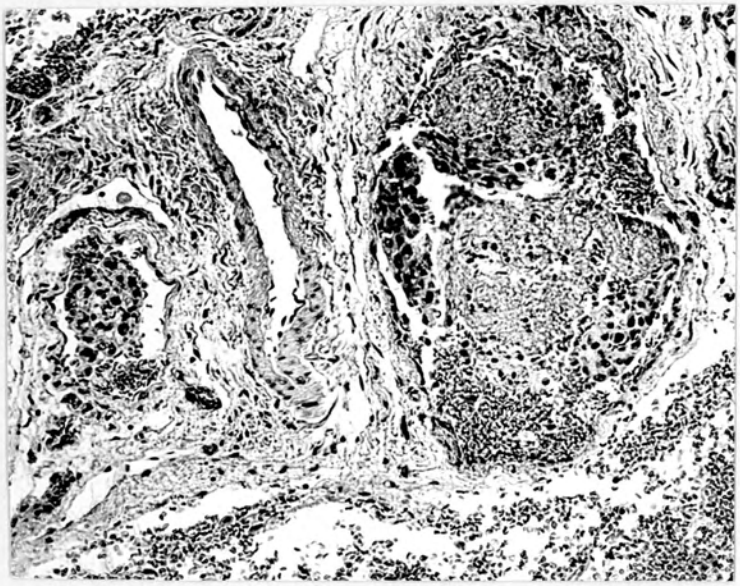


Fig. 5 a. Prostate. Carcinomatous emboli in blood vessels. Haematoxylin & Eosin x 150.

(d) Perineural lymphatic involvement (Kahler, 1939): Moore (1935).

(e) Carcinomatous emboli in blood vessels.

(f) Excessive proliferation of epithelial cells with rupture of basement membrane.

(g) Presence of mitotic figures.

(4) RESULTS.

(a) Age distribution.

Unsuspected carcinomatous change was detected in 32 of the 142 prostates examined, 22.5%. The greatest number of cases was seen in the age group 61-70 years. This does not agree with the findings of Moore (1935) who found an increasing incidence up to the 9th. decade. There was only one Cancer case before the age of 40, the youngest being 34 years of age and the oldest 88 years of age. The age distribution of unsuspected carcinoma of the prostate gland is shown in the table below :

Table I. /

Table I.

Age distribution of glands examined.

Age	Total No. of Prostates	Prostates without Carcinoma	Prostates with Carcinoma	Prostates with Carcinoma & Simple Enlarge-ment.	Prostates with Simple Enlarge-ment.
Under 20	2	2	Nil	Nil	Nil
20-30	5	5	Nil	Nil	Nil
31-40	9	6	1	1	1
41-50	27	21	2	Nil	4
51-60	24	9	5	1	8
61-70	39	19	5	8	8
71-80	27	13	4	2	8
81 +	7	3	2	Nil	2
Unknown	2	1	1	Nil	Nil
Total	142	79	20	12	31

Andrews (1949) found no cancer cases before the age of 40 years. His observations are in agreement with mine with regard to the age distribution for he too found " a significant rise in the incidence between the 6th. and 7th. decade but not beyond the 7th. "

(b) Macroscopic features.

i) Size & Weight. ii) Consistence.

iii) Cut surface.

i) Size and Weight.

The size and weight of the normal prostate gland are as follows :

Table 2.

Measurements + Weights of normal Prostate glands.

(Observations from the Literature).

Size. in Cm. Length	Width	Depth	Weight. in Gms.
3	3.6	1.8	20.5 WALLACE
3.5	4.3	1.75	20-25 McMURRICH
			18.2 THOMPSON
			22 PIERSOL

My figures obtained from an analysis of the cancer of prostate cases are as follows :

Table 3. /

Table 3.

Measurements and Weights of glands examined.

Condition	Size (Cms.) Length	Width	Depth	Weight	No. of Prostates
Cancer of Prostate	2.45	3.3	1.1	29.6 approx. (30.)	12
Cancer + Simple Enlargement	2.85	3.08	1.4	39.6 approx. (40)	20
Simple Enlargement	2.7	4.2	1.7	46.8 (47) approx.	31
Normal	2.16	3.04	1.6	26.5 (27) approx.	79
					142

An examination of these figures reveals the fact that carcinoma containing glands are smaller in size but slightly heavier than normal, also Cancer associated with simple enlargement are both bigger and heavier than those not accompanied by simple prostatic enlargement. Simple enlargement prostates are the heaviest of all. I quote Andrews figures for comparison. His findings are in agreement with mine as regards cancer.

	Condition	No. of Prostates	Mean. Vol. m/l
ANDREWS (1949)	Cancer	16	41.56
	Simple Enlargement	63	30.35
	Normal	49	21.4

(ii) Consistence.

The degree of"firmness " estimated in the three pathological entities Carcinoma of prostate, Carcinoma + Simple enlargement of prostate and Simple enlargement of prostate is listed below :

Table 4./

Table 4.

Macroscopic features of glands examined.

Consistence	Carcinoma No. of Cases.	Carcinoma & Simple Enlargement. No. of Cases.	Simple Enlargement. No. of Cases.
Hard (Stony)	1	Nil	1
Hard nodules	3	2	1
Firm	5	3	5
Rubbery or Elastic	4	3	14
Spongy	3	2	5
Rubbery Nodules	4	4	11

Thus we see that " firmness " is a feature met with in Simple enlargement of the prostate and in Carcinoma. This fact in itself is of sufficient importance to encourage Surgeons, and Medical practitioners, to insist, nay demand a histological examination of every prostate gland be it shavings from a simple resection or total enucleation of the gland, before making a final diagnosis.

Elasticity or a gland which is of a Rubbery consistence is invariably a feature of Simple enlargement of the prostate as evidenced by the fact that this feature was recorded in 45% of the simple enlargement prostate glands.

Rubbery nodularity is also found more commonly in/

in glands which have undergone simple hyperplasia (35%).

The presence of hard nodules on the surface of a gland is " highly suspicious " of carcinomatous change. It is not possible to make any more accurate conclusion in view of the fact that only a small number of glands exhibited this feature. However, the presence of hard nodules to the palpating finger should necessitate a more detailed examination of such a patient.

(iii) Cut surface.

An examination of the cut surface of the prostate gland is a most interesting and fascinating exercise to the individual pathologist. The interest lies in the fact that no two prostate glands are alike ; there are many pathological changes detectable naked eye which any competent pathologist could discern without much difficulty ; for instance, areas of infarction appear as dark brown to red structureless masses, areas of degeneration and necrosis appear as yellowish grey to black pultaceous portions, steel blue to black peppery particles studded irregularly are the characteristics of prostatic calculi ; thrombosed vessels are dark mauve to black in colour and could be compared to the characteristic " Scotch black pudding " - the reader will forgive me using this simile - however, it is in keeping with the traditional custom in Medicine of using various food stuffs as descriptive terms ; whorls of fibrous/

fibrous tissue coursing amidst both small and large cystic spaces is a picture familiar to all pathologists who examine prostate glands. Then again there are homogeneous white masses here and there on the cut surface which might be areas of prostatic hyperplasia, or cancer deposits, or old healed infarcts or areas of calcification, - prostatic stones, foci of tuberculosis, or pyogenic abscesses. The interpretation of these pathological changes on microscopic examination and their correlation with macroscopic appearances might be compared to the fascination derived from the solving of a crossword puzzle.

The outstanding macroscopic features detected in the glands examined are summarised in the following table :-

Table 5.

Summary of Macroscopic appearances following Examination with hand lens.

	Carcinoma	Carcinoma & Simple Enlarge-ment.	Simple Enlarge-ment.
Cystic areas	11	2	16
White masses	1	Nil	4
Calculi	4	2	1
Compact tissue) Whorls of) fibrous tissue)	6	3	1

For an examination of this table it would appear/

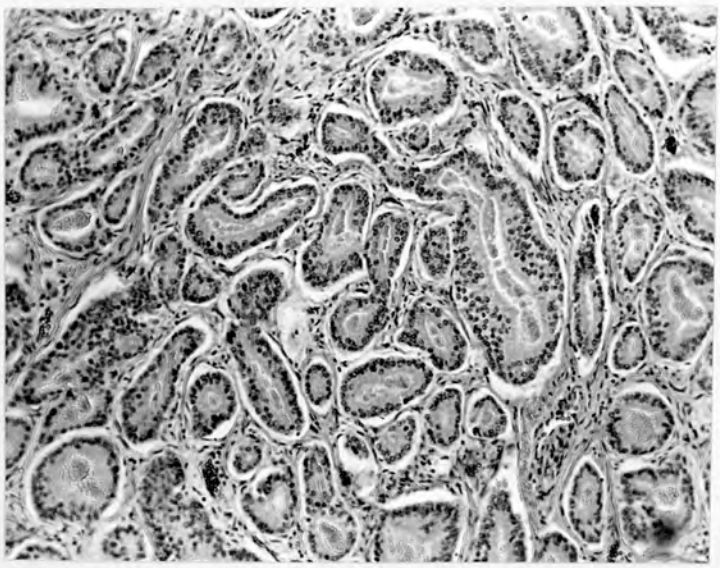


Fig. 1. Prostate. Well differentiated adenocarcinoma. Haematoxylin & Eosin x 120.

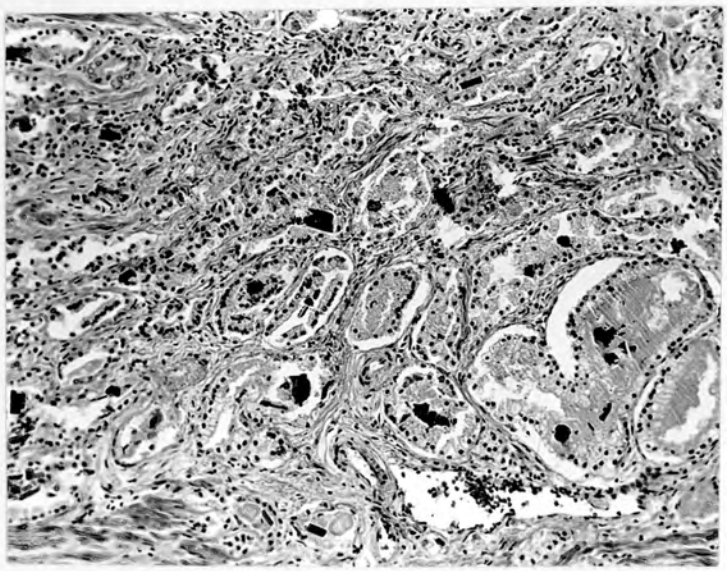


Fig. 2. Prostate. Moderately well differentiated adenocarcinoma. Haematoxylin & Eosin x 120.

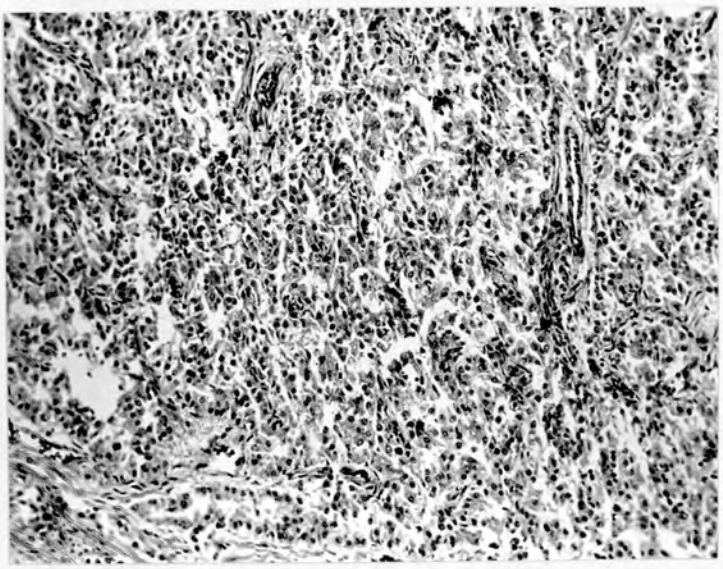


Fig. 3. Prostate. Poorly differentiated adenocarcinoma. Haematoxylin & Eosin x 120.

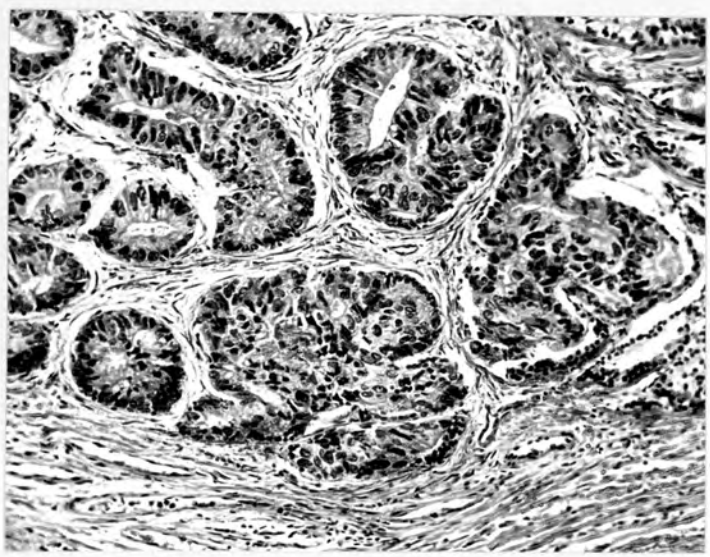


Fig. 4. Prostate. Well differentiated adenocarcinoma. A few acini with basophilic cytoplasm. Heaping up of nuclei. Mitotic figures scanty. Haematoxylin & Eosin x 120.

appear that the presence of cystic areas is a feature of both Simple enlargement and Carcinoma of the prostate. Compact tissue with the characteristic yellowish white strands and whorls of fibrous tissue are seen most commonly in Carcinomatous prostate glands.

What lessons could we learn from this part of our study?

Briefly they may be summed up by stating that :

1) Carcinoma containing prostate glands appear to be of firm consistence.

2) Hard nodules on the surface of the gland are highly suggestive of malignant change though they are seen sometimes in cases of simple enlargement too.

3) Rubbery nodularity is characteristic of simple prostatic enlargement.

The cut surface presents varying pathological changes and therefore needs careful microscopic examination.

In a nutshell - no certain diagnosis could be made on mere macroscopic examination even when it is amplified with the aid of a hand lens.

(d) Microscopic appearances.

i). Histological types. ii) Distribution of elastic and fibrous tissues.

i) Histological types.

I have made use of the same classification as was mentioned in the first part of my thesis. The type distribution of the unsuspected Cancer cases amongst/

Fig. 5. Prostate. Moderately well differentiated adenocarcinoma. Intra acinar proliferation with collections of malignant acini around. Haematoxylin & Eosin x 120.

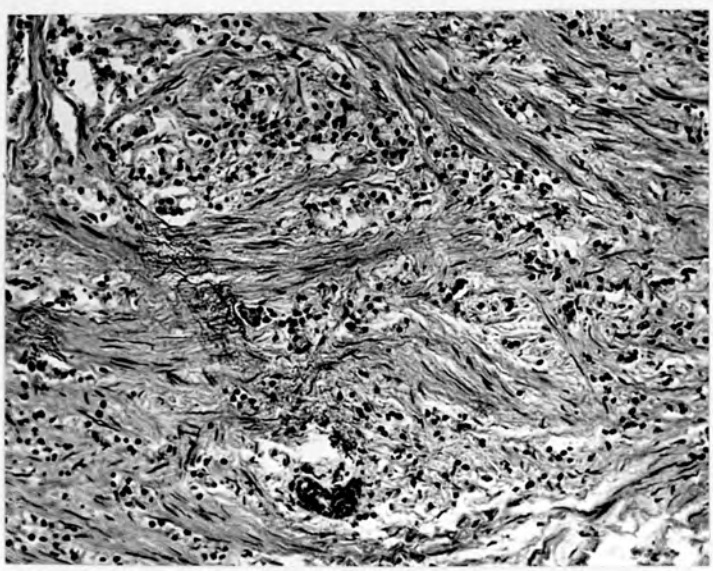


Fig. 6. Prostate. Poorly differentiated adenocarcinoma. Nuclei pyknotic. Appearance similar to oestrogenic effects on prostatic carcinoma. Haematoxylin & Eosin x 120.

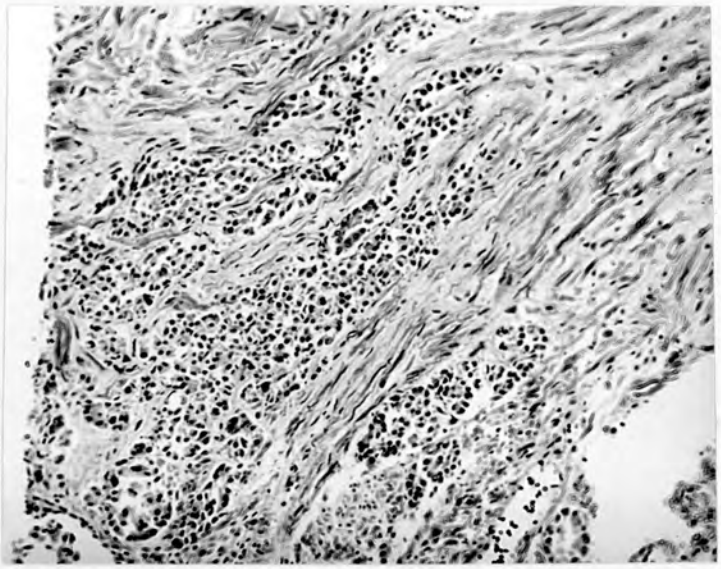


Fig. 7. Prostate. Poorly differentiated adenocarcinoma. Carcinomatous cells infiltrating muscle fibres. Haematoxylin & Eosin x 120.

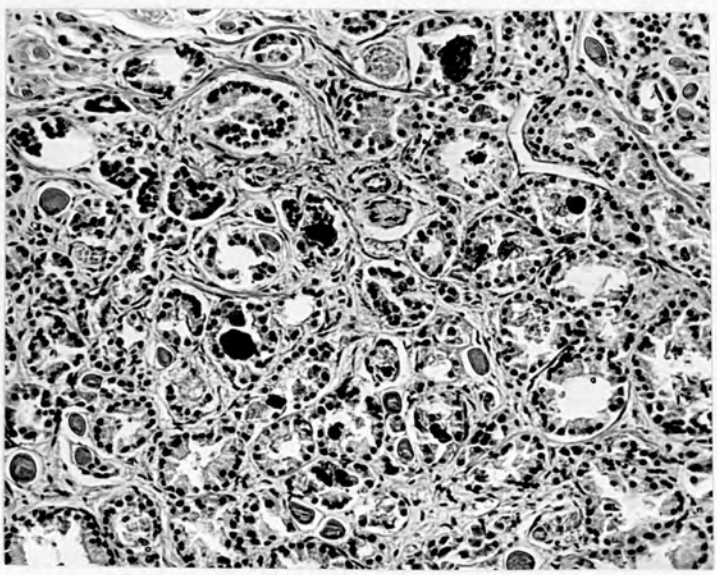


Fig. 8. Prostate. Well differentiated adenocarcinoma. Another portion of same gland as Fig.7. Haematoxylin & Eosin x 150.

amongst the prostate glands examined is noted below :-

Table 6.

Histological types of Carcinoma.

Type of Carcinoma	No. of Cases.
Well differentiated adenocarcinoma	8
Moderately well differentiated adenocarcinoma	7
Poorly differentiated adenocarcinoma	4
Scirrhous carcinoma	1
Simple enlargement + well differentiated adenocarcinoma	5
Simple enlargement + moderately well differentiated adenocarcinoma	6
Simple enlargement + poorly differentiated adenocarcinoma	1
Total	32

The most striking feature regarding the histological types of unsuspected carcinoma of prostate in this study is the fact that no less than 25% of the cases were well differentiated adenocarcinomas in either a focal or diffuse form. There were no cases exhibiting mitotic figures. This observation is interesting for it throws light on the biological nature of early carcinoma of this organ. One cannot make any definite observations in view of the fact that the number of carcinoma cases/

cases is small. However, the figures appear to suggest that early carcinoma is a slow growing tumour which, in general, metastasizes slowly except in very special circumstances when there is a flare up in the metabolic activity of the cancerous processes. It may be likened to a volcano which suddenly belches into furious activity. The conditions causing this increased tempo of growth are still a mystery. Jocelyn Swan (1923) suggests that the stresses of life are responsible for this heightened activity. It would be a most fascinating problem to study the pathological life history of neoplasms in general and that of carcinoma of the prostate in particular. I mentioned earlier that nothing is known of the factors that govern the metabolic activity of tumour growth. Another and equally mysterious entity is the unknown "X" factor of the individual biological characteristics of each tumour and the reaction of the host to them. This concept of variable biological behaviour in cancer is finding more and more adherents today (Crile, 1953). The surgical importance of the fact that the majority were cases of a well differentiated adenocarcinoma suggests that early diagnosis of prostatic carcinoma and early removal offers an excellent prognosis.

(ii) <u>Distribution of elastic and fibrous tissue</u>.

The many studies on latent carcinoma of the prostate deal with the histological features in great detail especially the works of Andrews (1949) and Totten et al, (1953) who discuss very lucidly the extremely/

extremely important aspect of the microscopic differential diagnosis of latent carcinoma of the prostate. Under these circumstances I would spare the reader the boredom of reviewing well trodden ground and go on to another interesting aspect of the microscopical appearances of Carcinoma of the prostate. All pathologists will agree with me when I say that there is a similarity in both structure and pathological changes in breast and prostate glands. With regard to the distribution of elastic tissue and fibrous tissue in the senile type of breast Berka (1911) found an increased amount of elastic tissue with increasing age, also it is found to exist in situations in which it is not normally present in the interacinar tissue and within the glandular lobules. Fraser (1927) puts forward the hypothesis that breast carcinoma develops because the elastica which ought to seal the duct terminates has failed to do so. The freedom from restraint which the absence of elastica implies suggests that the cul-de-sac epithelium might readily extend beyond its natural boundaries into the parts around. There is no reference in the literature as regards the distribution and amount of fibrous and elastic tissue in Carcinoma of the prostate gland. This prompted me to investigate this feature in a series of prostate glands under examination.

Table 7. /

Table 7.

The table below summarises the results of this investigation :

Amount of Elastic & Fibrous Tissue in glands Examined.

Type of gland.	Elastic Tissue.			Fibrous Tissue.		
	+	++	+++	+	++	+++
Carcinoma	3	6	11	3	6	11
Carcinoma and Simple enlargement	4	6	2	4	5	3
Simple enlargement	24	5	1	29	2	0
Normal	74	5	0	77	1	1

I found that there was an increased amount of fibrous and elastic tissue in the carcinoma-containing glands especially those glands not associated with simple enlargement. The delicate strands of elastic tissue and fibrous were distributed unevenly. There did not appear to be a more scanty distribution of elastic fibrils in the carcinomatous area as compared with that in the rest of the gland. Normally the elastic fibrils are in close apposition to the lamina propria. It would thus appear that in the prostate the paucity of elastic fibrils is not a factor in facilitating the rupture of the basement membrane in the local spread of the cancer cells.

Summary :-

1. Unsuspected carcinoma of the prostate gland may occur either focally or in diffuse form.

2. The commonest variety encountered was the well differentiated adenocarcinoma.

3. There was an absence of mitotic figures and gross anaplastic forms in the sections of carcinoma examined.

4. The fibrous and elastic tissue were present in greater abundance in carcinoma-containing glands.

5. This paucity of elastic fibrils is not a factor facilitating the rupture of the basement membrane by the cancer cells.

(e) Associated pathological changes.

An examination of the postmortem diagnosis of the cases of unsuspected carcinoma of the prostate gland revealed a few interesting observations. No less than six of the patients had carcinoma in other organs (See Appendix). There were two cases (P.M. 52 and P.M. 179) where there were numerous metastatic deposits from the Carcinoma of the prostate. This was noticed in P.M. 52 - the local lymph nodes - para-aortic nodues -, in the vertebral column, sternum, lymphatics of the mesentery, 9th, 10th and 11th. vertebrae. In the 2nd. postmortem case (P.M. 179) - a diagnosis of Carcinoma of the bladder had been made. This condition had been diagnosed since 1946. On postmortem examination no papillomatosis of the bladder benign or otherwise were seen. In this case too there was involvement of the mesenteric and para-aortic lymph nodes. The ureters were also involved in the cancerous process.

My/

My findings are in agreement with those of Andrews (1949) as regards the lack of association between calculi as an etiological factor in Carcinoma of the prostate. However, he describes a characteristic type of hyperplasia which is associated with carcinoma. These hyperplastic acini are said to be large and composed of large cells columnar in form with deeply eosinophilic cytoplasm, the nuclei being strikingly large and usually oval in shape, although occasionally rounded, with a well defined though delicate chromatin network and situated centrally in the cell. These acini usually had a basal layer of epithelial cells and always had a normal stroma propria. I was not able to detect any such association in the series of glands examined by me.

(5) SUMMARY.

1) A study has been made, based upon an examination of 142 prostate glands obtained from routine autopsies held at the Edinburgh Royal Infirmary.

2) The patients' ages ranged from 9 yrs to 88 yrs. The greatest number of cases occurred in the age group 61-70 yrs. The youngest patient with carcinoma was 34 years of age and the oldest with carcinoma 88 yrs of age.

3) Carcinoma-containing glands are smaller in size, but slightly heavier than normal. Carcinomatous glands when associated with simple enlargement are both larger and heavier than those/

those not accompanied by simple prostatic enlargement.

4) Firmness in a prostate gland appears to be met with almost as commonly in simple enlargement as in carcinoma of the prostate.

5) Elasticity or a rubbery consistence is found most commonly in glands that have undergone simple prostatic enlargement.

6) The presence of hard nodules is " highly suspicious " of malignant change.

7) The presence of cystic areas is noted in both simple enlargement and carcinoma of the prostate.

8) There appears to be a tendency for the tissue in Carcinomatous glands to be compact with whorls and yellowish white strands of fibrous tissue which are seen on the cut surface.

9) An accurate diagnosis of unsuspected carcinoma of the prostate cannot be made on simple naked eye examination or even when a hand lens is used. On microscopic examination the commonest type seen is the well differentiated adenocarcinoma which occurs either in a local or in a diffuse form.

10) There appears to be a tendency for unsuspected carcinoma-containing glands to have an increased proportion of both fibrous and elastic tissue in general. Paucity or lack of elastic fibrils in carcinomatous areas does not appear to be a possible causal factor in the local spread of malignant/

malignant cells. No less than 6 of the cases examined were associated with carcinoma of other organs.

11) No correlation was discovered between calculi and carcinoma.

12) Finally, no relationship between simple enlargement and carcinoma was discovered.

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Section II.

(7) APPENDIX.

Contents.

Incidence of Unsuspected Carcinoma of the Prostate.

(observations from the Literature).

Author.	Age of Patient (yrs)	Incidence %
MUIR	60 +	13
BARON & ANGRIST	70+	23
	50 +	46
	All ages	14.8
BARRINGER	50 +	17.4
MEYER	50 +	29.4
KAHLER	60 +	25
	All ages	13.9
RICH	50 +	14.0
MOORE	50 +	20.5
ANDREWS	All ages	16.7
AUTHOR	All ages	22.5

Summary.

I.	Normal	79
	Simple enlargement	31
	Simple enlargement + Cancer	12
	Cancer	20
	Total	142
II.	Simple enlargement	31
	Simple enlargement + well differentiated adenocarcinoma	5
	Simple enlargement + Moderately differentiated adenocarcinoma	6
	Simple enlargement + poorly differentiated	1
	Well differentiated adenocarcinoma	8
	Moderately differentiated adenocarcinoma	7
	Poorly differentiated carcinoma	4
	Scirrhous Carcinoma	1
	Squamous metaplasia	5

Age Distribution of Prostate Glands Examined.

Age Groups	Total No. of Prostates	Prostates without Carcinoma	Prostates with Carcinoma	Prostates with simple enlargement	Prostates with Simple enlargement and Carcinoma
Under 20	2	2	Nil	Nil	Nil
20-30	5	5	Nil	Nil	Nil
31-40	9	6	1	1	1
41-50	27	21	2	4	Nil
51-60	24	9	5	8	1
61-70	39	19	5	8	8
71-80	27	13	4	8	2
81 +	7	3	2	2	Nil
Unknown	2	1	1	Nil	Nil
Total	142	79	20	31	12

25.

Table. 3.

Ages of cases examined.

P.M. No.	Age.	P.M. No.	Age.	P.M. No.	Age.	P.M. No.	Age	P.M. No.	Age
724	47	66	75	140	75	199	68	320	67
727	60	70	65	141	80	200	47	325	21
728	52	71	64	142	63	201	68	326	69
729	79	76	81	146	73	202	69	327	67
730	56	77	50	148	70	203	68	328	52
731	34	78	48	149	49	204	58	331	62
733	60	81	64	150	84	208	69	332	50
735	35	N.P. 5631	??	154 156	68 56	212	48	333	36
736	49	86	52	155	61	219	69	339	77
737	68	87	68	158	74	221	73	340	35
747	35	89	68	160	49	226	60	341	29
766	46	90	67	161	69	229	75	342	84
768	79			163	31	231	53	349	84
769	72	97	54	164	62	234	70	356	48
22	50	98	63	165	64	238	71	358	68
40	75	99	67	168	84	247	69	360	42
41	21	100	67	177	88	271	65	369	52
42	56	101	26	178	46	273	66	370	76
43	66	104	48	179	52	276	76	371	81
47	43	106	44	180	72	277	48	375	53
N.P. 5607	-	111 114	53 62	182	56	286	73	378	56
52	53	117	68	183	47	287	54	379	78
53	9	120	58	184	76	288	73	384	62
56	49	124	17	185	72	290	41	386	65
57	73	125	66	192	56	294	76	395	66
59	40	130	62	193	32	298	69	397	59
60	64	132	49	194	72	300	45	400	42
63	79	133	46	197	47	301	38	401	75
								420	48

Table. 4.

MORBID HISTOLOGY
of
UNSUSPECTED CARCINOMA of PROSTATE GLAND.

Age groups	Well differ-entiated Carcinoma	Moderately differ-entiated	Poorly differ-entiated	Scirrhous Carcinoma	Carcinoma + Simple Enlargement			
					Well diff.	Mod. diff.	Poorly diff.	Scirr-hous
Under 20	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
21 - 30	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
31 - 40	Nil	Nil	1	Nil	Nil	1	Nil	Nil
41 - 50	1	1	Nil	Nil	Nil	Nil	Nil	Nil
51 - 60	2	2	1	Nil		Nil	1	Nil
61 - 70	1	2	1	1	4	4	Nil	Nil
71 - 80	1	2	1	Nil	1	1	Nil	Nil
81 +	2	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Unknown	1	Nil	Nil		Nil	Nil	Nil	Nil
	8	7	4	1	5	6	1	-
	20				12			

Table 5.

MACROSCOPIC APPEARANCES OF CARCINOMATOUS PROSTATE GLANDS.

Cancer		Cancer + simple enlargement	
P.M.No.	Description.	P.M.No.	Description.
766	Firm : oval uniformly scattered cystic areas. Coarse strands of fibrous tissue running across cut surface.	729	Rubbery, firm raised nodular areas, creamy white.
N.P. 5607	Very firm : small pin-head nodules, Fibrous tissue +++.	730	Firm : cystic spaces in collections at centre. Below periphery, soft fibrous tissue.
42	Firm : cystic spaces : yellow strands irregularly scattered.	731	Firm, white nodules about size of millet-seed, irregularly scattered.
52	Spongy, cystic spaces. Whitish nodules.	125	Spongy, cystic spaces in periphery ; nodular areas.
59	Spongy : cystic spaces, greyish white strands.	141	Firm : nodular : fibrous compact tissue.
63	Firm compact whorls of fibrous tissue. Gritty.	142	Gritty sensation : sand-like, brown particles : nodular whorls of fibrous tissue.
71	Firm nodular masses, white in colour.	165	Spongy, cystic spaces. Whorls of fibrous tissue towards centre.
104	Uniform size : rubbery nodules : cystic areas.	199	Hard : compact tissue : slight fibrous tissue whorls.
111	Gritty particles : bluish-brown, millet-seed like. Large cysts.	208	Hard, irregular : compact small nodules +, fibrous tissue +.
117	Uniform : nodular areas. Rubbery small cystic areas in periphery.	384	Spongy and firm areas with cystic spaces within. Small brown calculi. Gritty.
177	Spongy, microcysts ; nodules of fibrous tissue : brown calculi in periphery.	386	Firm : compact. Coarse fibrous tissue strands. No nodules.
179	Fibrous : compact fibrous tissue strands, minute cystic spaces.		

MACROSCOPIC EXAMINATION OF PROSTATE GLANDS.

Cancer

P.M. No.	Description
184	Hard, raised nodules : fibrous tissue strands. Cysts +.
201	Rubbery : light brown sand-like calculi. Macrocysts in periphery.
219	Firm compact nodules. Whorls of fibrous tissue +.
231	Smooth. Compact. Micro-cysts + in periphery. Very firm areas.
273	Nodular projections ; spongy cystic spaces.
286	Spongy : cystic spaces ; few small nodular areas.
342	Rubbery : Nodular microcysts. Blue-black particles. Gritty.
371	Firm fibrous, small, compact. Few small pin-head nodular areas.

Cancer + Simple Enlargement.

P.M. No.	Description.
226	Well differentiated adeno-carcinoma. Simple enlargement and lymphorrages +.

Table 6.

ROUTINE EXAMINATION of PROSTATE GLANDS (AUTOPSIES)

P.M. No.	Size. (cms) W. L. D.	Weight.	Cut Surface Macroscopic Appearance	Microscopic appearance
724	$4\frac{1}{2}$ x $3\frac{1}{2}$ x $2\frac{1}{2}$	50 Gm.	Spongy, small cystic spaces, white strands of fibrous tissue running across sections.	Simple enlargement of prostate.
727	4 x $2\frac{1}{2}$ x $1\frac{1}{2}$	41 Gm.	Firm, elastic ; small nodules, yellow.	Simple Enlargement.
728	4 x 3 x 1	32 Gm.	Firm, elastic ; cystic spaces in periphery.	Simple Enlargement.
729	$5\frac{1}{2}$ x $4\frac{1}{2}$ x 2	152 Gm.	Rubbery, firm, raised nodular areas ; creamy white.	Mod. differentiated carcinoma + Simple Enlargement.
730	3 x $1\frac{1}{2}$ x 1	41 Gm.	Firm : cystic spaces in collections at centre and below periphery : Whorls of fibrous tissue.	Poorly differentiated carcinoma + simple enlargement.
731	3 x $3\frac{1}{2}$ x 2	22 Gm.	Firm ; white nodules about size of millet seeds irregularly scattered.	Mod. differentiated carcinoma. Simple enlargement.
733	5 x 3 x 1	57 Gm.	Firm : elastic. Cystic spaces : greyish-white fine particles embedded irregularly.	Simple enlargement.
735	4 x $2\frac{1}{2}$ x 2	42.6 Gm.	Firm : Elastic ; thick yellowish strands of fibrous tissue coursing cut surface.	Simple enlargement.
736	4 x 3 x 1	30 Gm.	Firm : strands of fibrous tissue / cystic spaces ; thick gelatinous secretion in some spaces.	Simple enlargement.
737	$4\frac{1}{2}$ x $3\frac{1}{2}$ x 2	55 Gm.	Firm : yellowish white, homogeneous areas : patchy distribution.	Simple enlargement.

ROUTINE EXAMINATION OF PROSTATE GLANDS.

P.M.No.	Size(Cms) W. L. D.	Weight	Cut surface Macroscopic Appearance.	Microscopic appearance
747	3 x 2 x 2	38 Gm.	Spongy : cystic spaces : irregularly scattered throughout cut surface.	No cancer. Acini of various sizes. No simple enlargement.
766	4 x 2 x 2	35 Gm.	Firm : oval, uniformly scattered cystic areas. Coarse strands of fibrous tissue running across cut surface.	Well-differentiated adenocarcinoma. No simple enlargement.
768	5 x 2½ x 2	75 Gm.	Enlarged middle lobe : firm areas, yellowish-cream nodules.	Simple enlargement.
769	3½ x 2 x 2	30 Gm.	Spongy: cystic spaces : greenish-yellow fluid exudes on pressure.	Simple enlargement + secondary infection.
22	3 x 1 x 2	25 Gm.	Firm : close texture : no cystic spaces : no coarse strands.	Varying sizes of acini. Slight to severe exfoliation of cells. No cancer. NO S.H.P.
40	3½ x 2 x 1	58 Gm.	Rubbery : small cystic areas and coarse strands of fibrous tissue throughout cut surface.	Simple enlargement.
41	2 x 2 x 1½	20 Gm.	Spongy, whitish nodules varying sizes.	Small acini, exfoliated cells +. NO cancer.
42	3 x 3 x 1	18 Gm.	Firm : cystic spaces and yellow strands irregularly scattered.	Well differentiated adenocarcinoma No simple enlargement.
43	4 x 3 x 2	38 Gm.	Rubbery, cystic spaces. Gritty particles ; bluish-grey in colour.	Poorly lined acini with fragmented basement membrane. NO cancer ; No simple enlargement.
47	3½ x 2 x 2	45 Gm.	Spongy, cystic spaces : fibrous tissue runs across glands.	Low cubical lining of acini, which are poorly formed. No cancer ; NO simple enlargement.
N.P. 5607	2 x 1 x 1½	15 Gm.	Very firm ; small pinhead nodules : fibrous tissue ++.	Well-differentiated adeno-carcinoma. No simple enlarge-ment. Lymphocytic accumulations

Table 6. (Contd.)

ROUTINE EXAMINATION OF PROSTATE GLANDS.

P.M.No.	Size(Cms) W. L. D.	Weight (Gms.)	Cut Surface Macroscopic Appearance	Microscopic appearance
52	4 x 2 x 1	35	Spongy, cystic spaces. Whitish nodules.	Moderately differentiated adeno-carcinoma. No simple enlargement.
53	3 x 2 x 1	22	Firm, compact tissue ; fibrous tissue strands.	Slit-like acini. Very poor lining of epithelial cells. Peri-acinar lymphocytes ; fibrous tissue ++.
56	4 x 2 x 2½	45	Compact, firm : No cystic areas.	Small, slit-like, poorly lined acini. Spindle shaped cells ++. Lymphorrhages ++. NO Cancer.
57	4½ x 2 x 1	50	Rubbery ; cystic spaces ; thrombosed veins.	Dilated, thin, low cubical epithelium. Few desquamated cells. Stroma with hyaline changes.
59	3 x 2 x 2	26	Spongy : cystic spaces. Greyish white strands.	Poorly differentiated adeno-carcinoma. NO simple enlargement.
60	3 x 3 x 1	25	Spongy:cystic areas in periphery. White nodules.	Slightly enlarged acini. Slight round cell infiltration. NO cancer. NO simple enlargement.
63	2½ x 3 x 1	38	Firm : compact whorls of fibrous tissue. Gritty.	Well-differentiated adenocarcinoma. Calcified corpora : No simple enlargement.
66	3 x 2 x 2	25	Spongy : brown calcili : gritty sensation.	Slightly dilated acini. Lumina contain large, pink laminated corpora.
70	4½ x 3 x 2	100	Enlarged middle lobe : Nodular ; Rubbery. Raised areas.	Simple enlargement.
71	2½ x 2 x 2	38	Nodular areas : firm, white masses.	Moderately differentiated adeno-carcinoma. No simple enlargement.
76	4 x 1 x 2½	40	Smooth surface ; compact except in margin, cystic spaces present.	Simple enlargement.

Table 3. (Contd.)

ROUTINE EXAMINATION OF PROSTATE GLANDS.

P.M.No.	Size(Cms) W. L. D.	Weight Gm.	Cut Surface Macroscopic Appearance	Microscopic Appearance
77	3½ x 1 x 2	36	Rubbery : cystic areas ; areas of congestion in periphery.	Acini well-formed. Tall columnar epithelium. NO Cancer.
78	4 x2½x 1	40	Rubbery : large cystic areas. Brown gelatinous areas.	Simple enlargement.
81	3 x 2½x 2	42	Nodular areas with cystic spaces : fibrous tissue coursing through.	Small, poorly-formed acini. Degenerate exfoliated cells.
N.P. 5631	4 x 2 x 1½	35	Spongy ; cystic areas ; nodular areas.	Dilated and elongated acini. Fragmentation of basement membrane. Lymphocytic accumulations.
86	1½x 2 x 1	15	Hard : no cystic spaces ; compact tissue.	Poorly formed. Linear shaped acini. Traces of pink-staining secretion ; small corpora amylacea.
87	2 x 1½x 2	35	Rubbery : circumscribed nodular areas : small cystic spaces in periphery.	Simple enlargement.
89	2½x 1 x 2	35	Cystic areas : whitish nodules scattered in and around periphery.	Elongated, dilated acini. Reticular tall columnar epithelium. Oedema of stroma.
90	2 x 1½x 2	38	Hard : compact, whitish nodules : No cystic spaces seen.	Small acini : a few dilated, multiple small corpora amylacea. Lymphocytes ++ around degenerate acini.
97	2 x 2½x 2	40	Spongy : cystic spaces, small nodules present.	Irregular-shaped acini ; a few dilated acini with degenerate cells within : NO lymphocytes.
98	1½ x 2 x 1	20	Spongy : cystic areas in periphery.	Small, poorly formed acini. Lining epithelium fragmented. Lymphocytes ++. around degenerated acini.

Table 6. (Contd.)

ROUTINE EXAMINATION OF PROSTATE GLANDS.

P.M.No.	Size(Cms) W. L. D.	Weight (Gm.)	Cut Surface Macroscopic Appearance	Microscopic Appearance.
99	3 x 2½x 2	45	Rubbery nodules. White areas in cut surface.	Simple enlargement of prostate.
100	1½x 1 x 1	20	Uniform ; firm : homogeneous ; compact.	Acini small. Some show immature epithelial growth. NO carcinoma. NO simple enlargement.
101	1 x 1½x 2	17	Rubbery cystic areas ; small nodules.	Acini in different stages maturity. Lymphorrhages +. NO carcinoma.
104	1 x 2 x 1	15	Uniform ; nodules, rubbery ; cystic areas.	Mod. differentiated adenocarcinoma. Lymphorrhages : NO simple enlargement.
106	1 x 1½x 1	15	Firm : dense areas, bluish-grey in colour.	Slight dilatation of acini. Lining epithelium low. NO carcinoma ; NO simple enlargement.
111	4 x2½x 2	40	Gritty particles, bluish-brown ; millet-seed like . Large cystic.	Poorly differentiated adenocarcinoma NO simple enlargement.
114	3½x 1 x 1½	25	Creamy-white, soft areas : Fluctuant mass in periphery ; hard nodule on surface.	Simple enlargement of prostate. No secondary infection.
117	2 x 2 x 1	20	Uniform : nodular areas. Rubbery small cystic areas in periphery.	Poorly differentiated adenocarcinoma.
120	2 x 1½x 1	15	Firm, gritty sensation ; compact, fibrous. NO cystic spaces.	Small immature acini. Others large and dilated with single corpora amylacea. NO cancer. NO simple enlargement.
124	2½x 1 x 1½	15	Uniform ; nodular, rubbery, white areas.	Acini closely packed. Compact. Lining epithelium tall columnar.
125	2 x 1 x 1	20	Spongy : cystic spaces in periphery. Nodular areas.	Simple enlargement. Well differentiated adenocarcinoma.

Table 6. (Contd.)

ROUTINE EXAMINATION OF PROSTATE GLANDS.

P.M.No.	Size (Cms) W. L. D.	Weight (Gm.)	Cut Surface Macroscopic Appearance	Microscopic Appearance.
130	2½x 2 x 2	20	Spongy : cystic areas, greyish-white masses.	Acini small. Multiple faceted corpora : NO secondary infection. NO cancer.
132	2½x 1 x 1½	22	Rubbery ; nodular areas, few strands of fibrous tissue.	Very poorly formed small acini, almost all show marked exfoliation of cells.
133	2 x 1 x 1½	18	Spongy ; white nodular areas : No cystic spaces.	Many dilated acini with degenerate pink staining material in lumina. Lymphorrhages +. Fragmented basement membrane.
140	2 x 1½x 1	15	Regular, firm : whorls of fibrous tissue.	Small acini, poorly formed. Desquamated cells in lumen. Fibrous tissue ++. NO cancer.
141	2 x 1½x 1	15	Firm : nodular : fibrous compact tissue.	Well differentiated adenocarcinoma + Simple enlargement. Calcified corpora +.
142	3½x 2 x 2	25	Gritty sensation - brown particles sand-like ; nodular : whorls of fibrous tissue.	Moderately differentiated adenocarcinoma Lymphorrhages +. Simple enlarge - ment +.
146	5 x 3½x 1	55	Enlarged ; nodular, hard ; no cystic spaces ; white fleshy nodules.	Simple enlargement. No carcinoma.
148	2 x 1 x 1½	15	Firm : gritty : calculi : whorls of fibrous tissue.	Poorly formed acini varying shapes and sizes. No lymphorrhages. NO cancer.
149	3 x 2 x 1	17	Firm, solid areas ; fibrous tissue in coarse strands. Cystic spaces in periphery.	Acini slightly dilated. Lining epithelium low. Fragmented basement membrane. NO carcinoma.
150	3½x 2 x 1½	30	Rubbery, raised nodules : cystic areas in periphery.	Simple enlargement. (early)

ROUTINE EXAMINATION OF PROSTATE GLANDS.

P.N.No.	Size(Cms) W. L. D.	Weight (Gm.)	Cut surface Macroscopic Appearance	Microscopic appearance.
154	4 x 2 x 1	30	Nodular areas : rubbery : whorls of fibrous tissue. Gritty.	Low cubical epithelium. Poorly formed acini. Some acini dilated with number of corpora. Some calcified. NO cancer.
155	3 x 1½ x 1	20	Rubbery : compact tissue ; no fibrous tissue strands.	Small, poorly formed acini. NO simple enlargement. NO cancer.
156	5 x 3½ x 2	55	Enlarged, nodular masses ; number of cystic spaces.	Simple enlargement of prostate, with plasma cells and round cells near degenerate acini.
158	4 x 2 x 1	35	Rubbery ; whorls of fibrous tissue around nodular areas.	Low lined cubical epithelium in small acini. NO cancer. NO simple enlargement.
160	4 x 3 x 1	35	Spongy : cystic spaces in periphery. Nodules in centre.	Simple enlargement of prostate. NO carcinoma. No secondary infection
161	4½ x 3½ x 2	40	Spongy ; uniform ; small cysts in periphery. Raised nodular areas.	Many dilated acini with thin, epithelial lining. Pink staining degenerate cells in lumina. Hyaline change in stroma.
163	2½ x 2 x 1	18	Small, hard, compact ; even nodular areas, white in colour.	Tall columnar epithelial lining. Lymphocytic foci ++. Fibrous tissue++
164	3 x 2½ x 2	30	Enlarged middle lobe ; whorls of fibrous tissue around nodular areas.	Low cubical epithelial lining. Multiple corpora amylacea. Slight round cell infiltration.
165	3½ x 2 x 1	23	Spongy, cystic spaces : whorls of fibrous tissue towards centre.	Simple enlargement of prostate + moderately differentiated adeno-carcinoma.
168	4 x 2½ x 2	17	Spongy : honeyeomb-like spaces; small, brown calculi present ; whorls of fibrous tissue.	Low cubical epithelial lining. Multiple laminated corpora. NO cancer.

173.

ROUTINE EXAMINATION OF PROSTATE GLANDS.

P.M.No.	Size (Cms) V. L. D.	Weight (Gm.)	Cut Surface Macroscopic Appearances	Microscopic Appearance.
194	1½ x 1 x 1	17	Hard : compact tissue, slight fibrous tissue whorls.	Elongated acini showing much desquamation. Large single corpora amylacea. NO cancer.
197	2½ x 2 x 1	20	Rubbery ; brown, greyish blue areas ; no nodules.	Well formed acini ; tall columnar epithelium. Some contain desquamated cells. Squamous metaplasia +. NO simple enlargement.
199	3 x 2 x 2	25	Hard. Compact tissue, no nodules : strands of fibrous tissue ++.	Simple enlargement of prostate + well differentiated adenocarcinoma.
200	2½ x 2 x 1½	25	Rubbery : bluish grey areas just below periphery. Microcysts +.	Small acini ; hardly any epithelial lining. Multiple corpora amylacea. Degenerate acini contain lymphocytes around. NO simple enlargement.
201	3½ x 2½ x 1	27	Rubbery ; light brown sand-like calculi, macrocysts in periphery.	Moderately differentiated adeno-carcinoma. No simple enlargement.
202	3 x 2 x 2½	20	Firm : slight enlargement of middle lobe. Macrocysts in periphery.	Acini slit-like. Poorly lined. Spindle shaped cells ++ also round cells ++. NO simple enlargement.
203	4 x 2 x 1½	35	Spongy : whitish nodules raised above surface.	Simple enlargement of prostate. NO carcinoma.
204	5 x 3 x 2	55	Enlarged : rubbery, nodular. Macro and Microcysts present.	Simple enlargement of prostate. Lymphorrhages.
208	3 x 1½ x 1	15	Hard ; irregular, compact ; small nodules +. Fibrous tissue +.	Simple enlargement + moderately differentiated adenocarcinoma.
212	2 x 1½ x 2	20	Firm ; one small spongy area.	Small immature acini, in areas of fibrous tissue. NO cancer.
219	4½ x 2 x 3	40	Firm, compact nodules; whorls of fibrous tissue.	Scirrhous carcinoma. NO simple enlargement. Fibrous tissue ++.

ROUTINE EXAMINATION OF PROSTATE GLANDS.

P.M.No.	Size(Cms) W. L. D.	Weight (Gm.)	Cut surface Macroscopic Appearance.	Microscopic Appearance.
177	3½x 2½x 1	27	Spongy ; microcysts, nodules of fibrous tissue : brown calculi in periphery.	Well differentiated adenocarcinoma. NO simple enlargement.
178	4 x 3 x 2½	30	Fibrous ; compact, few small cystic spaces. Very small whorls of fibrous tissue.	Very poorly lined small acini. NO lymphorrhages : NO cancer: Simple enlargement.
179	3½x 2 x 1½	25	Fibrous, compact ; minute cystic spaces ; fibrous tissue strands.	Moderately differentiated adeno-carcinoma. Scanty mitoses. No simple enlargement.
180	2½x 1 x 1½	22	Small, rubbery, whorls of fibrous tissue ; microcysts in periphery.	Slit-like acini with nodules of fibrous tissue. NO cancer. NO simple enlargement.
182	3 x 2½x 2½	25	Rubbery ; nodules, whorls of fibrous tissue ; cysts in periphery.	Well formed acini with tall columnar epithelium. Corpora concentric. NO cancer. No simple enlargement.
183	3 x 3 x 2½	25	Firm : fibrous, compact. Coarse strands of fibrous tissue : calculi +.	Acini very thin lining epithelium; atrophic type ; laminated corpora amylacea large size. NO lymphorrhages.
194	4 x 4½x 2	40	Hard : raised nodules in cut surface ; fibrous tissue strands ; cysts +.	Moderately differentiated adeno-carcinoma. NO simple enlargement
185	4½ x 3 x1½	35	Rubbery ; whorls of fibrous tissue ; microcysts, brown calculi.	Simple enlargement of prostate ; multiple corpora : NO cancer.
192	2 x 1½x 1	22	Spongy : macrocysts ; gritty grey blue particles.	Early simple enlargement of prostate ; lymphorrhages around degenerate acini.
193	3 x 1 x 1½	20	Firm : compact, one nodule near surface, few whorls of fibrous tissue.	Poorly formed small acini. Corpora amylacea +. NO simple simple enlargement. NO carcinoma.

ROUTINE EXAMINATION OF PROSTATE GLANDS.

P.M. No.	Size(Cms) W. L. D.	Weight (Gm.)	Cut Surface Macroscopic Appearance	Microscopic Appearance
221	5 x 3½x 2	48	Spongy, cystic areas, nodules on surface.	Simple enlargement. NO cancer of prostate.
226	5 x 3 x 1	90	Hard nodules, fibrous tissue strands ++.	Well differentiated adenocarcinoma. Simple enlargement and lymphorrhages +.
229	2 x 1½x 2	15	Firm, compact ; no nodules. No whorls of fibrous tissue.	Dilated acini poorly lined. Few corpora. NO cancer. NO simple enlargement.
231	3 x 2½ x2	23	Smooth, compact : microcysts in periphery ; very firm areas.	Well differentiated adenocarcinoma + infection. NO simple enlargement. Scanty mitosis.
234	2 x 1½x 1	15	Pigmented areas. Compact : no nodules.	Small acini. Lining epithelium shed into lumen. Squamous metaplasia +.
238	3½x 3 x 2	40	Spongy : microcysts in periphery; fibrous tissue strands ++.	Acini full of exfoliated cells. Fragments of basement membrane. Multiple corpora amylacea.
247	4 x 4 x 2	30	Spongy , microcysts in periphery. White and brown nodules especially near centre.	Some acini show complete exfoliation of cells even basement membrane. Squamous metaplasia +. NO carcinoma.
271	3½x 4 x 2	35	Hard, compact, fibrous strands. nodules. Macrocysts.	Low cubical epithelium. Colloid goitre like areas of acini. Some acini contain laminated corpora amylacea. NO cancer. NO enlargement of prostate.
273	4 x 3 x 3	42	Nodular projections. Spongy cystic spaces.	Well differentiated adenocarcinoma. No mitoses. No simple enlargement.
276	5 x 4½x 3	50	Nodular : gritty. Brownish sand-like calculi. Macrocystic areas. White nodules.	Acini within normal limits. No evidence of Carcinoma or simple enlargement.
277	5 x 5 x 3	55	Irregular. Enlarged. Spongy. Macro- and Microcysts in periphery.	Slight dilatation of acini. Lumina filled with exfoliated cells. NO secondary infection.

ROUTINE EXAMINATION OF PROSTATE GLANDS.

P.M. No.	Size (Cms) W. L. D.	Weight (Gm.)	Cut Surface Macroscopic Appearance.	Microscopic Appearance.
286	4 x 3 x 1½	25	Spongy : cystic spaces. Few small nodular areas.	Poorly differentiated adenocarcinoma Pleomorphism : no mitoses : no simple enlargement.
287	4 x 3½ x 1	30	Fibrous. Nodular circumscribed, Areas. No calculi.	Acini normal size and shape ; a few degenerate with exfoliated cells in lumina. Few inflammatory cells seen.
288	4 x 2½ x 1	31	Rubbery. Calculi in periphery. Nodular white homogeneous areas.	Lining epithelial cells well formed. No evidence of cancer or simple enlargement.
290	3 x 2 x 2	22	Fibrous, gritty. Yellowish white strands : compact.	Acini normal in size and shape. Lumina contain degenerate eosinophil staining material. Multiple corpora amylacea. NO carcinoma.
294	4 x 3 x 2½	30	Hard, nodular, white areas few microcysts. Fibrous tissue strands.	Acini of varying shpes and sizes and grades of maturity. Slight round cell infiltration. NO cancer.
298	3 x 2 x 1½	15	Spongy : cystic spaces. Thrombosed vessels in capsule.	Thin lining epithelial cells. Lumen contains infected degenerate material. Marked round cell infiltration.
300	3½ x 3 x 2	17	Rubbery, homogeneous, white areas. No nodules ; fibrous tissue +.	Slightly dilated acini with lumina filled with degenerate pink-staining material. NO cancer. NO simple enlargement.
301	4 x 3 x 2	28	Fibrous, compact, cysts ; close texture. Bluish areas.	Acini small and irregular. Majority contain exfoliated degenerate cells. Facetted corpora amylacea. NO carcinoma. No simple enlargement.
320	4 x 3½ x 2	35	Spongy, microcysts. Yellowish white nodules in centre.	Simple enlargement of prostate. No cancer. No secondary infection.

ROUTINE EXAMINATION OF PROSTATE GLANDS.

P.M. No.	Size(Cms) W. L. D.	Weight (Gm.)	Cut Surface Macroscopic Appearance	Microscopic Appearance.
325	4 x 3 x 2	25	Spongy, brownish areas of discoloration. No calculi.	All acini full of desquamated epithelial cells. Desquamated cells with necrotic material in lumen. No cancer. No simple enlargement.
326	3½x 3 x 2	35	Rubbery : Raised white areas ; Sponge like.	Very poorly formed acini. Lining epithelium almost completely desquamated. Lymphorrages +.
327	3 x 2 x 1	22	Firm, small nodules. Compact. Fibrous tissue strands +.	Well developed acini but lining epithelium shed into lumen. NO cancer. NO simple enlargement.
328	2½x 2 x 1	19	Rubbery, microcysts +. Nodular.	Acini of varying degrees of maturity. Multiple corpora +. NO cancer. NO simple enlargement.
331	4 x 3½x 2	30	Rubbery, Brownish areas. Vessels in capsule congested ; gritty particles.	Small poorly lined acini. Lymphorrages +. NO cancer : NO simple enlargement.
332	3 x 1½x 1	20	Very fibrous. Stony hard, compact tissue ; white area near capsule.	Slit-like poorly formed acini. Some slightly dilated and desquamated cells in lumina. NO cancer. NO simple enlargement.
333	3 x 2½ x 2	22	Rubbery. Slightly fibrous. Brown speckling : Central area yellow.	Small acini showing desquamation of lining cells. Some elongated. NO cancer.
339	5½x 4 x 3½	117	Enlarged, rubbery. Nodular Cystic areas, below capsule.	Simple enlargement of prostate. Secondary infection +.
340	3½x 2 x 2	25	Small, uniform, spongy. No nodules.	Elongated acini. Low cubical epithelium. Few corpora : No cancer: No simple enlargement.
341	3 x 3 x 2	25	Spongy : flecks of fibrous tissue below capsule. Microcystic areas.	Small acini low cubical epithelium. Lumina filled with desquamated cells. NO cancer.

ROUTINE EXAMINATION OF PROSTATE GLANDS.

P.M. No.	Size(Cms) W. L. D.	Weight (Gm.)	Cut Surface Macroscopic Appearance	Microscopic Appearance
342	4 x 3 x 2½	35	Rubbery ; nodular. Microcysts. Blue black calculi ; gritty particles.	Well differentiated adenocarcinoma. No simple enlargement. Squamous metaplasia +.
349	4 x 3 x 2½	30	Fibrous, whorls of fibrous tissue. Circumscribed areas. No nodules.	Some acini distended with corpora amylacea, others poorly formed. Peri-acinar round cell infiltration. NO cancer. NO simple enlargement.
356	3 x 2 x 1	20	Leathery. Markedly cystic. Gritty particles.	Acini low cubical epithelium ; exfoliated cells in lumina. Multiple facetted corpora. Large cystic spaces. NO cancer. NO simple enlargement.
358	3 x 2½ x 1	30	Rubbery : one small nodule whitish ; gritty particles.	Simple enlargement of prostate. NO cancer.
360	3½ x 2½ x 2	30	Spongy ; microcystic spaces just below capsule. No nodular white areas : few strands of fibrous tissue.	Acini dilated. Some small. Some completely devoid lining epithelium. Corpora +. Squamous metaplasia +. NO cancer. NO simple enlargement.
369	4 x 3 x 2	37	Spongy. Dark bluish black stippling. No nodular areas and no cystic spaces.	Acini poorly formed. Some dilated with degenerate material in centre. NO cancer. NO simple enlargement.
370	3½ x 2 x 1	27	Rubbery, white nodules with cystic spaces within them. Fibrous tissue strands +.	Acini well formed. A few small degenerate acini with basement membrane, shed into lumen. No cancer. NO simple enlargement.
371	2 x 1½ x 2	20	Firm, fibrous, small, compact Few small pinhead nodular areas	Moderately differentiated adeno-carcinoma.
375	2 x 1½ x 2	22	Spongy. Microcystic area below capsule ; bluish stippling. No nodules.	Acini of varying shapes and sizes. NO evidence of Carcinoma or Simple enlargement.

Table 6. (Contd.)

ROUTINE EXAMINATION OF PROSTATE GLANDS.

P.M. No.	Size (Cms) W. L. D.	Weight (Gm.)	Cut surface Macroscopic Appearance.	Microscopic Appearance
378	4½x3½x 1½	50	Rubbery. Nodular, firm, white masses ; fibrous tissue +.	Simple enlargement of prostate.
379	5 x4½x 2½	58	Elastic : nodular ; macro and microcysts ; greenish yellow secretion.	Simple enlargement of prostate with secondary infection. NO cancer.
384	3½x2½x 2	25	Spongy, firm areas with cystic spaces within ; small brown calculi +. Gritty.	Moderately differentiated adenocarcinoma + simple enlargement of prostate.
386	2 x1½x 1	22	Firm ; compact ; coarse fibrous tissue strands. No nodules.	Well differentiated adeno-carcinoma + simple enlargement.
395	4 x 3x 1½	30	Rubbery, nodular areas with fibrous tissue around.	Varying sizes and shapes of acini. Multiple corpora amylacea ; NO simple enlargement. NO Cancer.
397	3½x2 x 1½	28	Rubbery, opaque white areas, macrocystic spaces +. No calculi.	Small poorly lined acini. Varying sizes of corpora amylacea. NO Cancer. NO simple enlargement.
400	3 x1½x 1	25	Firm areas with spongy honey-comb-like areas. Circumscribed fibrous whorls.	Small immature acini pale blue cytoplasm : desquamation slight. NO cancer. NO simple enlargement.
401	4 x3½x 2	43	Rubbery. Nodular white areas ; soft necrotic mass in centre.	Simple enlargement of prostate + secondary infection (slight). NO cancer.

Table 6. (Concluded).

ROUTINE EXAMINATION OF PROSTATE GLANDS.

P.N. No.	Size (Cms) W. L. D.	Weight (Gm.)	Cut Surface Macroscopic Appearance	Microscopic Appearance
420	2½ x 1 x 1	20	Spongy, few cystic areas. One small whitish nodule.	Acini commencing regrowth of lining epithelium. Acini small and poorly formed. NO cancer; NO simple enlargement.

Total No. of prostate glands examined = 142.

Study completed on July 8th, 1953.

SIZE & WEIGHT.

CANCER			CANCER AND SIMPLE ENLARGEMENT			SIMPLE ENLARGEMENT OF PROSTATE.					
P.M.No.	Size. (cm)	Weight (gm)	P.M.No.	Size (cm)	Weight (gm)	P.M.No.	Size (cm)	Weight (gm)	P.M.No.	Size (cm)	Weight (Gm.)
	W. L. D.			W.L.D.			W.L.D.			W.L.D.	
766	4x 2 x2	35	729	5½x4½x2	152	724	4½x3½x2½	50	221	5x3½x2	48
N.P.5607	2x1½x1½	20	730	3x1½x1	41	727	4x2½x1½	41	320	4x3½x2	35
42	3x3x1	18	731	3x3½x 2	22	728	4 x3x 1	32	339	5½x4x3½	117
52	4 x2x 1	35	125	3x 1x 1	20	733	5 x3x 1	57	358	3 x2½x1	30
59	3 x2x 2	26	141	2x1½x 1	15	735	4x2½x 2	42.6	378	4½x3½x1½	50
63	2½x3x 1	38	142	3½x2x 2	25	736	4x 3x 1	30	379	5x4½x2½	58
71	2½x2x 2	38	165	3½x2x 1	23	737	4½x3½x2	55	401	4x3½x2	43
104	1 x2x 1	15	199	3 x2x 2	25	768	5x2½x 2	75			
111	4x2½x 2	40	208	3x1½x 1	15	769	3½x2x 2	30			
117	2 x2x 1	20	226	5x 3x 1	90	40	3½x2 x1	58			
177	3½x2½x2	23	384	3½x2½x2	25	70	4½x3 x2	100			
179	3½x2½x1	27	386	2 x1½x1	22	76	4 x1x2½	40			
184	4x4½x 2	40				78	4x2½x 1	40			
201	3½x2½x1	27				87	2x1½x 2	35			
219	4½x2½x3	40				99	3x2½x 2	45			
231	3x2½x 2	23				114	3½x1x1½	25			
273	4 x3x 3	42				146	5x3½x 1	55			
286	4x3 x1½	25				150	3½x2x1½	30			
342	4x3 x2½	35				156	5x3½x 2	55			
371	2x1½x 2	20				160	4x 3x 1	35			
						185	4½x3x1½	35			
						192	3 x1½x1	22			
						203	4 x2x1½	35			
						204	5 x3x2	55			

W = Width. L = Length. D = Depth.

NON CARCINOMATOUS PROSTATE GLANDS.

(SIZE & WEIGHT).

P.M.No.	Size (Cms.)	Wt. (Gms.)	P.M. No.	Size (Cms.)	Wt. (Gms.)
747	3 x 2 x 2	38	106	1 x 1½ x 1	15
22	3 x 1 x 2	25	120	2 x 1½ x 1	15
41	2 x 2 x 1½	20	124	2½ x 1 x 1½	15
43	4 x 3 x 2	38	130	2½ x 2 x 2	20
47	3½ x 2 x 2	45	132	2½ x 1 x 1½	22
53	3 x 2 x 1	22	133	2 x 1 x 1½	18
56	4 x 2 x 2½	45	140	2 x 1½ x 1	15
57	4½ x 2 x 1	50	148	2 x 1 x 1½	15
60	3 x 3 x 1	25	149	3 x 2 x 1	17
66	3 x 2 x 2	25	154	4 x 2 x 1	30
77	3½ x 1 x 2	36	155	3 x 1½ x 1	20
81	3 x 2½ x 2	42	158	4 x 2 x 1	35
NP 5631	4 x 2 x 1½	35	161	4½ x 3½ x 2	40
86	1½ x 2 x 1	15	163	2½ x 2 x 1	18
89	2½ x 1 x 2	35	164	3 x 2½ x2	30
90	2 x 1½ x 2	38	168	4 x 2½ x 2	17
97	2 x 2½ x 2	40	178	4 x 3 x 2½	30
98	1½ x 2 x 1	20	180	2½ x 1 x 1½	22
100	1½ x 1 x 1	20	182	3 x 2½ x 2½	25
101	1 x 1½ x 2	17	183	3 x 3 x 2½	25

NON CARCINOMATOUS PROSTATE GLANDS.

(SIZE & WEIGHT).

P.M. No.	Size (Cms.)	Wt. (Gms.)	P.M.No.	Size (Cms.)	Wt. (Gms.)
193	3 x 1 x 1½	20	325	4 x 3 x 2	25
194	1½ x 1 x 1	17	326	3½ x 3 x 2	35
197	2½ x 2 x 1	20	327	3 x 2 x 1	22
200	2½ x 2 x 1½	25	328	2½ x 2 x 1	19
202	3 x 2 x 2½	20	331	4 x 3½ x 2	30
212	2 x 1½ x 2	20	332	3 x 1½ x 1	20
229	2 x 1½ x 2	15	333	3 x 2½ x 2	22
234	2 x 1½ x 1	15	340	3½ x 2 x 2	25
238	3½ x 3 x 2	40	341	3 x 3 x 2	25
247	4 x 4 x 2	30	349	4 x 3 x 2½	30
271	3½ x 4 x 2	35	356	3 x 2 x 1	20
276	5 x 4½ x 3	50	360	3½ x 2½ x 2	30
277	5 x 5 x 3	55	369	4 x 3 x 2	37
287	4 x 3½ x 1	30	370	3½ x 2 x 1	27
288	4 x 2½ x 1	31	375	2 x 1½ x 1½	22
290	3 x 2 x 2	22	395	4 x 3 x 1½	30
294	4 x 3 x 2½	30	397	3½ x 2 x 1½	28
298	3 x 2 x 1½	15	400	3 x 1½ x 1	25
300	3½ x 3 x 2	17	420	2½ x 1 x 1	20
301	4 x 3 x 2	28			

Table 9.

AMOUNT OF FIBROUS TISSUE & ELASTIC TISSUE.

Cancer.			Cancer + Simple Enlargement.		
P.M. No.	E.	F.	P.M. No.	E.	F.
766	+++	+++	729	++	+++
5607	+++	+++	730	++	+++
42	+++	+++	731	+++	+++
52	++	+	125	++	+
59	++	+	141	++	+
63	+++	+	142	+	++
71	+	++	165	+++	+
104	+++	++	199	+	++
111	+++	++	208	+	+
117	+++	+++	226	++	++
177	+	+++	384	+	++
179	+++	++	386	++	++
184	++	++			
201	+++	+++			
219	+++	+++			
231	++	+++			
273	++	+++			
286	++	+++			
342	+	++			
371	+++	+++			

E. = Elastic tissue.

F. = Fibrous tissue.

Table 10.

AMOUNT OF FIBROUS TISSUE & ELASTIC TISSUE.

Simple Enlargement.

P.M. No.	E.	F.	P.M. No.	E.	F.
724	++	+	114	+	+
727	+	+	146	+	+
728	+	+	150	+++	+
733	++	+	156	++	+
735	++	+	160	++	+
736	+	+	185	++	+
737	++	+	192	+++	+
768	+++	++	203	++	+
769	+++	++	204	+	+
40	++	+	221	+	+
70	+	+	320	++	+
76	+	+	339	++	+
78	+	+	358	+	+
87	++	+	378	+	+
99	+	+	379	+	+
			401	++	+

E. = Elastic tissue.

F. = Fibrous tissue.

Table II.

POST MORTEM DIAGNOSIS

of

UNSUSPECTED CANCEROUS GLANDS.

P.M. No.	Post mortem Diagnosis.
766	Miliary tuberculosis.
N.P. 5607	?
42	Sub-hepatic abscess.
+ 52	Carcinoma pyloric antrum - extensive deposits including vertebral column.
59	Thrombo-angeitis.
63	Accident - Fracture of femur : Fat embolism.
+ 71	Bronchial carcinoma.
104	
111	
117	Accident - Multiple fractures.
177	Post-operative bronchopneumonia.
+ 179	Bladder carcinoma.
184	Congestive cardiac failure.
201	Silicosis.
+ 219	Papillomatosis of bladder.
231	Bronchiectasis.
273	?
286	Recent coronary thrombosis.
342	Acute oeteomyelitis : Fracture of neck of femur.
371	

Table 11. (Concluded).

POST MORTEM DIAGNOSIS OF

UNSUSPECTED CANCER + SIMPLE ENLARGEMENT CASES.

P.M. No.	Diagnosis
729	Myocardial infarcts with rupture
730	Perforated duodenal ulcer.
731	Hodgkin's disease.
125	?
141	Chronic duodenal ulcer.
142	Chronic pulmonary tuberculosis.
165	Subacute liver atrophy.
199	Peptic ulcer - Pulmonary embolism.
+ 208	Epithelioma of anus - Hypertensive cardiac failure.
226	Pulmonary embolism.
+ 384	Carcinoma of tail of pancreas.
386	Cirrhosis of liver.

Table 12.

POST MORTEM DIAGNOSIS OF ALL GLANDS EXAMINED.

P.M. No.	Diagnosis
724	Cerebral tumour
727	Silicosis of lungs
728	Silicosis of lungs
729	Myocardial infarct with rupture
730	Perforated duodenal ulcer
731	Hodgkin's disease
733	Bronchopneumonia & bronchiectasis.
735	Malignant melanoma
736	? Encephalitis
737	Bronchopneumonia
747	Lymphosarcoma
766	Miliary tuberculosis
768	Fractured right femur ? Fat embolism.
769	Hypertension. Bronchopneumonia.
22	Reticulum-cell sarcoma.
40	Fracture of skull - accidental.
41	Accident - crush injury : Fracture of femur.
42	Subhepatic abscess
43	Malignant Hodgkin's disease
47	? Hodgkin's disease. Bronchopneumonia
N.P. 5607	
52	Carcinoma pyloric antrum. Deposits vertebral column.
53	Hydrocephalus following meningitis.
56	Bronchial carcinoma
57	Bronchiectasis. Bronchopneumonia
59	Thrombo-angitis
60	Acute peritonitis
63	Accident - fracture of femur. Fat embolism.
66	Cerebral haemorrhage.
70	Congestive cardiac failure.
71	Carcinoma of bronchus.
76	Paralytic ileus. Carcinoma of colon.
77	Granular contracted kidneys.
78	
81	Multiple myeloma.
N.P. 5631	
86	Diabetic gangrene.
87	Peritonitis - subphrenic
89	Gastric carcinoma.
90	Pulmonary tuberculosis.
97	Bronchial carcinoma
98	Bronchiectasis.
99	Cardiac infarction
100	Acute myocardial failure.

Table 12 (Contd.)

POST MORTEM DIAGNOSIS OF ALL GLANDS EXAMINED.

P.N.No.	Diagnosis	P.M.No.	Diagnosis	P.M.No.	Diagnosis.
101	Coronary thrombosis	149	Chronic bronchiectasis & emphysema.	183	Bronchial carcinoma
104		150	Bronchopneumonia	184	Congestive failure
106	Aortic incompetence	154	Bronchopneumonia	185	Unknown
111		155	Hodgkin's disease	192	Carcinoma of colon.
114		156	Silicosis of lung	193	Mitral stenosis
117	Accident. Multiple fractures.	158	Lymphosarcoma	194	Mitral stenosis
120	Polyarteritis nodosa	160		197	Bronchial carcinoma
124	Malignant reticulosis	161	Silicosis of lung. Myocardial infarction.	199	Peptic ulcer & pulmonary embolism
125		163		200	
130	Emphysema : Cardiac failure	164	Glioblastoma	201	Silicosis of lungs
132	Bronchial carcinoma	165	Subacute liver atrophy.	202	Carcinoma of oesophagus
133	Cirrhosis of liver.	168	Portal pyaemia	203	Bleeding duodenal ulcer.
140	Bronchial carcinoma	177	Post-operative bronchopneumonia	204	Hypertensive cardiac failure.
141	Chronic duodenal ulcer.	178	Chronic bronchitis	208	Epithelioma of anus. Hypertensive cardiac failure.
142	Chronic pulmonary tuberculosis	179	Bladder carcinoma	212	Marked anaemia. ? Leukaemia.
146	Hypertensive cardiac failure	180	Acute cholecystitis		
148		182	Capillary bronchitis		

Table 12. (Contd.)

POST MORTEM DIAGNOSIS OF ALL GLANDS EXAMINED.

P.M.No.	Diagnosis
219	Bronchopneumonia. ? Coronary thrombosis
221	Papillomatosis of urinary bladder.
226	Pulmonary embolism. Cerebral infarcts.
229	Carcinoma of pancreas.
231	Bronchiectasis. Pulmonary emphysema.
234	?
238	Pulmonary embolism.
247	Bronchial carcinoma
271	Pulmonary embolism.
273	?
276	Bronchopneumonia
277	Bronchiectasis
286	Recent coronary thrombosis.
287	Fracture of skull. Subdural haematoma.
288	Arteriosclerosis. Gangrene of lower limb.
290	Partial gastrectomy. Paralytic ileus.
294	Cerebral & cardiac infarction.
298	N.P.
300	Diabetes mellitus. Myocardial infarction.
301	Tumour of pituitary.
320	Right renal carcinoma.
325	Multiple fracture of lower jaw.
326	?
327	Bronchopneumonia.
328	Carcinoma of left lung.
331	Chronic rheumatic aortitis.
332	? Hydrocephalus
333	Carcinoma of stomach
339	Prostatic hypertrophy.
340	Acute lymphatic leukaemia.
341	Accident : Multiple injuries.
342	Acute oesteomyelitis
349	Carcinoma of oesophagus
356	Silicosis of lung. Coronary thrombosis.
358	Silicosis of lungs.
360	?
369	Subarachnoid haemorrhage. Rupture of cerebral aneurysm.
370	Carcinoma of colon.
371	Perforated duodenal ulcer. General peritonitis.
375	Cerebral haemorrhage
378	Carcinoma of pelvic colon.
379	Duodenal ulcer.
384	Carcinoma tail of pancreas.
386	Cirrhosis of liver.
395	Cerebral haemorrhage
397	Bronchopneumonia following gastrectomy.

Table 12. (Concluded).

POST MORTEM DIAGNOSIS OF ALL GLANDS EXAMINED.

P.M. No.	Diagnosis	P.M. No.	Diagnosis	P.M.No.	Diagnosis
400	Myocardial infarcts. Coronary insufficiency.	401	Perforated duodenal ulcer.	420	

Section III.

The Response of the Prostate Gland

to

Experimental Injury.

Section III.

Section III.

(1) INTRODUCTION.

" Since Pathology is essentially the science of abnormality produced by injury, our first task is to find out how tissue cells are affected by harmful agents " (Cameron, 1952).

This investigation records experiments performed with a view to studying the prostate gland in the light of this context.

The problem of response to injury has been studied in the canine prostate by previous workers (Piccoli, 1901 ; Baiardi, 1904) in only one phase - namely the mechanism of regeneration after excision.

Thus a more detailed study of the behaviour of prostatic glandular tissue to different forms of simple trauma appears to be desirable.

(2) MATERIALS and METHODS.

Rats were selected for this study not only because of their availability in sufficient numbers to warrant extensive use but because they withstand surgical procedures. In addition post-operative mortality among them is usually low. Their natural resistance to infections makes them desirable surgical risks.

In all 125 healthy Wistar strain male albino rats were studied. They weighed between 150 and 180 Gm.

Three pilot experiments were performed to

(a)/

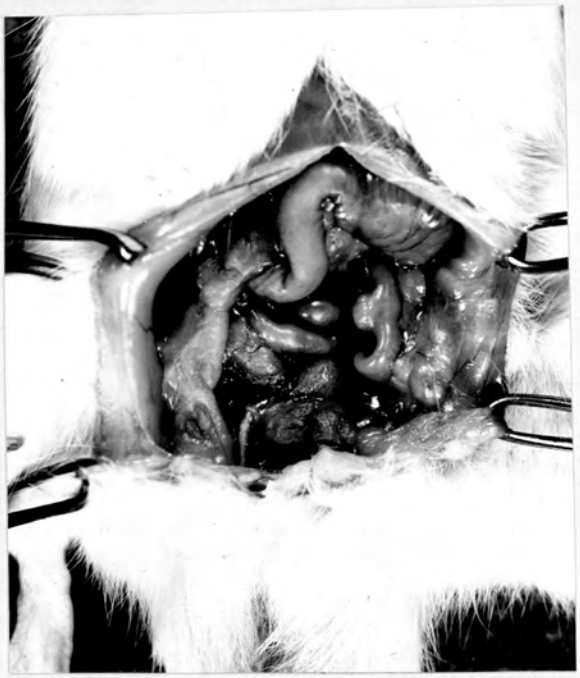

Fig. 9. Prostate. Rat. Showing position of prostate gland in situ.

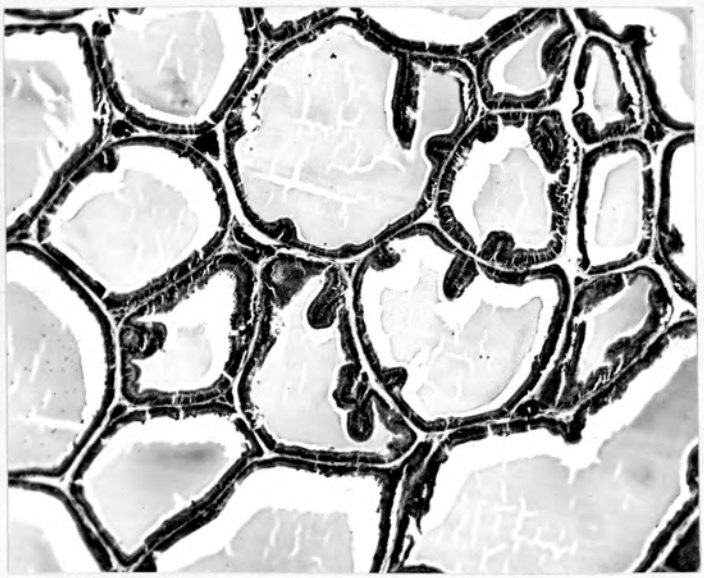

Fig. 10. Prostate. Rat K. Normal gland. Acini well filled. Epithelial lining columnar type. Uniformly staining. All acini closely set. No stromal connective tissue seen. Haematoxylin & Eosin x 90.

(a) Find out the best surgical approach to the prostate gland

(b) Study the optimum time required to traumatise adequately the prostate gland with Carbon dioxide snow

(c) Determine what strength of bacterial culture should be used to produce adequate damage to the prostate gland.

The rats were fed on MRC rat cubes and were given as much water as they wished.

A mid line incision was made as the blood supply here was most sparse and therefore bleeding is minimal. This mid line incision was in the lower third of the anterior abdominal wall.

The coils of intestine which were in the field of operation were gently lifted and held aside by being wrapped up in small pieces of gauze wrung out in hot normal saline solution. The bladder was easily seen usually as a distended globular structure of an opalescent creamy white colour. The prostate gland was clearly demarcated as a fleshy pink ovoid mass around the base of the urinary bladder. There was a thin fibrous tissue capsule surrounding the prostate and this was attached to the posterior surface of the anterior abdominal wall.

The different methods of traumatising the prostate gland were carried out on the prostate gland thus exposed.

Extreme gentleness was observed in the handling/

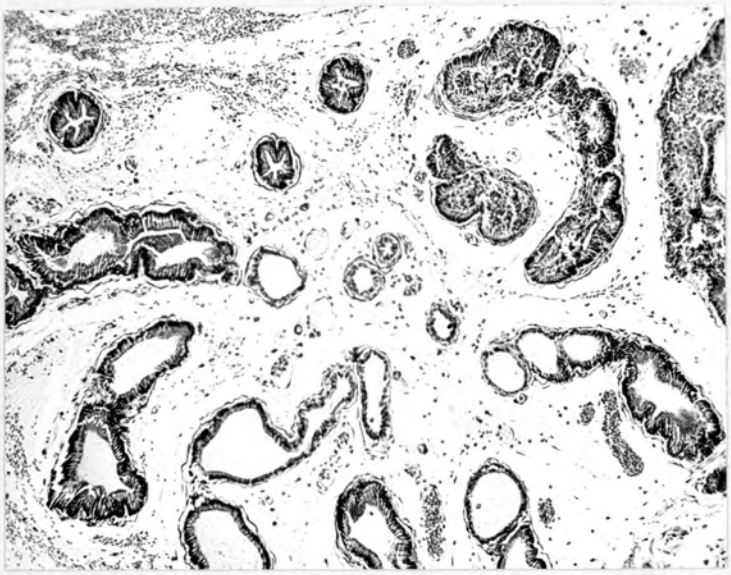

Fig. 11. Prostate. Rat N 18. ONE DAY.
Traumatised acini necrotic. Acute inflammatory cell reaction in stroma. Haematoxylin & Eosin x 90.

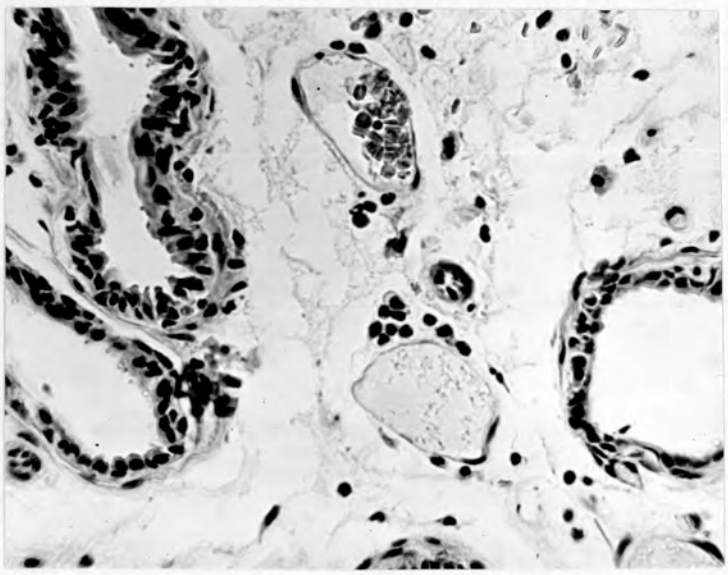

Fig. 12. Prostate. Rat N 18. Dilatation of all vessels. Part of acute inflammatory response. Haematoxylin & Eosin x 400.

handling of all tissues.

The animals were killed with ether at intervals after the operation ranging from one day to eight weeks.

Small pieces of prostatic tissue were removed and fixed at once in Zenker's solution for a period of twenty four hours.

Paraffin sections were prepared in the usual way. They were stained with Ehlrich's acid haematoxylin and eosin, Weigerts iron haematoxylin and Vierhoff Van Gieson's stain for fibrous tissue. A few sections were stained with Grams iodine and Von Kossa for Calcium respectively.

(3) EXPERIMENT I. RESPONSE TO THERMAL INJURY.

Apparatus. - CO_2 snow, cork borer, forceps with blunt points, scalpel, blunt pointed scissors, fine sharp pointed scissors, one inch curved needle with suturing material.

Description - The rats were anaesthetised and operated upon in the manner described above. For the production of injury an area of about 16 sq.mm. and approximately 0.5-1 0mm thick, was frozen for one minute with CO_2 snow according to the technique of Cameron and Mehrotra (1953).

Results.

Microscopic appearances. Twenty four hours. There is much necrosis over the site of freezing in addition to intense acute inflammatory reaction. The severely damaged/

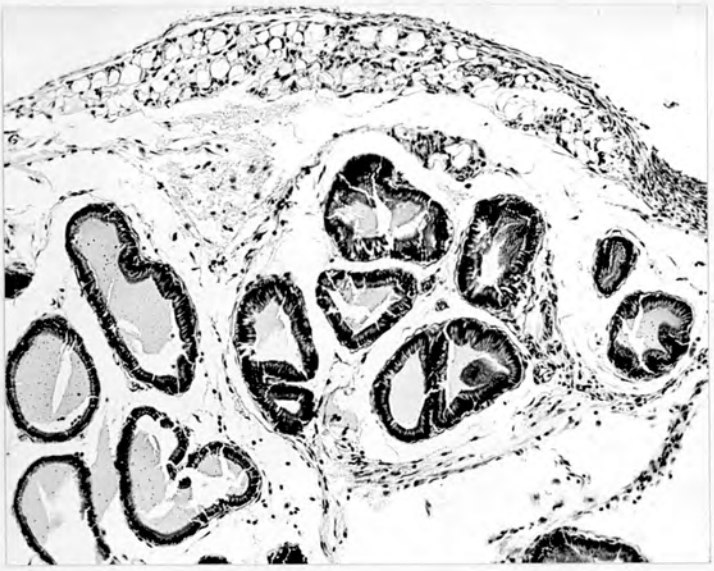

Fig. 13. Prostate. Rat N 23. THIRD DAY. Traumatised acini shrunken. Diminution of secretion within lumina. Increased cellularity of capsular connective tissue. Traces of oedema fluid in inter glandular tissue, also commencing laying of fibrous tissue. Haematoxylin & Eosin x 90.

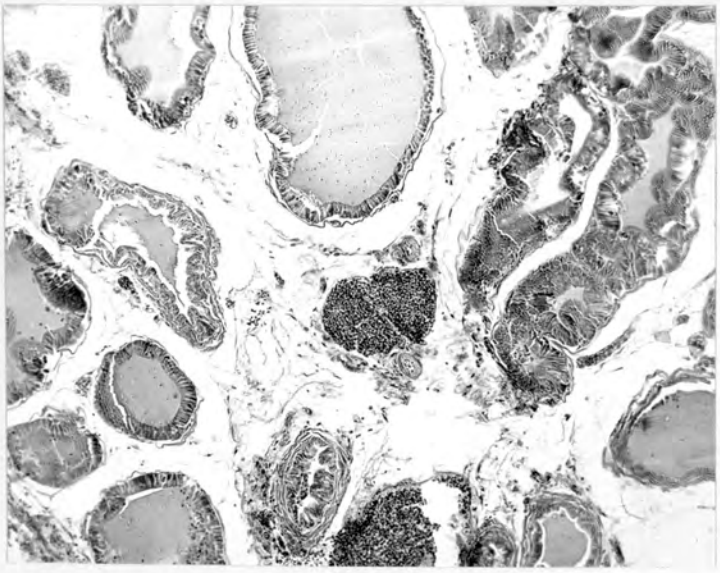

Fig. 14. Prostate. Rat N 2. FIFTH DAY. Damaged acini shrunken. Epithelium necrotic. Traces of oedema fluid still present. Fibrous tissue strands coarse. Few inflammatory cells and congested vessels seen. Van Gieson x 90.

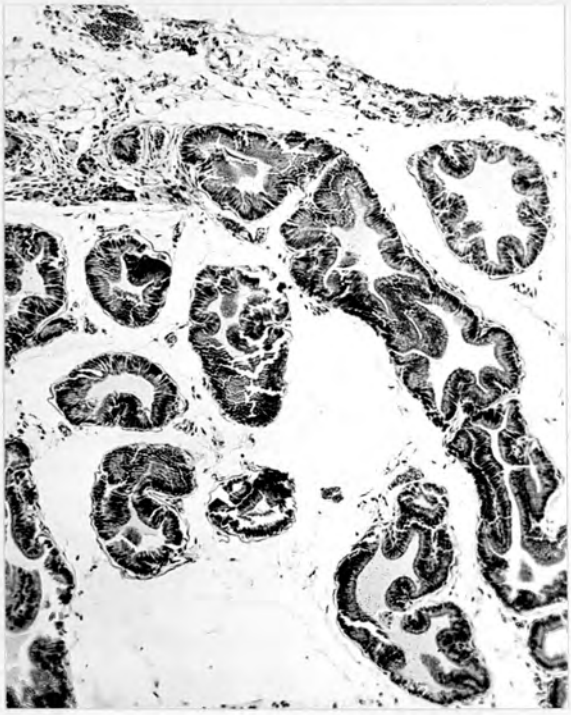

Fig. 15. Prostate. Rat N2. FIFTH DAY. Commencing phagocytic activity especially in region of connective tissue of capsule. Increased number of spindle cells in region of damaged acini. Haematoxylin & Eosin x 90.

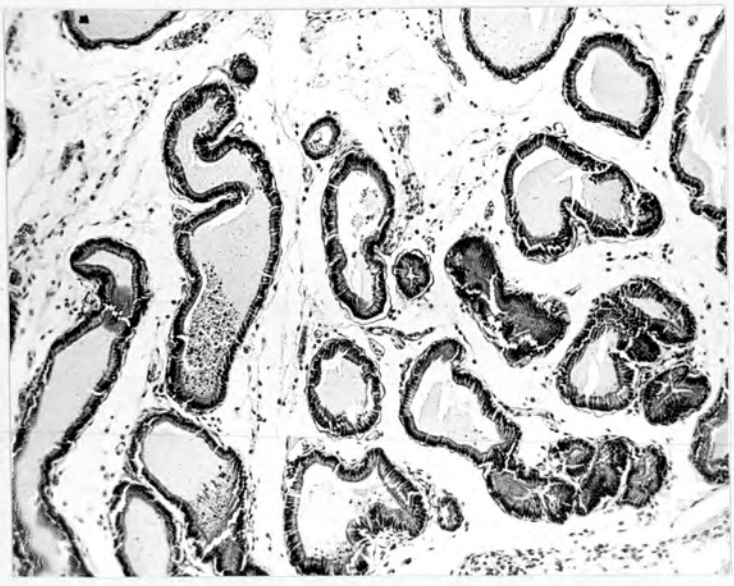

Fig. 16. Prostate. Rat N 6. ONE WEEK. Increased phagocytic activity together with large numbers of spindle cells and fibrils. Haematoxylin and Eosin x 90.

damaged acinar epithelium is deep purple in colour and appears smudgy with infolding and loss of " light areas " of the normal epithelium. The less severely damaged areas show acini with regularly formed cubical epithelium. The stroma shows a large quantity of pink staining fluid (inflammatory oedema) with a small amount of fibrin. All blood vessels are dilated and congested, there is also a dilatation of lymphatic vessels. No red blood cells were seen in the stroma despite the fact that there was an intense inflammatory reaction. The cells (leucocytes) were chiefly mononuclear in type. There were in addition, small numbers of a mixture of lymphocytes, eosinophil polymorphs and reticulo-endothelial cells. Plump spindle shaped cells are seen running across in the stroma of the damaged region. The connective tissue capsule which encircles the prostate contains many dilated blood vessels and a mixture of mononuclear cells and polymorphonuclear leucocytes. The innermost portion of this capsule is lined by spindle shaped fibroblasts.

Third day. There is commencing phagocytic activity around the degenerate acini of the damaged area. This is indicated by the presence of increasing numbers of reticulo-endothelial cells. Some of the severely damaged acini are ringed by fine strands of fibrous tissue and lymphocytes. In general the stroma shows a slightly smaller quantity of pink staining oedema fluid and also a small amount/

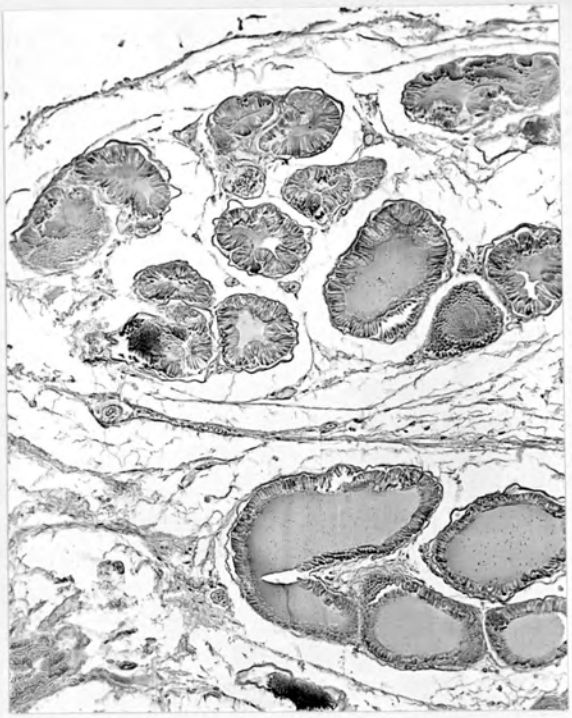

Fig. 17. Prostate. Rat N 6. ONE WEEK. Well formed strands of fibrous tissue coursing amidst damaged acini. Van Gieson x 90.

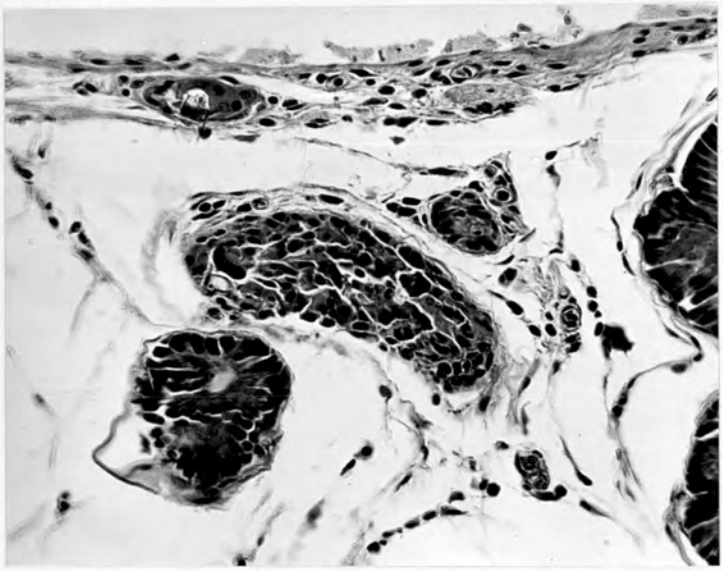

Fig. 18. Prostate. Rat N 7. TWO WEEKS. Commencing pseudo acinar tissue formation in region of connective tissue of capsule. Haematoxylin & Eosin x 285.

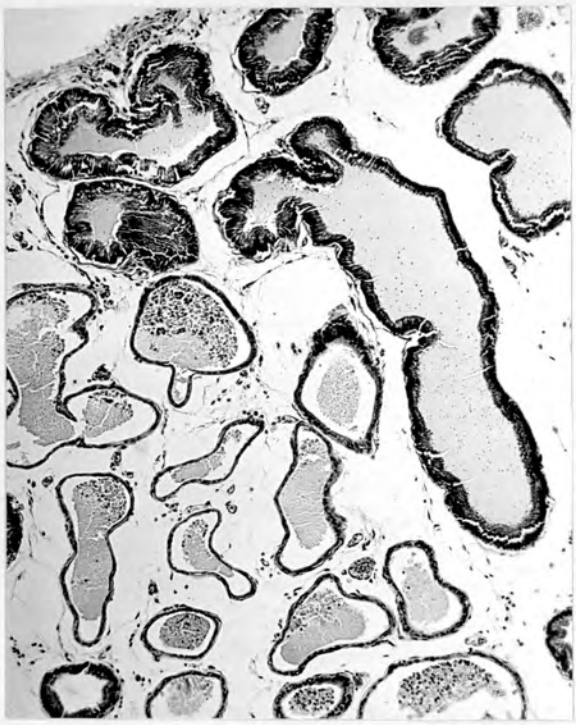

Fig. 19. Prostate. Rat N 7. TWO WEEKS. Damaged acini lined by low cubical epithelium. Lumina containing necrotic debris. Haematoxylin and Eosin x 90.

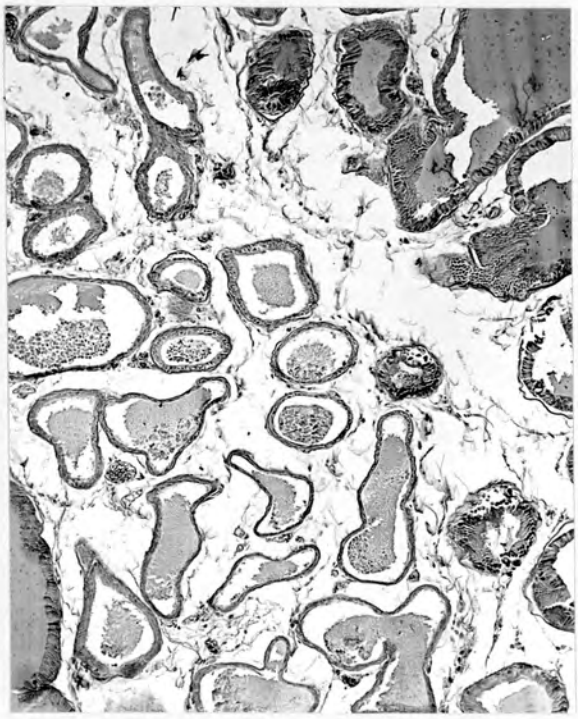

Fig. 20. Prostate. Rat N 7. TWO WEEKS. Increased formation of strands of fibrous tissue around damaged acini. Van Gieson x 90.

amount of fibrin. The cellular response is still the same that is mononuclear leucocytes, a few polymorphonuclear leucocytes and fibroblasts. The fibroblasts are more plentiful and are seen to proceed from the connective tissue of the encircling capsule. Also large numbers of fibroblasts are seen budding off from the vicinity of blood vessels.

Fifth day. There is a greater degree of fibrosis around the severely damaged acini. The undamaged acinar epithelium is large and well developed. No oedema fluid and fibrin are seen in the stroma. Fewer mononuclear cells seen. The fibrous tissue strands are slightly thicker and more elongated.

Seventh day. There is an increase in the number of cells and amount of fibrous tissue seen in the stroma. The strands are still broad. The damaged acini are smaller and more degenerate looking. The vessels are less congested. The epithelium of the undamaged acini shows marked compensatory hyperplasia.

Two weeks. There are very few damaged acini seen. Almost all necrotic debris has been removed together with a few strands of fibrous tissue and fibroblast cells, few mononuclear cells, and few polymorphs seen in stroma. Other acini show marked epithelial growth. There is evidence of pseudo-acinar formation in outermost areas of the connective tissue capsule. These islets are surrounded by deeply staining elongated cells.

Four/

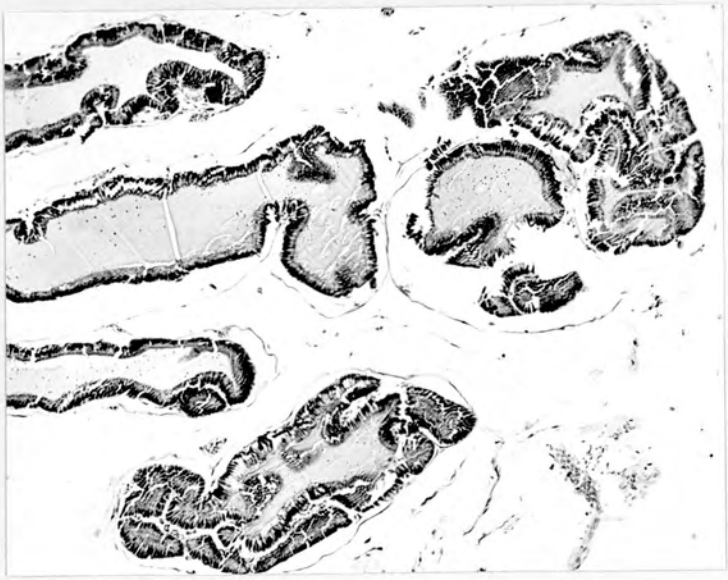

Fig. 21. Prostate. Rat N 11. FOUR WEEKS. Compensatory hyperplasia of undamaged acini. Haematoxylin & Eosin x 90.

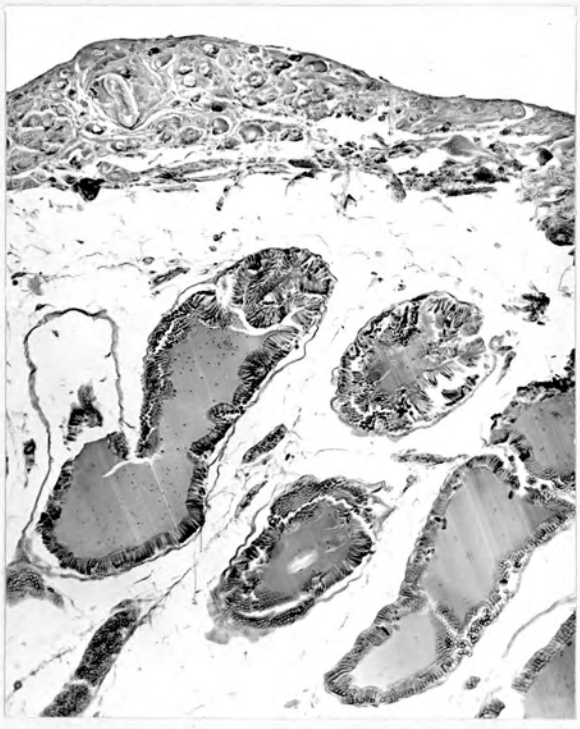

Fig. 22. Prostate. Rat N 10. FOUR WEEKS. Area of regenerated tissue in region of capsular connective tissue. Fibrous tissue strands running in between acini. Van Gieson x 90.

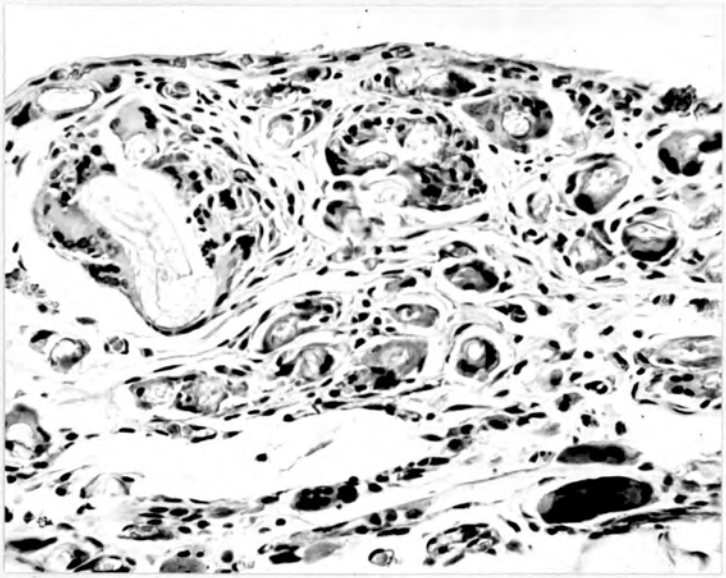

Fig. 23. Prostate. Rat N 10. FOUR WEEKS. Some areas as Fig. 22. Regenerating acini at a more advanced stage of growth. Note secretion within lumina. Haematoxylin & Eosin x 285.

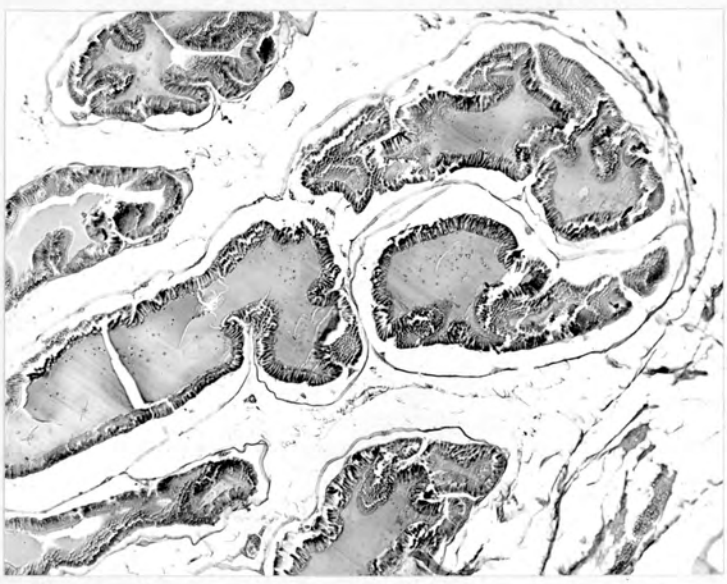

Fig. 24. Prostate. Rat N 14. EIGHT WEEKS. Marked fibrosis around severely damaged acini. Van Gieson x 90.

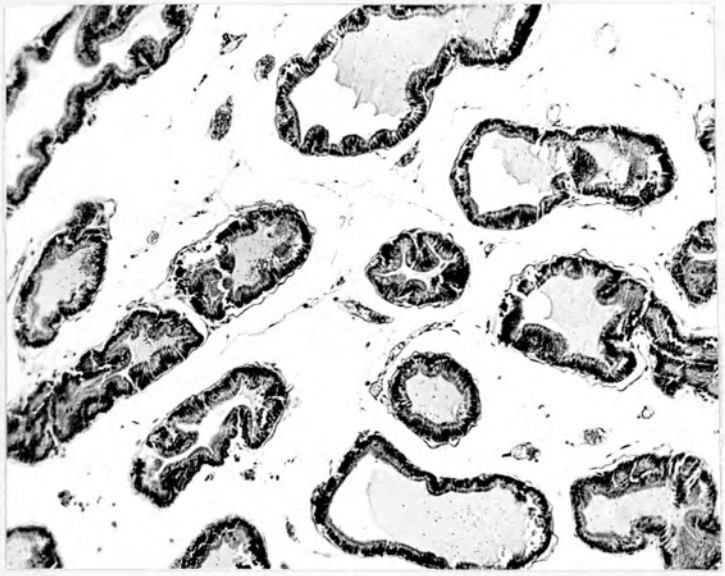

Fig. 25. Prostate. Rat N 14. EIGHT WEEKS. Young capillaries in stroma together with a few mononuclear cells.

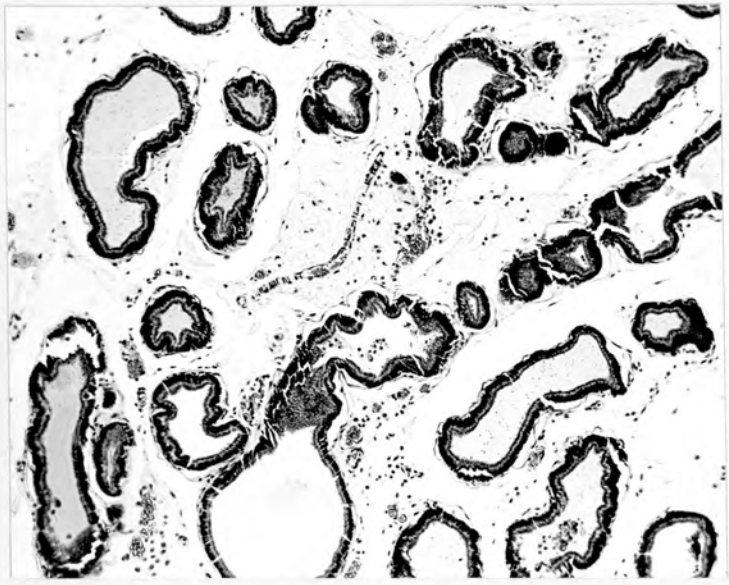

Fig. 26. Prostate. Rat L 12. ONE DAY. Acute inflammatory reaction with infolding of damaged acini. Haematoxylin & Eosin x 90.

Four weeks. Marked glandular epithelial growth with well filled regularly lined acini. Thick strands of fibrous tissue. Very few mononuclear cells seen. Less severely damaged acini are closely set and elongated. The regenerated acini in capsular area is in a more advanced state of development and more numerous regenerating acini seen. Now slight eosinophil staining secretion seen in lumen. Undamaged acini markedly distended and well filled with regular lining of cubical epithelium.

Six weeks. A few necrotic acini still seen. Other acini show luxuriant glandular epithelial growth. Hardly any fibrous tissue seen in stroma. Still more advanced state of development of newly formed glandular tissue (pseudoacini).

Eight weeks. A few necrotic acini still present but no evidence of calcification. Regeneration of damaged capsular connective tissue complete.

(4) EXPERIMENT II. RESPONSE TO SIMPLE EXCISION.

Apparatus. A pair of sharp pointed scissors and a pair of forceps with blunt points.

Description. The rats were anaesthetised and operated upon as described earlier. A small piece of prostatic tissue was snipped off : care was taken NOT to damage the prostate in any other way, e.g. pressure of forceps.

Results/

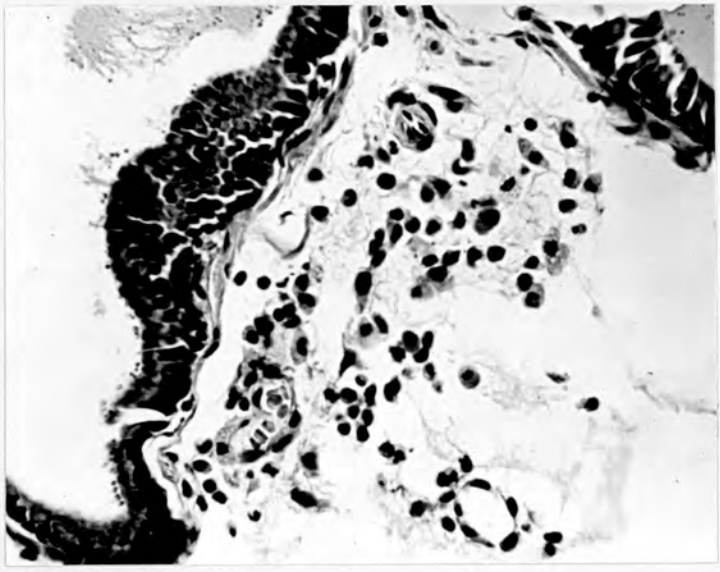

Fig. 27. Prostate. Rat L 12. ONE DAY. Mononuclear cell response with numerous dilated vessels. Haematoxylin & Eosin x 400.

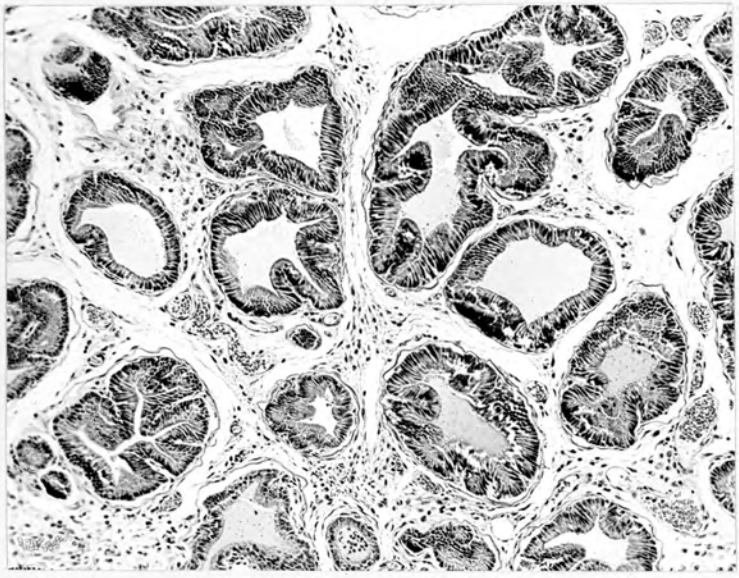

Fig. 28. Prostate. Rat A 3. THIRD DAY. Commencing phagocytic activity around damaged acini. Streaming in of spindle shaped cells from region of capsular connective tissue. Haematoxylin & Eosin x 90.

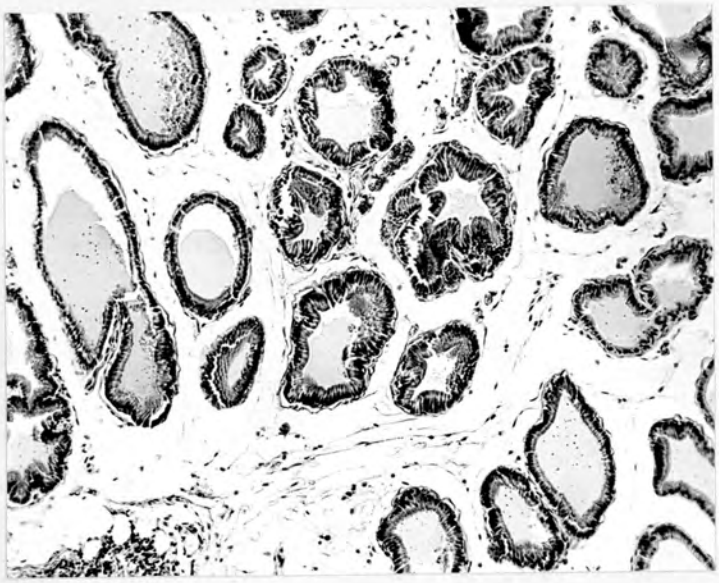

Fig. 29. Prostate. Rat L 14. FIFTH DAY. Spindle shaped cells more elongated and more plump. Fibrils thick. Damaged acinar epithelium shrunken and smudgy with necrotic material within lumina of acini. Haematoxylin & Eosin x 90.

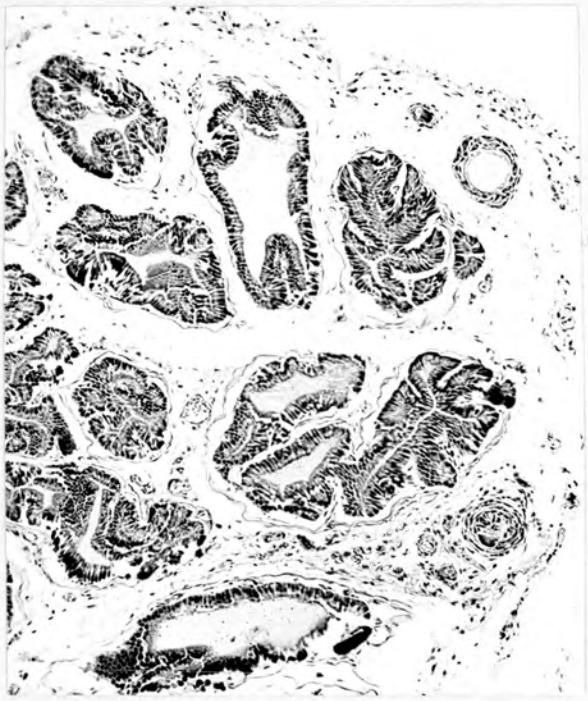

Fig. 30. Prostate. Rat E 1. ONE WEEK. Increased phagocytic activity. Fibrous tissue strands thicker. Haematoxylin & Eosin x 90.

Results.

Microscopic appearances.

Twenty four hours. Severely damaged acini shrunken. Cytoplasm dull and of a deep magenta colour. Necrotic cellular debris in lumina. Stroma contains oedema fluid, fibrin and masses of inflammatory cells chiefly mononuclear cells, eosinophil polymorphs and a few lymphocytes. All vessels including lymphatics dilated. A few fibroblasts could be seen. Large numbers of red blood cells amidst stroma.

Third day. Commencing phagocytic activity around damaged acini. The undamaged acinar epithelium is regular and well developed and fills the acinus to a great extent leaving only a small lumen. Mononuclear cells together with a greater number of fibroblasts were seen in the stroma. The connective tissue capsule is very cellular and vascular.

Fifth day. Less severely damaged acini show an increased nuclear content above basement membrane. Increased degree of fibrosis around necrotic acini. Traces of oedema fluid and no fibrin seen. In stroma still many mononuclear leucocytes and lymphocytes in clumps. The spindle shaped fibroblasts are tending to arrange themselves in an orderly fashion - parallel formation. They appear to have their origin from the connective tissue capsule which surrounds the prostate. Many elastic tissue fibrils seen in site of proliferating

fibroblast/

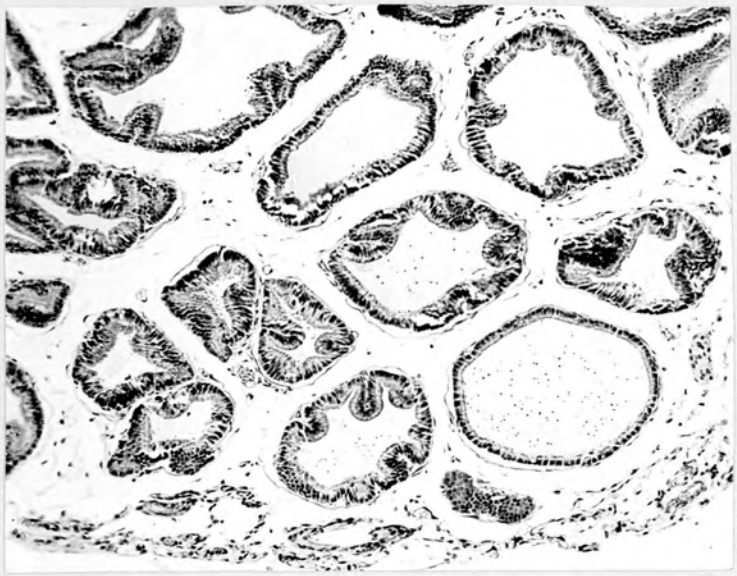

Fig. 31. Prostate. Rat I 24. TWO WEEKS. Few damaged acini seen. Phagocytic activity diminished. Few fibroblasts and mononuclear cells in stroma. Haematoxylin & Eosin x 90.

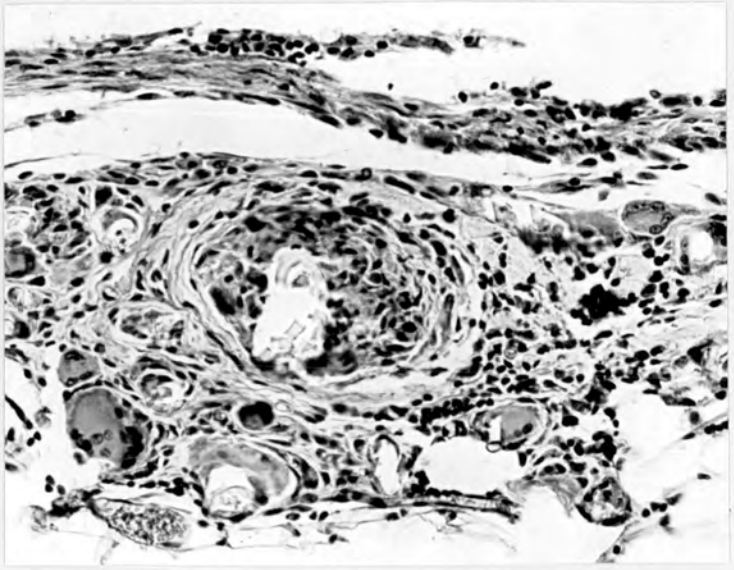

Fig. 32. Prostate. Rat I 26. TWO WEEKS. Regenerating tissue seen in region of capsular connective tissue. A few acini contain dark staining secretion within lumina. Haematoxylin & Eosin x 250.

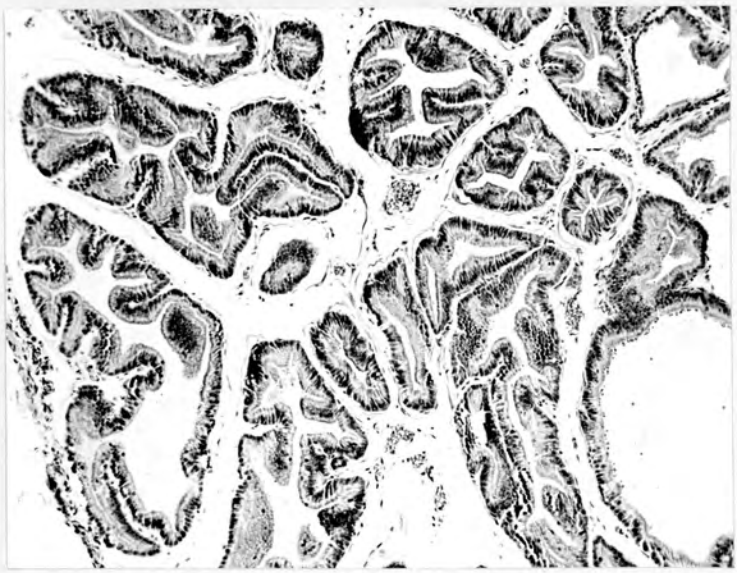

Fig. 33. Prostate. Rat H 13. FOUR WEEKS. Compensatory hyperplasia of undamaged acini. Few strands of fibrous tissue seen in stroma. Capillary vessels formation seen in stroma. Haematoxylin & Eosin x 90.

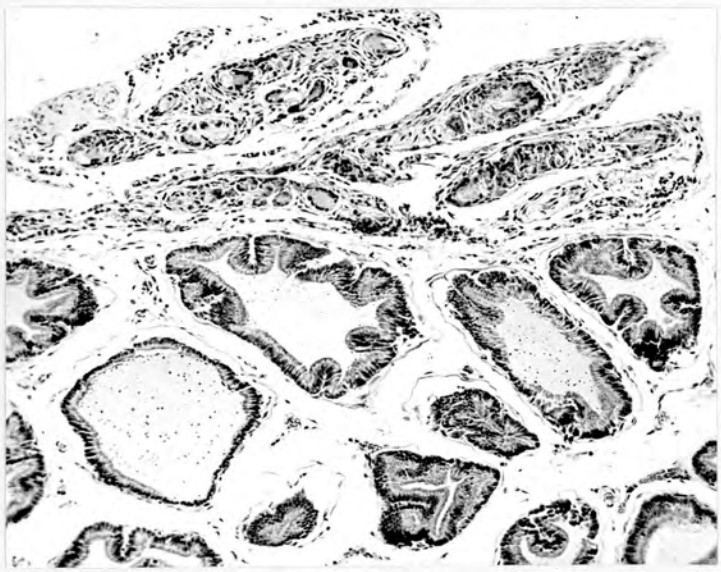

Fig. 34. Prostate. Rat H 16. FOUR WEEKS. More advanced stage of regenerating tissue. " Pseudo acini " more numerous and better developed. Haematoxylin & Eosin x 90.

fibroblast cells.

Seventh day. Few damaged acini seen with fibrous tissue strands commencing to form around them. Fibroblast cells and mononuclear leucocytes in stroma. Increase in phagocytic cells of Reticulo-endothelial system. Young blood vessels were seen to form in close proximity to the basement membrane of the acini. Capsule very cellular and vascular.

Two weeks. Commencing pseudo-acinar formation from epithelial cell accumulation. These areas are seen near the connective tissue of the capsule. The relatively undamaged acinar epithelium is well developed. Stroma contains fewer fibrils and capillaries. Mononuclear cells and Reticulo-endothelial cells still plentiful. Cellularity and vascularity of capsule less intense. Damaged acini low cubical epithelium and lumen contains necrotic debris. Stroma in these areas contain increased quantity of fibrous tissue.

Four weeks. Evidence of pseudo-acinar formation more certain. Other acini well developed with regular uniform epithelial lining. Capillaries still plentiful in stroma. Fewer mononuclear cells. Increased amount of fibrous tissue in area of injury.

Six weeks. Acini well developed. No trace of damaged acini. Acini closely set. Very few fibroblasts and mononuclear leucocytes.

Eight weeks. Only very few severely damaged acini present. The majority of acini large well filled uniformly lined structures. These acini are well/

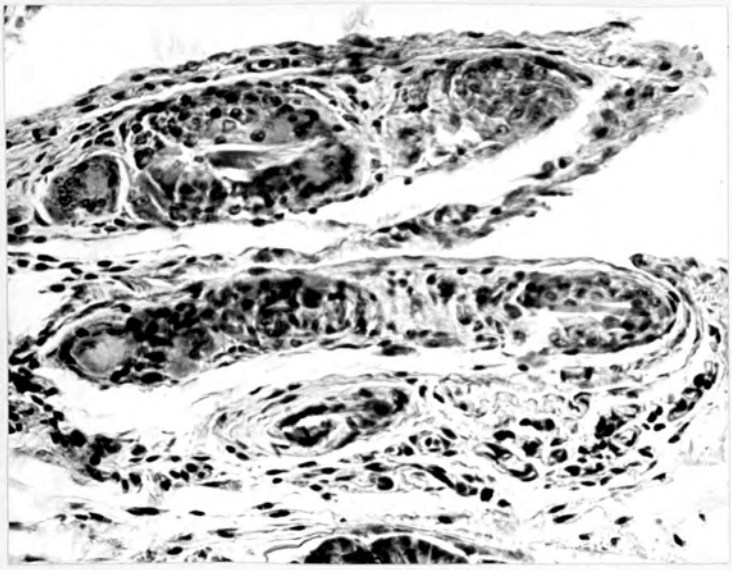

Fig. 35. Prostate. Rat H 16. Same field as Fig. 34. Haematoxylin & Eosin x 250.

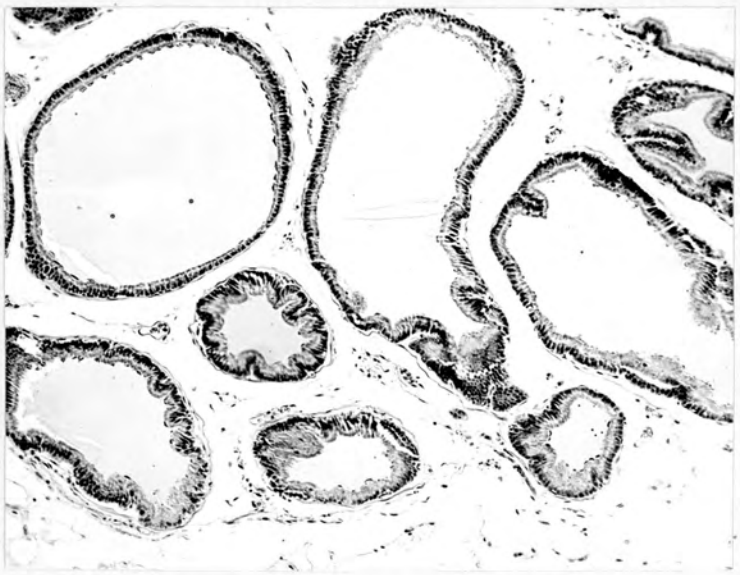

Fig. 36. Prostate. Rat H 12. SIX WEEKS. Undamaged acini markedly enlarged and lumina well filled. Lining epithelium regular and cubical in type. Haematoxylin & Eosin x 90.

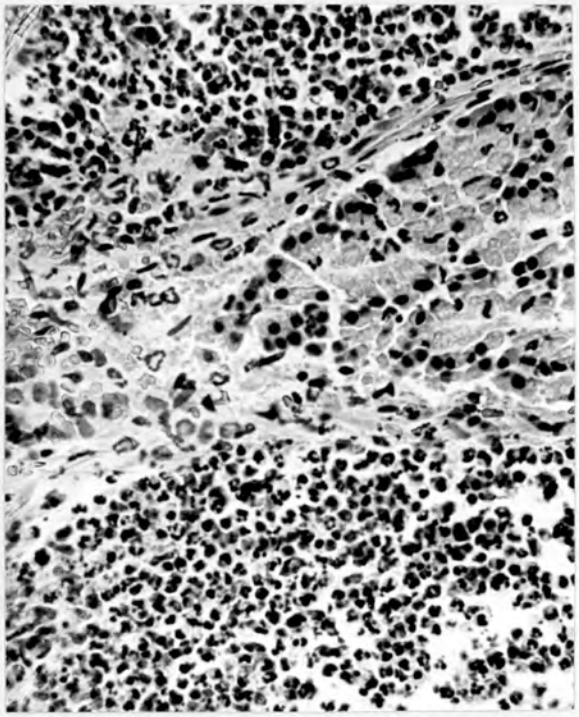

Fig. 37. Prostate. Rat M 8. ONE DAY. Acute inflammatory cell response. Polymorphonuclear leucocytes. Haematoxylin & Eosin x 400.

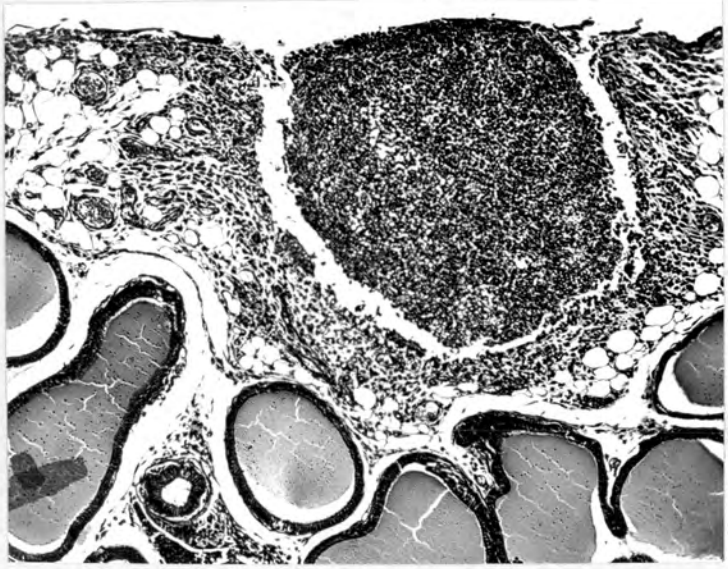

Fig. 38. Prostate. Rat M 17. THIRD DAY. Well developed abscess with large numbers of leucocytes and necrotic material within abscess cavity. Haematoxylin & Eosin x 90.

well away from site of injury. Young capillaries still seen in stroma with a few mononuclear cells and strands of fibrous tissue.

No evidence of calcification of the severely damaged acini.

(5) EXPERIMENT III. RESPONSE TO BACTERIAL INFECTION.

Apparatus. Tuberculin syringe ; a suspension in saline of a live culture of Staphylococcus aureus ; blunt pointed forceps.

Description. The rats were anaesthetised and operated upon in the manner described previously. The prostate gland was brought into view by packing off intestines aside with gauze packs wrung out in hot saline. With the aid of the forceps the gland was steadied. Great care was taken not to exert too much pressure on the gland, and 0.05 c.c. of the previously prepared bacterial suspension was gently injected into the gland. The tube containing the culture was shaken slightly before taking up the suspension of the culture into the syringe.

Results.

Microscopic appearances.

Twenty four hours. Intense hyperaemia of vessels with strands of fibrin and exudation of fluid into stroma. Large numbers of polymorpho-nuclear leucocytes, a few lymphocytes and mononuclear cells in abscess area. Marked destruction of glandular tissue.

Third day. Well developed abscess formed.

The/

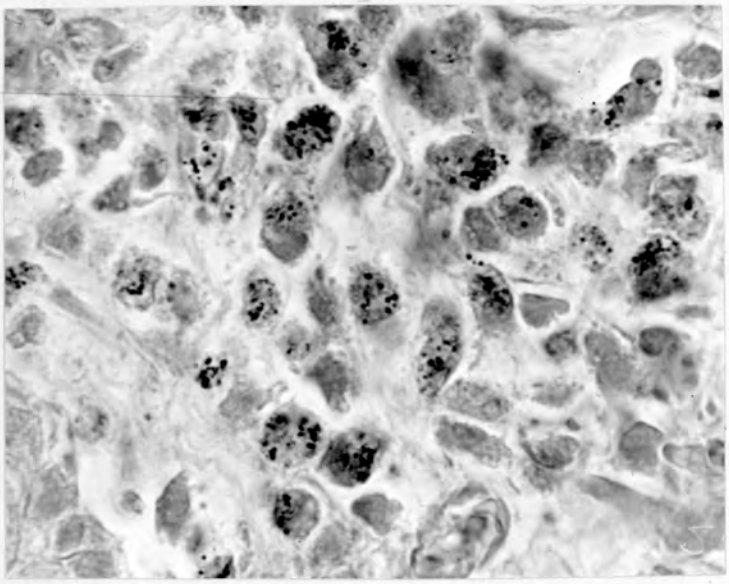

Fig. 39. Prostate. Rat M 15. THIRD DAY.
Staphylococci taken up by phagocytes. Gram x 1100.

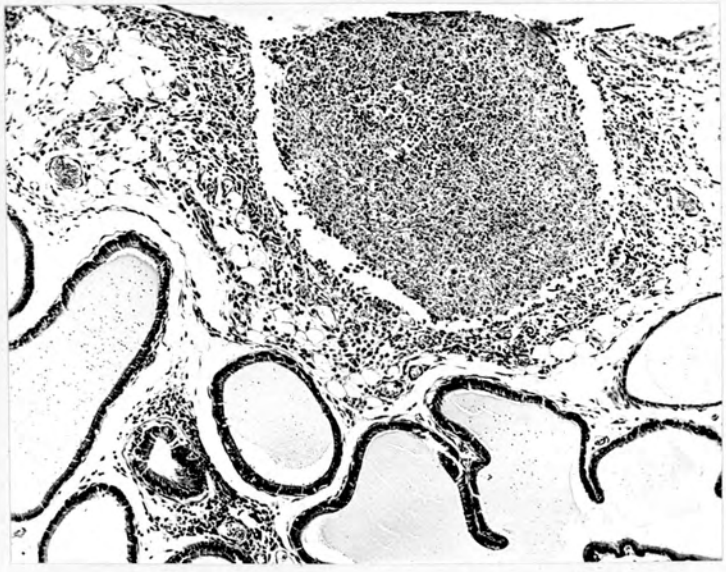

Fig. 40. Prostate. Rat M 17. THIRD DAY. Commencing fibroblast formation in periphery of abscess area.
Van Gieson x 90.

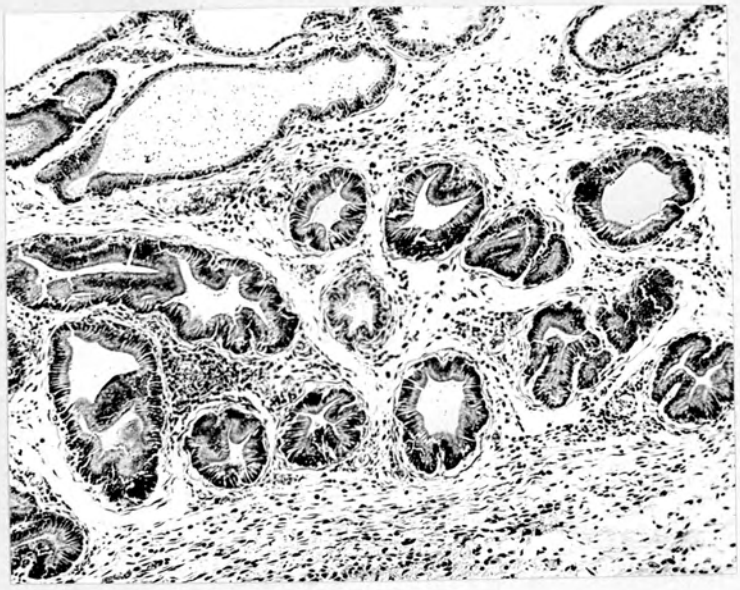

Fig. 41. Prostate. Rat M 18. FIFTH DAY. Numerous polymorphonuclear leucocytes with parallel arrangement of spindle shaped cells at periphery of abscess - bottom left. Haematoxylin & Eosin x 90.

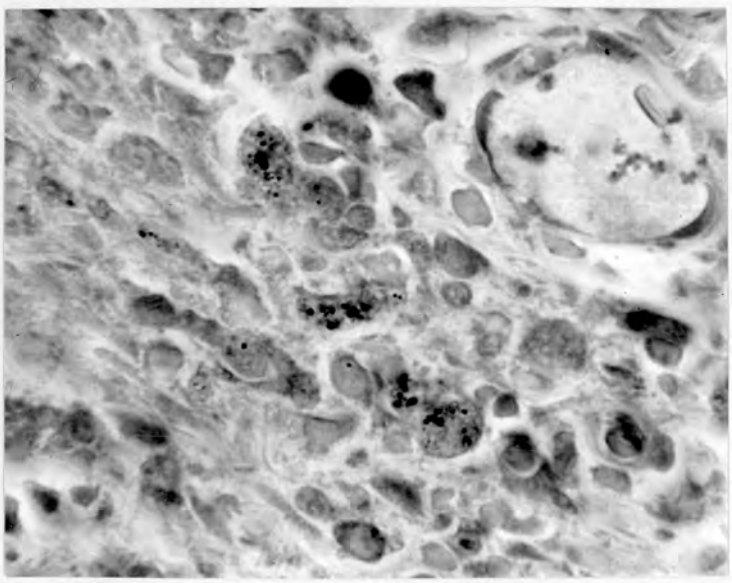

Fig. 42. Prostate. Rat M 18. FIFTH DAY. Bacteria still being phagocytosed. Gram x 1100.

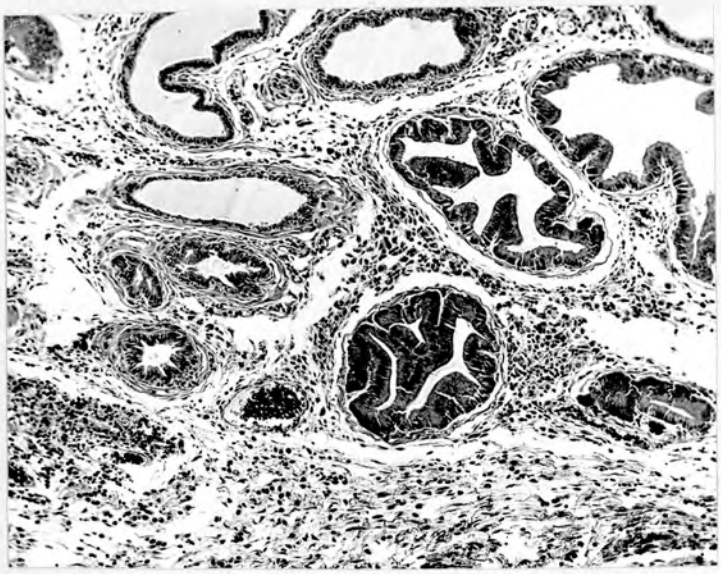

Fig. 43. Prostate. Rat M 22. ONE WEEK. Phagocytic activity still marked. Fibrous tissue formation around damaged acini. Haematoxylin & Eosin x 90.

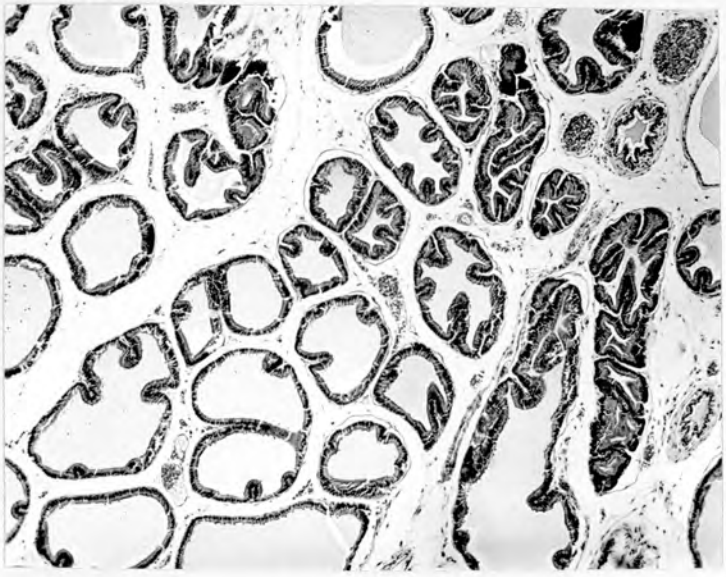

Fig. 44. Prostate. Rat M 6. FOUR WEEKS. Young capillaries being formed in stroma. Haematoxylin & Eosin x 60.

The inflammatory cell response is still very acute. There is evidence of commencing phagocytic activity. Ring of fibroblasts in periphery of abscess area. Bacteria phagocytosed by reticulo-endothelial cells.

Fifth day. Phagocytic activity very marked. Multinucleated cells seen together with newly formed capillaries. Vascular granulation tissue formed. Traces of fibrin seen in stroma. Bacteria still being phagocytosed.

Seventh day. Phagocytic activity still marked. Numerous polymorpho-nuclear leucocytes seen in stroma. Fibrous tissue more plentiful, especially in relation to damaged acini. Commencing increased growth of undamaged acinar epithelium. Mitotic figures seen.

Two weeks. Chronic inflammatory cells in abscess area. A few reticulo-endothelial cells. Many new capillaries present. No evidence of regeneration in the damaged portions of tissue was seen.

Four weeks. Young capillaries being formed in stroma especially in areas of damaged acini. Infection smouldering - plasma cells and lymphocytes now more abundant. No evidence of regeneration in the damaged portions of tissue was seen.

Six weeks. Surrounding undamaged glandular epithelium shows more abundant growth. Increased vascularity of stroma. Fibrous tissue strands coarser/

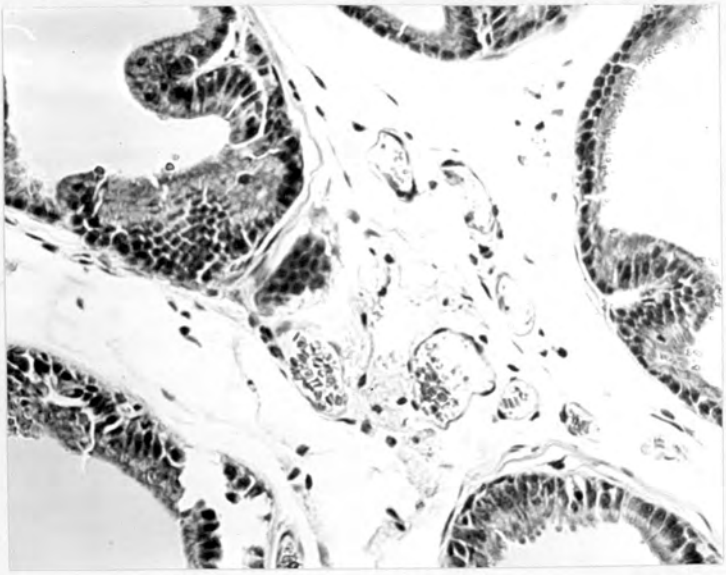

Fig. 45. Prostate. Rat M 6. FOUR WEEKS. Same field as Fig. 44. Haematoxylin & Eosin x 275.

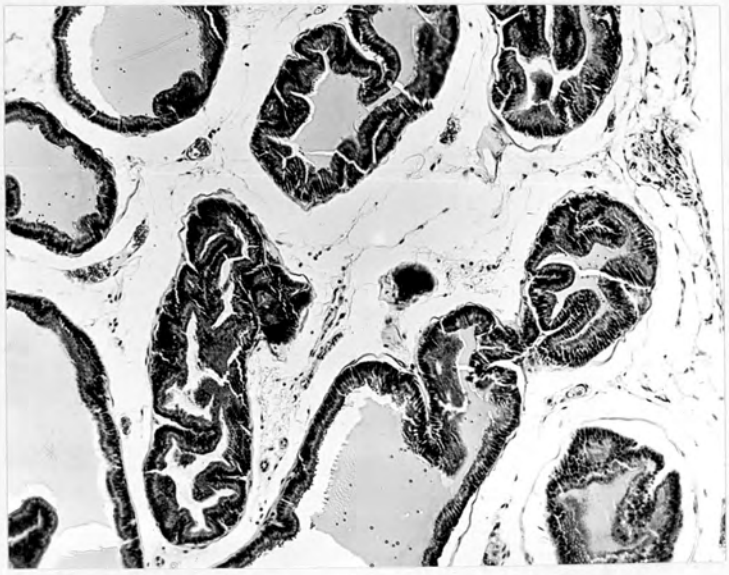

Fig. 46. Prostate. Rat M 11. SIX WEEKS. Compensatory enlargement of undamaged acini. Course strands of fibrous tissue together with vessel formation in stroma. Haematoxylin & Eosin x 90.

coarser around less severely damaged acini. Few chronic inflammatory cells seen. No evidence of regeneration. Compensatory enlargement of unaffected acini.

Eight weeks. Large well filled, closely set acini. Still some fibroblastic production from the vicinity of blood vessels. No evidence of regeneration. No evidence of calcification of damaged acini.

(6) GENERAL DISCUSSION.

This study serves to illustrate some of the principles of general pathology such as the features of acute and chronic inflammation and the reparative processes in the prostate gland.

The features of acute inflammation, namely congestion of vessels, emigration of leucocytes, exudation of fluid, compression of tissues by oedema fluid, etc - these were all present in the early stages of the injury (1-3 days). The only differences in the response in the three different types of injury were :-

(1) the degree or intensity of the response in relation to the severity of the damage inflicted .

(2) characteristic leucocytic cellular response.

The response to bacterial infection was the most intense of the three. The extent and severity of the reparative processes were directly proportional to the injury produced. This being the case, it was not surprising to find no microscopic evidence of commencing regeneration in the/

the glandular tissue injured by bacteria. Having stated these general principles the problem will be examined in greater detail. The pioneer studies of Cameron & Mehrotra (1953) on the effects of localised freezing have demonstrated the varying responses to this standard form of injury ; and the part played by cellular environment as distinct from the influence of damage to cells by the injury. They discovered that some tissues respond rapidly and intensely to necrosis, others are slow in their response and take a long time to remove necrotic material and replace it with fibrous tissue, while a few occupy an intermediate position in the scale of response. The results of their freezing experiments with a number of tissues are summarised below :-

Table 1.

RESPONSE TO THERMAL INJURY.

Tissue	Inflammatory Reaction.		Period necessary for complete removal of necrotic tissue and replacement fibrosis
Liver	Early	Intense	3-5 days
Spleen	do.	do.	3-5 days
Pancreas	do.	do.	3-5 days.
Voluntary Muscle	do.	do.	3-5 days
Skin of ear	do.	do.	7-12 days
Adrenal	Early	Moderate	12-21 days
Fatty Omentum	Delayed	Moderate	Incomplete in 28 days
Kidney	do.	do.	do. do.
Testis	do.	Mild	do. do.
Abdominal Aorta	do.	do.	Incomplete in media in 28 days
PROSTATE (Author)	Early	Moderate	Incomplete in 28 days.

When the behaviour of the prostate gland to this standardised form of tissue injury by localised freezing is examined it is found that the inflammatory cell response is early in onset and moderate in intensity. The products of cell injury were present even after 28 days. The reasons for this variability in tissue response are still unknown. Cameron & Mehrotra put forward the hypotheses that the differences in tissue reaction may be due to differences in the composition of the cells and the speed or fashion in which they set free compounds which induce the tissue reaction. The differences may also be conditioned by the manner in which the healthy tissue around the injured cells responds to the products of necrosis.

The mononuclear cell is the predominant cell seen after local injury by freezing with CO_2 snow. This inflammatory cell response appears to suggest that there may be some relationship between the type of cells seen in the field of injury and the chemical products of tissue destruction for Folkow et al (1948) have discovered that adeno-triphosphate is one of many compounds released at the site of injured tissues in general. Its local release at the site of injury may well contribute both to the active hyperaemia and to the movement of neutrophil polymorphs. Menkin (1941) has suggested that injured cells liberate one or possibly several proliferation factors into inflammatory exudates : these factors will, in all probability,/

probability, determine the cell response. It is for future research to unravel the mysteries linked up with the chemical structure of cells and the products of metabolism and so pave the way for a better understanding of this interesting problem of leucocytic cellular response to injury.

The next important topic to be considered is the reaction of the healthy tissues to the damaged areas. The most striking feature in this connection was the commencement of reparative activity in a whole series of processes namely :-

i. the presence of large numbers of mononuclear phagocytic cells in the stroma of the damaged areas ;

ii. marked activity of the connective tissue cells in the innermost part of the fine connective tissue capsule of the prostate gland. New formation of fibroblasts - plump spindle shaped cells - from existing cells and also from the macrophages. These phenomena were seen from the 3rd. day onwards ;

iii. a marked increase in the number of developing blood vessels ;

iv. collections of fibroblasts were noticed in close apposition to these developing blood vessels ;

v. there was also an increase in the number of lymphatic vessels in the stroma. By the 5th. day there was compensatory hyperplasia of the undamaged glandular epithelium. In the damaged/

damaged areas there were well defined bands of fibrous tissue around them. These fibrous tissue strands appeared to increase in thickness from week to week. Evidence of commencing regeneration was noted by the 14th. day after injury by the appearance of islets of epithelial cells deep in the connective tissue of the capsule. These " pseudo-acini " were surrounded by young connective tissue cells which took on a deep purple stain (when stained with both Haematoxylin and Eosin). By the eighth week the only structure which had completely regenerated was the connective tissue capsule. These changes are similar to those described by Baiardi (1904) except that they were not in evidence two weeks after operation.

When the features of regeneration of the prostate after localised freezing are compared with those of regeneration following simple excision, the tempo of activity is essentially the same for

(i) the cellular response was essentially mono-nuclear in type ;

(ii) phagocytic activity commenced on 3rd. day onwards ;

(iii) on the 5th. day - compensatory hyperplasia of existing undamaged acini was seen.

(iv) pseudo-acinar forms were seen on 14th. day onwards.

The response to bacterial infection is in striking/

striking contrast to the other two forms of trauma. In the first place this local bacterial infection produced a very severe acute inflammatory cell response of neutrophil polymorphonuclear leucocytes. This cellular response is in agreement with the work of Coman (1940), who found that monocytes were little attracted by either staphylococci or tubercle bacilli, to both of which neutrophils showed pronounced positive chemotaxis and similar findings have been recorded by Las Fargues and Delaunay (1947). Despite these favourable factors, giant cells were seen in some of the sections removed from glands of rats which were killed five days after operation. This finding suggests the inadequacy of the usual methods for the removal of damaged tissues e.g. increased activity of reticulo-endothelial cells, phagocytic activity of polymorpho-nuclear leucocytes, dilated lymphatic vessels. There was in addition an intense out-pouring of a more deeply pink staining fluid into the stroma - probably for the purpose of diluting any toxic metabolites following bacterial activity.

There was compensatory hyperplasia of existing undamaged acini on the 7th. day after operation. This phenomenon appeared on the 5th. day in the case of the other two forms of trauma. This delay in reparation is in accordance with the studies of Carrel (1924) and Kiaer (1927-28), who stressed the importance of sepsis in any part of the animal body as a retarding factor in any reparative process. Another very striking factor was the increased/

increased amount of fibrous tissue laid down following bacterial infection.

Finally, no evidence of regeneration of damaged tissue was seen in any of the sections examined following bacterial infection.

Briefly then, the composition of the products of bacterial activity differ significantly from the products of injury caused by the other two agents, as depicted by the difference in response to this form of injury. These observations raise the question as to how general factors such as age, hormones, dietetic deficiencies etc. will alter or modify the response to injury and how the injury will be influenced by such substances as Cortisone. These problems will form the basis of a most absorbing and interesting study at some future date.

In conclusion the principal changes in the response to injury by the three simple forms of trauma have been summarised in the following table.

Table 2./

Table. 2.

COMPARISON OF RESULTS IN DIFFERENT FORMS OF INJURY.

ays After peration	Change Produced	Thermal Injury	Simple Excision	Bacterial Infection
venty-four hours	Acute Inflammation	Mononuclear Leucocytes	Mononuclear Leucocytes	Polymorphs. Leucocytes
hird day	Repair	+	+	-
ifth day	Compensatory Hypertrophy	+	+	Vascular Granulation Tissue
eventh day	Focal Fibrosis	+	+	Compensatory Hypertrophy
wo weeks	Commencing Regeneration	+	+	-
our weeks	Regeneration	++	++	-
ix weeks	Necrotic Acinar Fibrosis	+	+	+
ight weeks	Large well-developed acini	+	+	+

(7) SUMMARY

(1) The problem of the response to injury by simple excision, local freezing, and bacterial infection of the prostate gland of the rat has been studied.

(2) This study illustrates the features of acute and chronic inflammation occurring in glandular tissue together with the ensuing reparative processes.

(3) The presence of islets of epithelial cells (pseudo acini) in the region of the connective tissue capsule of the prostate gland was evidence of regeneration when the traumatising agents were simple excision and thermal injury. There was no regeneration of damaged tissue when trauma was produced by a bacterial infection, namely Staphylococcus aureus.

(4) Reparation of damaged tissue is essentially through the formation of fibrous tissue although small islets of glandular tissue (pseudo acini) were present together with compensatory hyperplasia of undamaged acini.

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Section III.

(9) APPENDIX.

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The preparation of a bacterial culture.

9th. March, 1953 : The culture was prepared from a subcutaneous abscess in the abdominal wall of a rat. The abscess appeared as a raised button like structure - 2 mm. (approx.) in diameter. The skin overlying it was scaly and of a reddish grey colour. The area of skin surrounding the abscess was firm.

Procedure :- The overlying skin and surrounding tissue was carefully swabbed with a piece of cotton wool soaked in absolute alcohol cleansing from the centre towards the periphery. Each swab was used once only. The abscess was then lanced with a sharp sterile scalpel. The pus that exuded was thick and of a light greenish yellow colour. A little of it was removed with the aid of a sterile platinum loop. The pus was then plated out on two Blood agar plates and one McConkey plate. The plates were next incubated for a period of 24 hours.

10th. March, 1953 :- Examination of Blood agar plate showed mixed colonies of haemolytic Streptococcus, Enterococcus, Staphylococcus aureus, and Bacillus coli.

Examination of McConkey plate showed Non lactose fermenters, coliform organisms growth appearances of colonies resembling those of B. proteus.

The Staphylococcus aureus strain was picked up and a new Blood agar plate was used to obtain a pure/

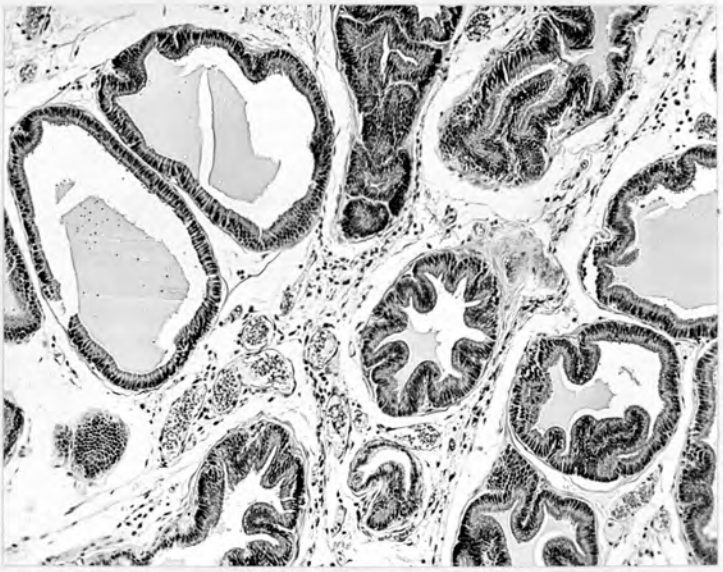

Fig. 48. Response following injection of Test dose 1 of live Staphylococcus culture. Haematoxylin & Eosin x 90.

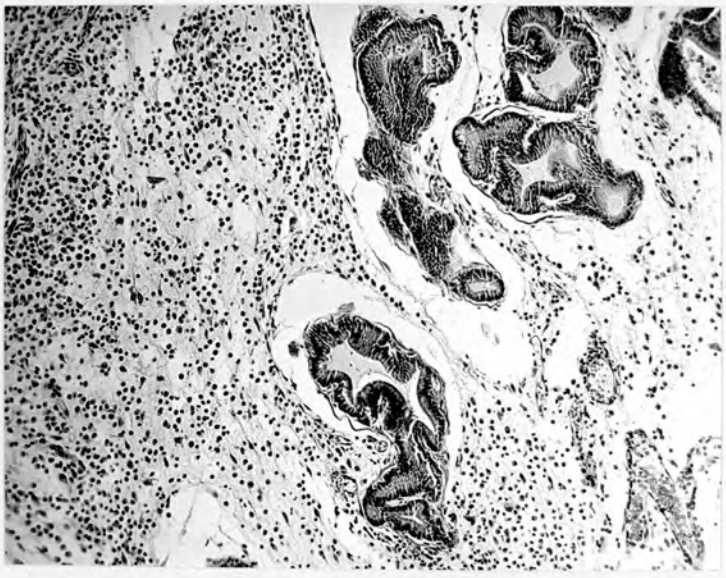

Fig. 49. Response following injection of Test dose 2 of live Staphylococcus culture. Haematoxylin & Eosin x 90.

pure growth of this strain.

In 24 hours - 11th. March, 1953 - a growth was obtained. A little of this was transferred on to a number of plain agar slopes. These were incubated for another 24 hours.

12th. March, 1953 - There was a profuse growth on each of the tubes. The growth was scraped lightly with the aid of a Platinum loop and suspended in sterile normal saline solution. Varying dilutions were made with the aid of Burroughs Welcome opacity tubes.

The effective dose for causing a local infection of the rat prostate gland was next determined.

Experiment - To determine the strength of dose which would be adequate for the production of bacterial infection of the prostate gland of the rat.

0.05 c.c. of each of the following strengths of bacterial culture were injected :

(a) 3030 organisms /cc.

(b) 758 organisms/ cc.

(c) 300 organisms/ cc.

Three Wistar strain albino rats of 180 Gm. body weight were used.

Procedure :- With full aseptic precautions the prostate gland was exposed and 0.05 c.c. of the staph culture was injected. The three rats were asphyxiated with an excess of ether after an interval of three days.

Macroscopic/

Macroscopic Appearances :- The gland (a) showed a well developed abscess area with an intense acute inflammatory cell response. I therefore decided to use the strength 3030 organisms/cc. as the optimum dose for the production of trauma by bacterial infection.

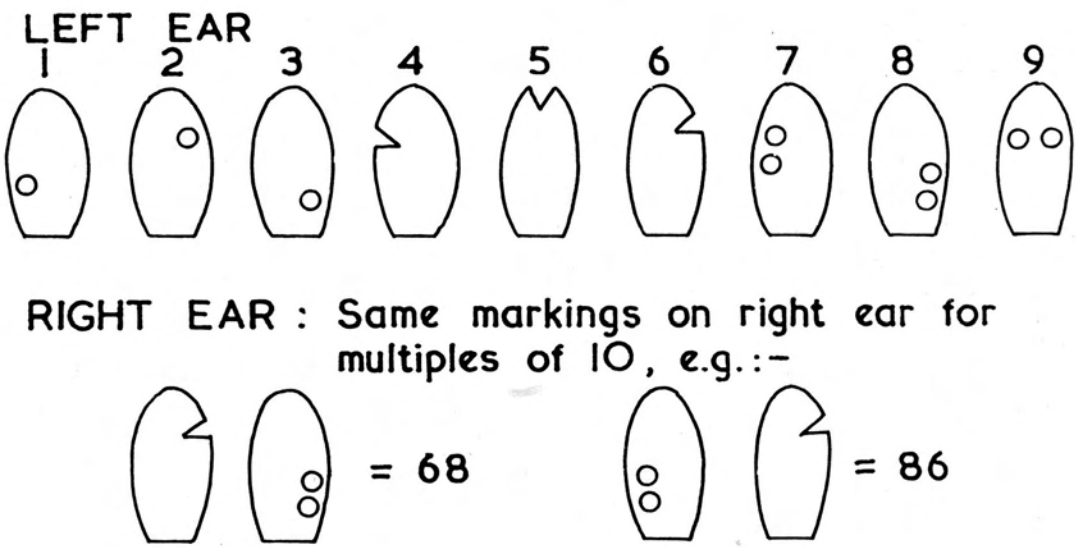

Fig. 47. Method of marking rats.