TESTICULAR TUMOURS

A Clinico-Pathological, Comparative and Experimental Study.

by

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Publications.

(1) Attempts to produce seminomata in the albino rat by inoculation of hydrocarbons and other carcinogens into normally situated and ectopic testes, by J. Guthrie. Br. J. Cancer, 10, 134, (1956).

(2) The chromosomes and genetic sex of experimental avian testicular teratomas, by J. Guthrie. Expl. Cell Res. 26, 304, (1962).

(3) Observations on the zinc induced testicular teratomas of fowl, by J. Guthrie. Br. J. Cancer, 18, 130, (1964).

(4) Histological effects of intra-testicular injections of cadmium chloride in domestic fowl, by J. Guthrie. Br. J. Cancer 18, 255 (1964).

(5) Effects of a synthetic antigonadotrophin (2-amino,5-nitrothiazole) on growth of experimental testicular teratomas, by J. Guthrie. Br. J. Cancer, 20, 582, (1966).

General Introduction.

From the point of view of structure and biological behaviour, considerable differences distinguish tumours of different tissues and organs. The same is probably true of aetiology. A particular organ or tissue may require a particular stimulus or a combination of several factors. This concept of co-carcinogenesis has recently been discussed by Saleman and Roe (1964). As each tissue or cell line has its own biological controls in vivo, it would seem possible that its particular tumours might depend on these controls for initiation or continued growth.

This thesis is restricted to a study of tumours of the testis. Tumours of the gonads in both sexes raise particularly problems of histogenesis. Is a particular tumour of the testis derived from the cells of the spermatogenic series and if so at what level of development, or is it derived from the cells of the supporting structures? The gonads are the most frequent site of the teratoma, an unique tumour which can contain tissues from all parts of the organism except the gonads themselves. This tumour reaches its greatest complexity in the testis where it attracted attention almost 300 years ago because of its apparently foetal nature (Saint Donat,1696). For some time the relationship of the teratoma to the germ cell series has been a matter of considerable speculation. Does this tumour arise from the germ cells before or after meiotic division? Does it arise from within or without the seminiferous tubules and does it differentiate from a

unicellular growth of primitive cells? The seminoma although a unicellular growth also presents the problem as to its cell of origin and whether from without or within the seminiferous tubules. The teratoma is well recognised as also occurring outwith the gonads (Willis, 1960), but although extragonadal origin of seminomas has been suggested (Phalakornkule and Woodruff, 1964) it has not been completely substantiated in view of the possibility of regression of the testicular primary in some cases (Azzopardi and Hoffbrand, 1965).

Part I of this thesis is a clinico-pathological study of spontaneous testicular tumours in man. Although there have been previous studies of larger series, a personal study seemed a necessary pre-requisite to the experimental work.

Part II is a study of spontaneous testicular tumours in animals. The main object of this has been a comparison of the different tumour types in various species.

Part III consists of the published experimental work. The initial experiments were designed to see if carcinogenic hydrocarbons could produce seminomas after their introduction into the testes of rats. In view of the alleged susceptibility of the ectopic human and canine testis to neoplasia (Gilbert and Hamilton, 1940), carcinogenic hydrocarbons were also introduced into rodent testes fixed intra-abdominally shortly after birth. In this way it was hoped that the early stages of tumour growth could be identified and that this would provide some evidence of histogenesis.

Later experiments have been concerned with the production of testicular teratomas in domestic fowl by the intratesticular injection of zinc salt solutions in the first three months of the calendar year. The main objectives of these experiments were:-

(a) To ascertain the chromosomal number and sex of these teratomas as this might reveal whether origin is from diploid or haploid germ cells.

(b) To ascertain the specificity of the zinc salt inoculum in inducing teratomas.

(c) To study histologically induced tumours and the endocrine glands in particular the adenohypophysis in tumour bearers.

(d) To ascertain if this teratoma, induced only in a restricted season of increasing spermatogenic development, was hormone dependent. In view of the availability of synthetic antigonadotrophins, an experiment was designed to see whether such a compound blocked the development of teratomas after zinc injection and whether it affected the growth rate of these tumours. If teratomas are dependent on gonadotrophins for their continued growth the use of antigonadotrophins would seem to be a possible therapeutic method of controlling their growth. As pointed out in Chapter III of Part I of this thesis, the human testicular teratoma is not readily controlled by X irradiation or chemotherapy directed at the tumour.

Part I

Clinico-pathological Study of Human Testicular Tumours.

Chapter I.

Human Testicular Tumours - General Aspects.

Of the tumours found within the scrotum about 95 per cent arise within the body of the testis. This is the percentage found in the larger series of surgically removed tumours (Dixon and Moore, 1953) and (Collins and Pugh, 1964). The others arise in the epididymis, spermatic cord, related tissues and other structures, and as they pose different problems of histogenesis, many not peculiar to the testis, they will not be considered here in detail.

Frequency.

Testicular tumours are rare in man and the reported incidence varies in the different parts of the world where adequate statistical records exist.

Proportion of Human Cancers.

Studies based on hospital records show the incidence in relation to other forms of cancer. To some extent this depends upon the type of hospital. In the United States of America, the Bureau of Census, (quoted by Dixon and Moore, 1953) found that testis tumours accounted for 0.64 per cent of all male cancer deaths. In London, the Registrar General's statistics for 1938-9 (Harnett, 1952) showed a rate of 0.52 per cent. Gilbert and Hamilton (1940) on the other hand estimated that 1.5 - 2.0 per cent of all male cancers were due to testicular tumour. In young age groups they are responsible however for a much larger percentage of malignant disease found.

A study of cases in the files of the Armed Forces Institute of Pathology in Washington by Dixon and Moore (1953) revealed a figure of 13.2 per cent for ages 25 - 29 years.

Incidence in populations.

Attention was first drawn to the annual incidence rate by Dixon and Moore (1953) who quoted an average figure of 2.88 per 100,000 males for the years 1940 - 47 in U.S. Armed Forces personnel aged mainly between 20 and 30 years.

A Connecticut State Department of Health survey over the years 1935 - 51 showed an average annual incidence rate of 2.1 per 100,000 males (Griswald et al., 1955). A rather similar incidence of 2.2 per 100,000 males was reported by Ferber et al., (1962) for New York State. Our knowledge of geographical or racial variation in incidence of a comparatively rare tumour is still rather scanty. Magnus (1964) quotes the Finnish Cancer Register's annual incidence of 1 per 100,000 males for 1953 - 56 and points out that Finland with a slightly larger population than Norway had 67 new cases during the period 1953 - 56 whereas Norway had 216 cases. Japan also shows a low rate (Kurihara, 1962, personal communication). Dixon and Moore (1953) found that 1.5 per cent of their germinal testicular tumours occurred in non-whites, who nevertheless accounted for 6.0 - 8.5 per cent of the total U.S. Armed Forces personnel in the relevant age groups. The mortality rate from testicular tumour for American negroes between the ages of 15 and 45 years was about one sixth the rate for whites (Grumet and MacMahon, 1958). Only four

cases in the present study originated from outside the United Kingdom and three of these came from continental Europe. A thorough study of the racial and geographical incidence has yet to be carried out.

Review of Classifications.

The earliest description of a testicular tumour has been attributed to Saint Donat who in 1696 identified a "rudimentary skull and pigmented optic cups in a scrotal mass". The next report was by Prochaska who recognised portions of a foetus in two similar tumours in 1809. A quarter of a century later Perrone (1833) found hairs and teeth in the cystic portions and bone in the solid portions of a testicular tumour, while shortly afterwards joint formations, skull, vertebrae, hair, rudimentary eyes, intestinal canal, fat and muscle were described by Velpeau (1841). Microscopic studies led Curling in 1853 to divide the growths into cystic, relatively benign and solid malignant tumours. In London, Johnson (1856) drew attention to the tridermal composition of these tumours and described one in an infant as a cystic sarcoma. Not surprisingly the teratomas were recognised before the other varieties of testicular tumour, presumably because of their unique variety of tissues and the possibility that they might represent some form of parthenogenesis or included twin. Langhans used the microtome as a foundation for his microscopic studies of testicular tumours and with Kocher (1887) established the foundations of a histological classification. Wilms (1898) referred to the fact that several of the testicular

growths had a tridermal character and proposed classification into (1) embryomata (cystic foetuses) and (2) embryoid or teratomatous tumours (solid non-foetal). By the end of the nineteenth century numerous classifications based on the predominance of one or more components of these tumours had appeared. Round cell sarcomas, endotheliomas, chondro-carcinomas and similar terms were frequently used in articles and laboratory reports of this period. A notable advance was the separation by Chevassu (1906) of the seminomas, which he believed to be derived from the cells lining the seminiferous tubules. Nicholson (1907) independently made a similar separation and considered that seminal carcinomas were common and that teratomas were a single group of variable structure.

Ewing (1911) felt that the presence of seminomatous tissue in some teratomas pointed to the derivation of seminomas, or embryonal carcinomas in his terminology, from teratomatous precursors. Support for this concept came undoubtedly from the finding of combined teratomas and seminomas, but it has gradually dwindled and very few pathologists can accept this theory of histogenesis today. Moreover seminomas occur in dogs in which teratomas are unknown (Cotchin, 1960), and in that species the coexistence of seminoma, Sertoli-cell and interstitial-cell tumours is frequent. The histogenetic separation of the last two is clear. Although the cell types giving rise to teratomas and seminomas have remained uncertain, the separation of these two main types of testicular tumour has been of great interest and value to surgeons and radiotherapists owing to the considerable

difference in prognosis and response to X and gamma irradiation.

The first comprehensive classification based on a large series appeared in the United States of America at the close of World War II. Friedman and Moore (1946) in a review of 922 cases from the United States Army re-introduced the term "embryonal carcinoma", but applied it to an anaplastic carcinomatous growth with little differentiation towards glandular structure, quite distinct from the seminomas and frequently associated with teratoma. They considered that there were four fundamental structural patterns, seminoma, embryonal carcinoma, chorionepithelioma and teratoma and that these were encountered alone or in combination.

The following classification was proposed:-

1. Seminoma (germinoma).
2. Embryonal carcinoma.
2A. Chorionepithelioma.
3. Teratoma.
4. Teratocarcinoma.

The new term teratocarcinoma, was proposed for the large group of pleomorphic tumours in which both differentiated teratoid structures and histologically malignant elements were present. This classification was amplified later by Dixon and Moore (1953) and is with minor modifications still in widespread use. It classified tumours of the testis and appendages into two main groups. (1) Germinal 96.5 per cent.

(2) Non-germinal 3.5 per cent.

The germinal, allegedly from germ cells, were classified histologically as:-

(A) Seminoma.

(B) Embryonal Carcinoma.

(C) Teratoma.

(D) Choriocarcinoma.

The non-germinal include the interstitial cell tumours, androblastomas, adrenal cortical rests, fibromas, sarcomas, neurilemmomas and adenomatoid tumours.

Of the germinal tumours they defined (B) embryonal carcinoma as primarily an undifferentiated anaplastic tumour composed of multipotential cells, large cells with indistinct cell boundaries, amphophilic cytoplasm, large round bean-shaped nuclei with coarsely clumped chromatin and multiple nucleoli of large size. Included in this category were tumours with organisation of the cells into layers resembling primitive epithelium and into reticulated masses resembling embryonic mesoderm. Apart from this somatic differentiation, development of chorionic epithelium might be found as well as the so-called "embryoid bodies" first described by Peyron and Limousin (1936). The concept of embryonal carcinoma undergoing either somatic or trophoblastic differentiation was also accepted by Nolicow (1956) who looked upon the process as a moving picture which could be frozen at any stage. If the tumour differentiated to tissue or organ level with derivatives of the three germ layers of the embryo, Dixon and Moore (1953) categorized this as (C) teratoma.

(D) Choriocarcinoma is defined as consisting of syncytiotrophoblast in recognisable villous formation.

In all Dixon and Moore (1953) recognise five groups consisting of these patterns puro or in combination viz.,

I Seminoma, pure.

II Embryonal Carcinoma, pure or with seminoma.

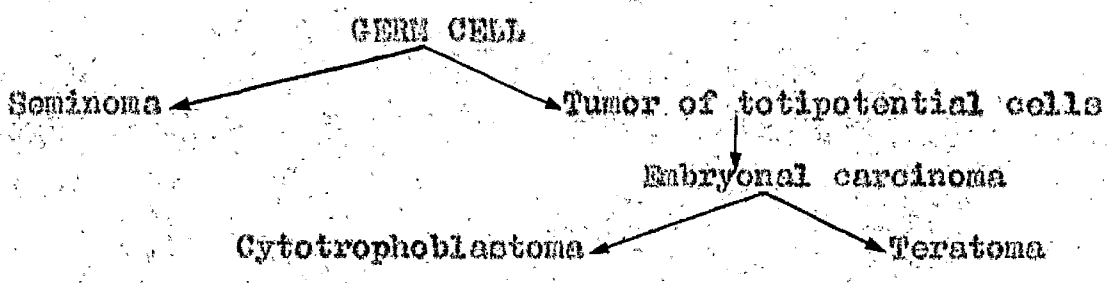
III Teratoma, puro or with seminoma.

IV Teratoma with either embryonal carcinoma or choriocarcinoma or both, and with or without seminoma.

V Choriocarcinoma, pure or with either embryonal carcinoma or seminoma or both.

In this grouping, the seminoma was regarded as the least malignant and the prognosis of the other groups was regarded as that of the most malignant type included.

They expressed their concept of morphogenesis as follows:-



Mellcov (1956) preferred to retain the term teratocarcinoma for those embryonal carcinomas with some attempts at differentiation into tissue elements and to separate as a distinct group "adult teratomas" consisting only of fully differentiated tissues. The

Testicular Tumour Panel and Registry set up in 1958 by the Pathological Society of Great Britain and Ireland in conjunction with the British Empire Cancer Campaign decided at an early stage in its work to abandon the designation "embryonal carcinoma" in view of its past ambiguity and to launch a new classification, (Pugh, 1960 and 1962). The main feature of this classification is the inclusion of the embryonal carcinomas, teratomas, teratomas and choriocarcinomas in the one group of teratoma, and a new terminology for the teratomas. The sub-groups are:-

Teratoma Differentiated (T.D.) A teratoma which comprises only fully differentiated tissues. This is the "adult teratoma" of Melicow (1956).

Malignant Teratoma Anaplastic (M.T.A.) This corresponds with the embryonal carcinoma in the classification of Dixon and Moore, except that any differentiation excludes it from this category.

Malignant Teratoma Trophoblastic (M.T.T.) This is distinguished by containing true trophoblastic tissues disposed in a papillary or villous manner.

Malignant Teratoma Intermediate Type B. (M.T.I.B.) This differs from M.T.A. in having some early differentiation, epithelial and mesenchymal, but being without mature tissue or organoid structure.

Malignant Teratoma Intermediate Type A. (M.T.I.A.) This shows some mature tissue or organoid structures. A tumour is placed in the appropriate category by virtue of its most highly differentiated part, but presence of trophoblast in villous or papillary arrangement

places tumours in the category M.T.T. The Panel defines teratomas as of uncertain histogenesis, arising in the testis and displaying an array of tissue structure foreign to the normal organ. Nevertheless they are prepared to include embryonal carcinomas in the definition. Many of these embryonal carcinomas show no trace of differentiation and to call them teratomas, albeit malignant, is inaccurate. As the Panel's material bears out it is never justifiable to assume especially in the young adult that "teratoma, differentiated (T.D.)" is benign. Hence the use of the term "malignant teratoma" would seem of doubtful value as a benign teratoma cannot be recognised. Apart from this the histogenesis of T.D. is unknown. Must it have an undifferentiated tumour as precursor? The spontaneous testicular teratomas of horses and certain experimental teratomas (Guthrie, 1964) have features that argue against this. These adult teratomas may have a different origin. It seems preferable to the author to retain the term embryonal carcinoma as defined by Dixon and Moore (1953).

The Panel's classification imposes upon pathologist and clinician the difficulty of remembering the distinction between categories A and B in the intermediate group. Only further experience will decide whether classifying a tumour in accordance with its most differentiated part will be of prognostic value. Friedman and Rienzo (1963) urged support for the recognition of embryonal carcinomas as a primitive placental tumour, trophocarcinoma. Many of the tumours described in this country as papillary adenocarcinomas

and associated with high urinary gonadotrophins could be placed in this category. Little controversy has surrounded the designation of the other types of testicular tumour. Teoh, Steward and Willis (1960) suggested orchioblastoma as the most appropriate name for the adenocarcinoma of the infant testis first described by Powell White (1910). The histogenesis of interstitial-cell tumours, Sertoli-cell tumours and carcinomas of the rete testis is clear. The lymphomas present similar problems in the testis as they do in other sites.

The classification proposed in this thesis is based on a clinico-pathological study of 157 human cases of testicular tumour, including one bilateral and a review of the previous classifications. It is set out in Table I. Of these 158 tumours, 156 were of the body of the testis and two were from the appendages. The classification uses almost entirely terms already in use as the use of a new name for an old established entity is not readily adopted.

In the field of knowledge relating to both teratomas and testicular neoplasms in general there has been no recent advance such as would justify a completely new and revolutionary classification. It would seem more desirable to re-define the terms used. This classification includes a group for combined seminomas and teratoma in the same testis. Dixon and Moore (1953) put their combined tumours in the appropriate group II to V depending on the tumour accompanying the seminoma.

Table I

Proposed Classification of Tumours of the Testis and Appendages.

Body of Testis.

Seminoma

Teratoma Group

a. Fully Differentiated Teratoma.

b. Partially Differentiated Teratoma.

c. Teratoma with Embryonal Carcinoma.

d. Embryonal Carcinoma.

e. Chorionepithelioma.

f. Chorionepithelioma in combination with a,b,c or d.

Teratoma Group with Seminoma.

Lymphoma.

Orchioblastoma.

Interstitial-Cell Tumour (I.C.T.)

Sertoli-Cell Tumour (S.C.T.)

Adenocarcinoma of Rete Testis.

Miscellaneous Tumours.

Metastases.

Appendages.

Adenomatoid Tumour of Epididymis.

Connective Tissue Tumours.

Teratoma.

Miscellaneous Tumours.

Metastases.

Definition of Nomenclature.

Fully Differentiated Teratoma.

This is a tumour consisting of a wide variety of tissues or organ formations foreign to the part and resembling those found in normal adult tissues in other parts of the body. Tissues derived from all three embryonic germ layers are usually present.

Partially Differentiated Teratoma.

This differs from the fully differentiated teratoma in having tissues, usually epithelial, which are still at an embryonic stage of development or show abnormal development towards carcinoma or sarcoma.

What is this teratoma?

Embryonal Carcinoma.

A malignant tumour consisting of a solid growth of pleomorphic cells with amphophilic cytoplasm, indistinct cell boundaries and large oval or irregular nuclei with multiple nucleoli and coarsely clumped chromatin. Giant cells often with multiple nuclei may be present. Embryoid bodies resembling the blastocyst can be associated with this type of tumour, but differentiation into tubular, glandular or papillary structures or into mesenchyme excludes a growth from this category.

Embryonal Carcinoma with Teratoma.

This combination usually shows an embryonal carcinoma with differentiating areas of glandular or other epithelial structure and areas of embryonic mesoderm. Teratomatous structures of varying differentiation may be intimately included in the tumour mass or

present at its periphery.

Chorionepithelioma.

A tumour containing as part of its construction cellular proliferation resembling the foetal syncytiotrophoblast and cytotrophoblast arranged in villous or papillary fashion.

Seminoma.

Seminoma is a tumour composed of rather uniform round or polygonal cells with clear or lightly stained cytoplasm and large round nuclei containing one or two nucleoli. The cells are arranged in thick cords or lobules usually separated by a delicate fibrous stroma, but occasionally by a more definite lymphoid, granulomatous or fibrous stroma.

Lymphoma.

This group includes the various types of lymphoid neoplasms as found in other sites. In the testis this consists of reticulum cell sarcoma, lymphosarcoma, and myeloma.

Orchioblastoma.

A papillary or tubular adenocarcinoma frequently mucin-secreting arising in the testis of infants or young boys.

Interstitial-cell Tumour.

A neoplastic proliferation of cells resembling the normal interstitial cells of Leydig and sometimes associated with hormonal effects.

Sertoli-cell Tumour.

In its well differentiated form this consists of a proliferation

of tubular structures lined by Sertoli cells, but considerable variation in structure is possible and solid growth of Sertoli type cells may be found without demonstrable basement membranes.

Adenocarcinoma of the Rete Testis.

An adenocarcinoma usually of papillary pattern arising in the rete testis.

Adenomatoid Tumour of the Epididymis.

A benign tumour of alveolar pattern probably derived from Mullerian remnants.

Present Material.

This consists of 158 tumours of the testis and its appendages removed at operation.

Sixty were removed at the Western Infirmary, Glasgow during the years 1907 - 1917 and 1929 - 1953. No slides could be obtained for the intervening years. Eight testicular tumours were obtained from St. George's Hospital, London during the period 1954 - 1961. This included a patient with bilateral tumours. Eighty-four were removed at St. Mary's Hospital, London from 1895 - 1964 and six from other hospitals in the London area.

All eight tumours from St. George's Hospital, 15 of the tumours from St. Mary's Hospital and four of the others were examined by the author at the time of operation, particularly for the making of squash preparations as a prelude to the study of their chromosomal constitution. This also allowed the selection of an adequate number

of blocks and optimum fixation. One half of the specimen was cut into serial slices and fixed in 4 per cent buffered formaldehyde in saline. The slices were further divided into blocks which were dehydrated in graded alcohol, cleared in chloroform or xylol and subsequently embedded in paraffin wax. In every case blocks included the junction of the tumour and the remainder of the testis, the rete, the epididymis and the spermatic cord at several levels.

In the case of material already in the files, all sections were examined and where available the paraffin blocks were recut. In most cases at least two blocks were present from each case and usually one block from the spermatic cord. In many of the older cases from the early part of this century, only one block was available.

The sections were stained by Ehrlich's haematoxylin and aqueous eosin and in appropriate cases by the periodic acid-Schiff method, Gordon and Sweet's method for reticulin and Weigert-Sheridan method for elastic fibre and phosphotungstic acid-haematoxylin. In the case of certain teratomas, four different methods for argentaffin granules were used as detailed by Pearse (1960) - alkaline diazonium method, Gomori's hexamine silver method, Gibbs' method and Schmorl's ferric ferricyanide method. Sections were in certain cases cut on the freezing microtome for staining lipids by Sudan III and IV and Oil Red O dyes.

The various clinical data, details of the treatment and histological features were recorded on punch cards. These were the basis for most of the analysis which follow.

Relative Frequency of Tumour Types.

This is set out in Table II.

Table II

Classification of 158 Tumours of Testis and Appendages.

Body of Testis.

Seminoma	67	(42 per cent)
Teratoma Group	59	(37 per cent)
Seminoma and Teratoma Group	10	(6 per cent)
Lymphoma	10	(6 per cent)
Orchioblastoma	5	(3 per cent)
Interstitial-cell Tumour	3	(2 per cent)
Adenocarcinoma of Rete Testis	1	
Argentaffin Tumour	1	

Appendages.

Adenomatoid Tumour of Epididymis	1
Fibroma of Tunica Albuginea	1

It will be seen that seminoma is the commonest tumour and the teratoma group only slightly less so. Seminoma, teratoma and their combination account for 85 per cent of the testicular tumours in this series.

Clinical Data.

Age at Orchidectomy.

The ages at which the patients with different types of testicular tumour experienced orchidectomy are tabulated in Table III for each decade of life and the age distribution of the main types is illustrated in Fig. 1. This is discussed later with reference to the different tumours, but it can be seen readily from the table and Fig.1, that the great majority of the tumours (72 per cent) occur between 20 and 50 years of age, with a rapid decline after the end of the sixth decade. In the present series only teratomas and orchioblastomas occurred under 20 years. Apart from the seminomas, the teratoma group and their combination the other tumour types consisted of only small numbers of cases. The 10 orchioblastomas occurred in the first few years of life and the 10 lymphomas were fairly evenly spread over adult life apart from a rise in the eighth decade. Of the main types the seminomas reached their peak in the fourth decade, the teratoma group a decade earlier.

Side Affected.

In the 157 cases studied, 69 tumours arose in the left testis, 59 in the right, in one case tumours involved both testes and in 28 the side was not known. The laterality of the main types is tabulated (Table IV).

Table III Age at Orchidectomy of Patients with Main Types of Testicular Tumour

Tumour Type	Age in years											
	No. of cases	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	Unknown	Range	Average
Seminoma	66	0	0	16	23	16	6	2	0	3	19-67	37.8
Teratoma Group	59	2	3	27	12	5	4	2	0	4	1-68	31.6
Teratoma Group + Seminoma	10	0	1	1	4	4	0	0	0	0	19-45	34.5
Lymphoma	10	0	0	1	1	0	1	2	5	0	23-79	60.4
Interstitial-cell Tumour	3	0	0	1	0	0	0	1	0	1	22-68	45.0
Orchioblastoma	5	5	0	0	0	0	0	0	0	0	0.7-2.5	1.6
Totals	153	7	4	46	40	25	11	7	5	8		

Table IV.

Laterality of Seminomas, Teratoma Group and Combined Tumours.

	Right	Left	Bilateral	Unknown	Total
Seminoma	32	26	1	7	66
Teratoma Group	16	31	0	12	59
Seminoma + Teratoma	5	3	0	2	10

The case with bilateral tumours, both seminomas and simultaneous in occurrence constituted 0.7 per cent of the total, a lower incidence than in most series. The Testicular Tumour Panel (Collins and Pugh, 1964) had a frequency of 2.5 per cent for bilateral tumours while Patton, Seitzman and Zone (1960) found a frequency of 1 per cent.

Maldescent of the Testis.

Six patients (3.8 per cent) had a history of undescended testis. In all six the affected testes were in the groin. In one the condition was bilateral and teratoma developed in the left testis. In three cases the right testis was undescended and seminoma resulted. In two cases the left testis was undescended; one of these had a seminoma, the other an embryonal carcinoma. Two had orchidopexies. In one of these, the case with both testes in the groin, right-sided orchidopexy was performed at eight years followed by left-sided at ten years. Teratoma of the left testis was discovered at 16 years. In the other orchidopexy was

done for a right-sided inguinal testis at 28 years. Right testis gradually enlarged after this and a seminoma was removed at age of 37 years.

Grove (1954), reviewing the cryptorchid problem, refers to Le Comte as stating in 1851 that the undescended testis frequently became malignant and mentions the numerous conflicting reports since that date. Two opposing schools of thought appeared and remain today. Campbell (1942, 1959) believed in the high incidence of malignancy in the undescended testis and advocated orchidectomy. On the other hand Cerroll (1949), from replies to a questionnaire sent to members of the American Urological Association, concluded that "the incidence of malignancy in cryptorchidism from the actual cases reported is so minute that the potentiality of its malignancy cannot be used as an indication for either orchidopexy or orchidectomy". Nevertheless, in published series of testicular tumours the frequency of a history of maldescent has varied from 4.7 per cent of 570 cases (Patton, Seitzman and Zone, 1960) to 14.3 per cent of 292 cases (Dean, 1935). The problem of a causal relationship between maldescent and malignancy has been bedevilled by uncertainty as to the true incidence of maldescent in the male population and the lack of a defined level in the scrotum above which the testis should be considered undescended. Recent surveys by the Society of Medical Officers of Health, East Anglian Branch (1958) and by Ward and Hunter (1960) showed the incidence of testicular undescent in pre-pubertal as compared with post-pubertal males to be in the

100,000 — 1 in 2000 symptomatic
100,000 N. → 2 [illegible]

ie 0.2 = c/o x 18 N.

ie incidence c/o is 1/1000 p.a.

proportions of 5.2 per cent: 0.4 per cent and 4.1 per cent: 0.23 per cent respectively. In a study of over 7,000 cases of testicular malignancy collected from published work, Gilbert and Hamilton (1940) found that over 11 per cent had cryptorchidism. If one compares this incidence of maldescent in males with testicular tumour with even the higher figure of incidence of maldescent in the adult male population quoted above (0.4 per cent) there can be no doubt of the significant association between maldescent and testicular tumour. A long term prospective study of a large group of cryptorchids to determine the incidence in them of testicular tumour would enable a true comparison to be made with the incidence in the general male population.

According to Gilbert and Hamilton (1940) malignancy in the undescended testis tends to occur several years later than in the scrotal testis, although Gordon-Taylor and Wyndham (1947) reported a malignant tumour in an undescended testis in a child of 5 months. Robinson and Engle (1954) stressed that atrophy and functional insufficiency of the undescended testis resulted as early as the fifth year of life and to prevent this recommended orchidopexy at an early age. Of the British Testicular Tumour Panel's 58 cases of malignant undescended testis 25 per cent had previous orchidopexies (Collins and Pugh, 1964). Tumour has followed orchidopexy at intervals varying from a few months (Gordon-Taylor and Wyndham, 1947) to 29 years (Sumner, 1959). Moreover tumour has developed in a 51 year old patient with pre-pubertal imperfect and later spontaneous descent (Raines and Hurdle, 1955). When tumour develops in one testis

in cases of bilateral maldescent, the probability of tumour developing in the other testis has been estimated at 1 in 4 (Gilbert and Hamilton, 1940). Whether early orchidopexy would prevent neoplasia is unknown.

Another aspect of the problem of cryptorchidism is the development of tumour in the scrotal testis where one testis is undescended. Of the 58 testicular tumours occurring in cases with unilateral undescent, 9 arose in the scrotal testis (Collins and Pugh, 1964). The statistical significance of this is uncertain, but seminomas have developed in ducks following partial surgical castration (Champy and Lavedon, 1939) and testicular teratomas have followed partial castration produced by the injection of metallic salts in fowl (Michalowsky, 1929). Although the undescended testis shows Leydig-cell hyperplasia, there is as yet no direct evidence of altered gonadotrophic output.

The increased exposure of the inguinal testis to trauma and torsion as compared with the scrotal testis has also been blamed for the development of malignancy, but tumours are even more likely to develop in the abdominal testis (Campbell, 1942) which although liable to torsion is the best protected of all.

Almost all types of testicular tumour have occurred in undescended testes (Collins and Pugh, 1964).

The relationship of neoplasia of the testis to maldescent will be discussed further in Part II of the thesis which is devoted to the comparative oncology of the testis.

Familial History.

One patient, a man of 38 years, with seminoma of the right testis gave a history that his father had had a similar swelling of the testicle, "the size of a cricket ball" and that the testis had been removed.

In the Testicular Tumour Panel's material (Collins and Pugh, 1964), five patients gave a familial history (about 0.5 per cent of the total). Two of their patients with seminomas were cousins and two with teratomas were brothers. One seminoma patient reported that his brother had died of "cancer of the testis".

Injury.

Of the 157 cases, 23 gave a history of previous injury (an incidence of 14.6 per cent). Of the 66 cases of seminoma 12 gave a history of direct trauma (an incidence of 18 per cent), whereas of the 59 cases in the teratoma group 10 gave such a history (an incidence of 17 per cent). Two of the ten cases in the combined seminoma and teratoma group had a history of previous injury. There is no evidence here of a significant relationship between trauma and subsequent tumour type. None of the patients with lymphoma give a traumatic history. A rather similar incidence is given by Notter and Ranudd (1964) who reported a history of preceding trauma in 15 per cent of their cases. Collins and Pugh (1964) however found that only 8 per cent of their seminomas, 11 per cent of their teratomas, 12.5 per cent of their combined tumours and 4.5 per cent of the malignant lymphomas had a history

of trauma.

The significance of trauma in the aetiology of testicular tumours is debatable. An area of tumour growth in the testis or some precancerous condition may be more liable to injury and as in the case of tumours of other superficial organs, breast, skin and bones, trauma may draw attention to a previously quiescent tumour. Experimental testicular tumours have been induced by the injection of certain metallic salts into the testis (Michalowsky, 1929) and the possible relationship of the resulting area of haemorrhagic necrosis in the testis to tumour induction has been discussed (Guthrie, 1964). It is possible that injury might result in similar areas in the human testis. Scarred areas are not infrequently found in relationship to testicular tumours in the human, but these may be due directly or indirectly to the tumour growth.

Previous Testicular Pathology.

Previous Testicular Pathology.

Two cases, both seminomas, had a history of previous gonococcal epididymitis. One case had a history of mumps orchitis at age of 14 years, 13 years before the removal of a seminoma. The significance of previous gonococcal epididymitis is exceedingly doubtful, but there have been several reports on the development of testicular tumour following mumps. Weyerbacher (1938) reported one case of teratoma and one of carcinoma following one year and four months respectively after mumps orchitis. In his review of the literature, Gilbert (1944) found records of 24 cases in over 5,500 detailed records, an incidence of 0.5 per cent.

9 were teratoid and 2 were miscellaneous. Gilbert added a case of his own, an embryonal carcinoma with lymphoid stroma following bilateral mumps orchitis at 12 years followed by atrophy of the right testis. This patient later married and was the father of one healthy child. At 30 years he developed embryonal carcinoma of right testis. Several other case reports have appeared.

In a recent review Kaufman and Bruce (1963) found examples of 28 testicular tumours arising in atrophic scrotal testes following mumps orchitis. The only other infection suspected of an association with testicular neoplasia is tuberculosis. Rea (1931) found co-existant tuberculous epididymitis in 3 cases. The possibility that malignancy is related to other types of atrophy was suggested by Haines and Grabstald (1950) who reported two cases of seminoma, one following mumps orchitis with subsequent atrophy and another following atrophy of unknown aetiology. Testicular malignancy arising in 3 patients with previously known atrophic scrotal testes has recently been described by Hausfeld and Schrandt (1965).

Clinical Presentation.

By far the commonest initial complaint, present in 81.5 per cent, was swelling of the testis, sometimes accompanied by discomfort or feeling of heaviness. The swelling was sometimes associated with pain, a dull ache in scrotum or groin and a sensation of heaviness. Pain alone as the presenting symptom was present in 5.7 per cent, but in a retrospective survey as was the greater part of this study it is impossible to exclude the presence

of coexisting swelling. This also applies to some extent to the cases seen personally, as the detection of swelling prior to consultation depends to a large extent on the patient's powers of observation. In all the cases personally examined the patient complaining of pain had an enlarged testis, even several times the size of the opposite testis, or an enlarged portion of the testis.

In a small number of cases the overall size of the testis was not enlarged. The significance of the various forms of presentation are discussed in the separate chapters on the different tumour types. Three patients were unaware of testicular abnormality (1.9 per cent of the total). One of these was referred to the urologist for infertility and had a fully differentiated teratoma. The other two were found to have testicular swellings at routine medical examination and had seminomas. The patient with the teratoma was alive 18 years after orchidectomy; the two patients with seminomas were alive 5 and 7 years after operation without evidence of metastases.

Three patients, two with tumours of the teratoma group and one with seminoma combined with chorionepithelioma presented with symptoms and signs due to distant metastases. In a few patients with the teratoma group of tumours gynaecomastia was among the early complaints. Only one patient presented with this as his initial complaint.

Chapter II

Seminoma

Definition.

This is a malignant testicular tumour consisting of a growth of uniform large round or polygonal cells, with well-defined cell membranes and clear or lightly staining cytoplasm and round nuclei with one or two nucleoli. The cells are arranged in columns with a stromal reaction, which is commonly lymphoid but may be granulomatous or scirrhous or in solid masses with little reticulin framework.

Frequency among Testicular Tumours.

In the present series of 158 testicular tumours, 67 were seminomas (42 per cent). Ten patients with tumours of the teratoma group also had distinct seminomas on the same side (6 per cent of the total). The proportion of seminomas in different series varies. Magnus (1964) refers to variations in registered cases ranging from 27 per cent in U.S. Teaching Hospitals (1945 - 49) to 67 per cent in England and Wales (1948 - 49). He feels that variations in pathological classification may be responsible as the lower figure has risen and more recent surveys give a more uniform proportion. Dixon and Moore (1953) found that seminomas, i.e., pure seminomas, constituted 38 per cent of their 990 cases. In Great Britain recently the Testicular Tumour Panel and Registry found that 40 per cent of their tumours were seminomas (Collins and Pugh, 1964). Their combined teratomas and seminomas constituted

14 per cent of the total. Owing to the high survival rate of patients with seminomas, mortality statistics do not give any useful information as to its relative incidence.

Age Incidence.

The age at orchidectomy of patients with seminomas are compared in Table III and Fig.1 with the other types of testicular tumour. It will be noted from Fig.1 that it reaches its peak in the fourth decade, a decade later than the peak incidence of the teratoma group. The youngest case in the present series was in a youth of 20 years, but the Testicular Tumour Panel (Thackray, 1964) record cases in youths of 12, 13, and 15 years and in the undescended testis of a boy of 7½ years.

Laterality.

As in most series more seminomas were found in the right testis than in the left (Table IV). Thirty-two seminomas arose in the right testis, twenty-six in left, while one was bilateral and in seven cases the side affected was not known. In the case with bilateral tumours, a man of 36 years, the right testis began to swell first, followed by swelling of the left. Both were removed at the same time, seven months after the first symptom. At the time of operation the left testis was larger. Eight of the Testicular Tumour Panel's 400 cases of seminoma were bilateral. Two of these had simultaneous tumours; six had tumours successive in timing (Thackray, 1964).

Multiple Malignant Tumours.

Five patients with seminomas (7.5 per cent of the total) died from other malignant tumours as recorded in Table V.

Table V.

Patients with Seminoma Dying from Other Malignant Tumours.

Patient	Age at Orchidectomy for Seminoma	Age at Death from other primary tumour	Type of other Primary
H.D.	67	67	Epidermoid Carcinoma of the Oesophagus.
T.W.	57	64	Malignant hepatoma with Cholangiocarcinoma.
J.D.	33	47	Carcinoma of ascending colon.
W.M.G.	27	38	Renal Adenocarcinoma.
J.L.	33	72	Bronchial Carcinoma.

H.D., T.W., and W.M.G., had post-operative X irradiation to common iliac and para-aortic areas. In the case of H.D., oesophagectomy for squamous carcinoma of the oesophagus was carried out 5 months before orchidectomy for seminoma. The diagnosis was histologically verified in respect of the squamous carcinoma of oesophagus, malignant hepatoma with cholangiocarcinoma and renal adenocarcinoma. Notter and Ramudd (1964) found that 7 of their patients with seminoma, 2 per cent of the total, developed a

second malignant tumour of another type.

Hormonal Effects.

None of the patients with pure seminomas in this series had a recorded history of hormonal disturbance. No case had gynaecomastia or gave a positive pregnancy test, but pregnancy tests on urine were only carried out pre-operatively in five cases. Symington and Wallace (1964) discuss the results of hormone investigations in a group of patients with testicular tumours. In particular they refer to the significantly higher level of urinary gonadotrophins in the majority of patients with seminoma and malignant teratoma. With seminoma they also found a high post-oprative level of total gonadotrophins in the urine of patients who had remained well after operation, though this gradually returned to normal in the few patients in which repeated assay had been possible.

Aetiology.

Genetic Factors.

Only one patient gave a history of familial affliction by testicular tumour. In this case the father of the patient had a testis removed for a swelling of cricket-ball size.

Trauma.

30

This has been considered in the last chapter (p30). Out of 66 cases of seminoma 12 gave a history of direct trauma (18 per cent of the total). In 10 cases the history antedated orchidectomy by less than 1 year (15 per cent of the total). An additional four

cases had previous herniorrhaphies and one had the adjacent leg amputated for severe electric burns.

The proportion with a traumatic history (18 per cent) is similar to that found with the teratoma group (17 per cent). The relationship of trauma to the development of seminomas appears to be no different from that of testicular tumours as a whole. The Testicular Tumour Panel (Thackray, 1964) found a record of recent injury in only 8 per cent of seminomas. From clinico-pathological study, the significance of trauma in relation to aetiology is no clearer here than in the case of the other malignant tumours of exposed tissues. The problem is re-opened in the final discussion and conclusions in the light of both experimental and clinico-pathological studies.

Undescended Testis.

Four of the seminomas i.e., 6 per cent of the total arose in inguinal testes, three on the right and one on the left. One case had a right-sided orchidopexy, nine years before orchidectomy. This compares with two tumours of the teratoma group arising in undescended testis. The percentages of seminomas and teratomas in undescended testis are given by the Testicular Tumour Panel (Collins and Pugh, 1964) as 59 and 31 respectively, approximately 2:1 as in the smaller numbers of the present series. It would appear that the undescended testis is more prone to develop seminoma than teratoma. This may indicate a relationship of seminoma to a certain state of arrest of seminiferous tubules.

Previous Testicular Pathology.

Apart from the undescended testis, seminomas do not show any special relationship to previous pathology from testicular tumours in general. The relationship to mumps orchitis and atrophy has been mentioned in the previous chapter. Possible development of seminomas as a sequel to teratomatous growth is discussed in the next chapter.

Method of Clinical Presentation.

This is set out in Table VI.

Table VI.

Clinical Presentation and Fatality of Seminomas.

Presenting Feature.	No. of cases	No. dead within 5yrs.
Painless swelling	45	15
Painful swelling	8	0 *
Pain	4	0
Routine examination	2	0
Inadequate history	7	-

* Two cases inadequately followed up

The commonest presenting symptom was painless swelling of the testis (present in 68 per cent). Another 12 per cent presented with painful or aching swelling. Thus 80 per cent presented with swelling painless or painful, a proportion little different from that of testicular tumours as a whole. None of the patients with seminoma in this series presented with symptoms of metastases although one

patient J.C., aged 42 years had evidence of distant metastases and another W.G., aged 29 years had local nodules of tumour in the spermatic cord at orchidectomy. Both died of metastatic disease within one year.

Naked Eye Appearances.

Although the testis is usually diffusely enlarged in seminoma some coarse nodularity of its surface is sometimes present (Fig. 2a). Some serosal thickening of the tunica vaginalis accompanies a co-existing hydrocele when present. The capsular veins are usually dilated. The testicular capsule or tunica albuginea usually shows some fibrous thickening over the tumour and on the sectioned surface fibrous septae extend from this into the substance of the tumour and give it a lobulated appearance (Fig. 2b).

The seminoma is of uniform appearance and in the fresh condition is whitish with a pinkish tinge. It is sharply demarcated from the normal yellowish brown testicular tissue and even before fixation bulges out from the cut surface (Fig. 3). Although single small nodules of seminoma are encountered, in the great majority of the 34 gross specimens available the testis is largely replaced by the tumour. In two the testis is within the normal size of 5 x 4 x 3 cms., in nine it is slightly enlarged and in 22 it is greater than 7 cms., in long diameter.

Approximately half of the seminomas (32 out of 67) show necrosis on naked eye or histological examination. Areas of necrosis visible on naked eye inspection have an opaque yellowish

appearance which contrasts markedly with the glistening appearance of the healthy tumour. Satellite nodules are seen around the main tumour in a number of cases. Multiple nodules of growth, occasionally in both testes, are also a feature of the so-called spermatocytic variety of seminoma. This variety also has a softer consistency than the classical seminoma with its fibrous trabeculae.

Histology.

Uniformity of cellular type is the main distinguishing feature of seminoma. As seen in sections of formalin fixed material embedded in paraffin wax, the cells are large and roughly spherical with clear or lightly staining cytoplasm and well-defined cell boundaries. The nucleus is rounded with a marked chromatin network and one or two distinct nucleoli (Fig. 4). The arrangement of the tumour cells reflects to some extent the type of stromal reaction. They are arranged in solid columns two or three cells thick with intervening fibrous trabeculae or as solid clumps of cells retaining a tubular form (Fig. 6). Sometimes the tumour cells form a solid sheet (Fig. 7) with minimal reticulin framework.

The cytoplasm stains with Best's carmine and a magenta colour, a positive reaction, after the periodic acid - Schiff technique. Prior treatment with amylase abolishes this reaction. The clear cytoplasm has therefore a high glycogen content and frozen sections reveal also some lipid by the affinity of some cytoplasmic vacuoles for Sudan dyes and Oil Red O.

The lipid is monorefringent.

Tumour Giant Cells.

Out of the 67 seminomas, 10 (15 per cent) show the presence of large multinucleated cells scattered throughout the tumour, usually singly but also in small groups. These cells in a 5 micron section may contain up to 50 nuclei. In three of the tumours showing giant cells the cells are arranged around small venules or capillaries and in that position they can be difficult to distinguish from syncytiotrophoblast (Fig. 8).

Stroma.

Lymphocytic Reaction.

One of the commonest features of the seminoma is a lymphocytic infiltration. It is present in 45 of the 67 seminomas and the reaction is marked (Fig. 9) in 15 (23 per cent). In seven tumours germinal centres are present (11 per cent).

Granulomatous Reaction.

This consists of a histiocytic and fibroblastic proliferation, sometimes diffuse and separating the aggregates of seminoma cells, but occasionally focal with tuberculoid collections of histiocytes and Langhans giant cells (Fig. 10). Lymphocytic infiltration usually accompanies this reaction, which is present in five seminomas (7.6 per cent).

Fibrous Reaction.

This might be considered to be the result of the granulomatous reaction described above, but sometimes even small tumours produce

a marked scirrhous responsive and active granulomatous foci may be seen in large tumours or parts of a tumour. Twenty-seven seminomas (41 per cent) showed a marked fibrous reaction and of these 23, (35 per cent) show fibrosis without granulomatous features (Fig. 11).

Changes in the Remainder of the Testis.

In the case of the large tumours replacing the greater part of the testis, the seminiferous tubules have almost disappeared and where present in a narrow rim of testicular tissue show atrophy and compression due to the secondary effects of the tumour. The growth of the tumour would be expected to produce alterations in the surrounding testis especially as the organ has a fairly strong fibrous capsule. Pressure effects of the tumour both directly and on the blood vessels are conducive to tubular atrophy. Of more interest is the state of the testis in small tumours and in parts of the testis away from the tumour. Out of the 67 seminomas examined 35 show testicular tissue outside the periphery of the tumour, but of these only 23 show tubules and interstitium more than 0.5 cms. from the periphery of the tumour.

Seminiferous Tubules.

In 11 of the 24 seminomas (46 per cent) showing testicular tissue at least 0.5 cms. from the tumour, spermatogenesis is present, but seven of these (29 per cent) show slight to moderate depression of spermatogenesis (Fig. 12). The remaining 13 cases (54 per cent) show atrophic and hyalinised tubules and these include the four cases of seminoma arising in undescended testes. It would appear that

seminomas can arise in testes which are the seat of spermatogenesis. If tubular atrophy is a pre-requisite for the development of seminoma, then it may be in a purely local sense in a testis otherwise active. Intratubular seminoma is present in the surrounding tubules (Fig. 13) in six of these 67 seminomas (9 per cent). In two of these spermatogenesis is present although depressed and in four the non-neoplastic tubules are atrophic and lined mainly by Sertoli cells. Tubules of larger diameter filled with seminoma cells are seen around one tumour (Fig. 13b). As in all cases interstitial growth is also present, it is not possible to decide whether the appearances indicate new formation of seminoma in situ or invasion along the tubules. Occasionally where large atypical hyperchromatic cells are found in tubules near a seminoma, lymphocytic infiltration of the affected tubule is conspicuous (Fig. 14). Lymphocytic infiltration around intratubular seminoma is common in dogs and is referred to in Part II.

Interstitial Cells of Leydig.

In 19 seminomas the Leydig cells in the surrounding testis are increased (Fig. 15) while in 18 they are normal in numbers and appearance. In the case illustrated, the Leydig cells form distinct nodules. The other 39 tumours do not have enough surrounding tissue available in the blocks to assess adequately changes in the interstitium.

Spread of Seminoma.

Local Spread.

Although the seminoma grows as a roughly spherical mass (Fig.3/

compressing the surrounding tubules within the relatively unyielding tunica albuginea, it infiltrates more directly between the tubules and at its periphery is frequently seen as an intertubular growth (Fig. 16). Satellite nodules of varying size are present outwith the main growth in many of the seminomas. Although the growth may produce nodularity of the capsular surface (Fig. 2a) infiltration through to the mesothelial lining of the tunica vaginalis is very rare. Seminoma also spreads to the rete and here it infiltrates both within and without the rete tubules (Fig. 17).

Two seminomas show gross epididymal invasion and one a microscopic focus in the wall of the epididymal duct.

Lymphatic and Venous Invasion.

Thirteen seminomas (20 per cent) show lymphatic permeation in the resected testis or spermatic cord and 10 of these (15 per cent) venous invasion as well. Infiltration of venous channels is in some cases confined to the wall, but in others there is definite intraluminal growth adherent to the wall (Fig. 18).

Owing to the possibility of artefact, free intraluminal tumour in vessels has been discounted. Channels without endothelium have not been classified as lymphatic. Experience in the sectioning of vascular tissues after previous slicing of tumour has suggested that clumps of tumour cells can be carried on the knife especially in the partly fixed or unfixed specimen.

Spermatocytic Seminoma.

This was considered by Masson (1946) to be distinct from the classical seminoma. He considered that its cells resembled spermatocytes. Although satellite nodules are not infrequently found in classical seminomas multicentric growth appears to be commoner in the spermatocytic variety (Masson, 1946 and Thackray, 1964). Two patients with spermatocytic seminomas are included in the 66 cases of this series. Fig. 19 illustrates characteristic multicentric growth in both testes removed from a monk aged 36 years with a history of 7 months swelling of the right testis and 6 months swelling of the left. At operation the left testis was larger. He did not have post-operative radiotherapy, but returned to his monastery and is at time of writing 4 years after operation free of recurrence.

The other case was from a man H.D., aged 67 years with two months' history of right testicular swelling. At orchidectomy his testis showed multiple nodules of soft whitish growth. Histologically the cells arranged in sheets have round hyperchromatic nuclei and compact amphophilic cytoplasm devoid of glycogen. Giant cells with two to four large central nuclei in sections are typical (Fig. 20). Lymphocytic reaction is not seen. This man died 7 months after orchidectomy from metastases of a carcinoma of oesophagus.

Metastases.

Two patients with seminomas had local metastases detected before orchidectomy, one in spermatic cord and the other in

inguinal lymph glands. Post-operatively they both had local and distant metastases and died within a year. Two patients with post-operative inguinal metastases have survived 17 and 9 years. A further 16 patients had post-operative distant metastases. The total number with post-operative distant metastases was therefore 18 and included in this figure were the 11 seminomas who died from metastases of their testicular tumour. Two of the patients with post-operative metastases died from the effects of other carcinomas, in one case from an antecedent squamous carcinoma of the oesophagus in a man aged 67 years and in the other from a malignant hepatoma at 64 years, seven years after removal of a seminoma. In both cases post-mortem examinations with histological studies were done. Three patients with post-operative distant metastases resolving after radiotherapy have survived 15, 8 and 5 years to date. One had enlarged left supraclavicular glands and two had large mediastinal or paravertebral masses.

Post-mortem Findings.

Five patients including two who died from the effects of other carcinomas had post-mortem examinations. The remaining three had metastases in the common iliac lymph glands on the side of the seminoma and extensive secondary growth in the para-aortic glands (Fig. 21) up to the coeliac axis. One had pulmonary and another hepatic metastases. The pituitary glands were available in all three cases dying from seminomatous metastases. In one dying one year after orchidectomy and radiotherapy there was a definite increase in the delta cells in the postero-lateral regions

of the pars distalis as seen in the sections stained by the periodic acid - Schiff - orange G method (Fig. 22)(Pearse, 1960). This was possibly a castration effect due to unilateral orchidectomy and X irradiation. In the other two pituitary glands the delta cells were reduced in number, an effect usually found after a prolonged illness (Ersin, Swanson, Humphrey, Dawson and Wilson, 1958).

Treatment.

All 66 patients with seminomas were treated by orchidectomy and in nearly all cases removal of the spermatic cord up to the internal inguinal ring. Forty-eight patients had subsequent X irradiation directed to the common iliac and para-aortic lymph glands. The dosage varied between 2,500 and 4,000 Roentgen units and was delivered over several weeks. The problems of radiotherapy in the treatment of testicular tumours will not be considered in this thesis. They have been recently discussed by Smithers and Wallace (1962) and Notter and Ranudd (1964). One patient had insertion of radium into common iliac and para-aortic lymph glands. Seven patients had radiotherapy of metastatic deposits. Two patients with metastatic disease were treated by cyclophosphamide following failure of radiotherapy to halt the lesions. Neither showed any improvement.

Prognosis.

Of the 66 patients with seminoma, 15 have died from the effects of metastatic growth. The particulars of these cases are recorded in Table VII. Five have died from the effects of other

Table VII

Particulars of 15 Fatal Cases of Seminoma

Case	Age at orch. (years)	Metastases prior to orch.	R.T.	Age at death. (years)	Post-operative survival. (months)
B.W.	23	-	+	25	20
A.T.	26	-	+	28	21
D.G.	28	-	+	32	47
W.G.	29	+	+	29	10
J.N.	32	-	-	32	5
A.McP	33	-	-	33	6
J.D.	34	-	-	34	1
D.U.	39	-	-	40	16
W.T.	42	-	+	43	13
L.S.	42	-	+	43	13
J.C.	42	+	+	43	11
G.McK.	44	-	+	45	11
G.H.	53	-	-	55	2
J.D.	59	-	+	65	69
D.McC.	64	-	+	69	58

R.T. Radiotherapy. Orch. Orchidectomy.

malignant tumours. Those have already been recorded in Table V. One patient died from vascular hypertension within two years of orchidectomy. One patient died from accidental or suicidal fall from building six years after orchidectomy and one died suddenly from unknown cause nine years after orchidectomy. The corrected survival rates are recorded in Table VIII.

The relationship to prognosis of the many histological and other features recorded in the punch cards has been difficult to assess as only 66 patients with seminoma have been analysed and of these the examination in many of the earlier cases has been limited to 2 or 3 paraffin blocks of the tumour. The number of cases showing each feature are of course too small to enable life table survival rates to be drawn up. Nevertheless it seems reasonable to compare various features of the cases which survived with those who succumbed from their tumours.

As can be seen from Table VII the age span of 15 fatal cases is unremarkable. The average age is 39.3 years as compared with 37.8 years for the total number of cases. Two out of the 15 fatal cases had metastases discovered at the time of orchidectomy or previously. None of the other seminomas had evidence of metastatic spread at time of orchidectomy.

Table VIII Life Table Survival Rates: Percentage Survivors of Patients with Seminoma

Year after orchidectomy	Alive at beginning of year	Lost sight during year	Dying from causes other than testicular tumour	Observed for only part of year	Exposed to risk of dying during year	Dying from testicular tumour during year		Surviving the year %	Surviving from orchidectomy to end of each year %
						No.	%		
1	62	3	0	0	60.5	7	11.6	88.4	88.4
2	52	1	1 *	0	51	5	9.8	90.2	79.7
3	45	1	0	0	44.5	1	2.2	97.8	77.9
4	43	2	0	0	42	1	2.4	97.6	76.0
5	40	5	0	0	37.5	1	2.9	97.1	73.8
6	34	0	1	0	33.5	1	3	97	72.5

* Hypertension

Chapter III

Teratoma Group.

Definition.

This is a group of tumours ranging from differentiated teratomas to undifferentiated embryonal carcinomas and chorion-epitheliomas. The teratoma is a neoplastic proliferation of a variety of tissues foreign to the organ of origin and frequently containing representative tissues from the three embryonic germ layers. These tissues although arranged in a somewhat haphazard fashion can show organoid development.

Classification.

The earlier classifications of testicular tumours in general have been discussed in Chapter I. There was little useful classification of the teratomas until the seminomas were separated as a distinct category by Chevassu (1906) and Nicholson (1907). When Ferguson (1933) found high quantities of Prolan in the urine from a patient with a teratoma testis, it was thought that this might provide a rational basis for classification. In 1946 Friedman and Moore, from a study of over 900 U.S. Army cases produced a comprehensive classification based on histological appearances. This was later consolidated by Dixon and Moore (1953) who postulated that germ cells gave origin to totipotent cells resulting in embryonal carcinoma, which with somatic differentiation led to a teratoma and with trophoblastic differentiation to a choriocarcinoma.

It will be recalled from Chapter I that Dixon and Moore (1953) had 5 groups of so-called germinal tumours.

I Seminoma.

II Embryonal Carcinoma, pure or with Seminoma.

III Teratoma, pure or with Seminoma.

IV Teratoma with either Embryonal Carcinoma or Choriocarcinoma or both, and with or without Seminoma.

V Choriocarcinoma, pure or with either Embryonal Carcinoma or Seminoma or both.

Melicow (1956) preferred to retain the term "teratocarcinoma" for those embryonal carcinomas with some differentiation into tissue elements. As already mentioned in Chapter I the Testicular Tumour Panel and Registry set up in 1958 by the Pathological Society of Great Britain and Ireland in conjunction with the British Empire Cancer Campaign decided at an early stage in its work to abandon the designation "embryonal carcinoma" in view of its past ambiguity and to launch a new classification (Pugh 1960, 1962 and Collins and Pugh, 1964). Basically this places the embryonal carcinomas, teratomas and chorionepitheliomas in one group of teratoma. The sub-groups are:-

Teratoma Differentiated (T.D.) A teratoma which comprises only fully differentiated tissues. This is the "adult teratoma" of Melicow (1956).

Malignant Teratoma Anaplastic (M.T.A.) This corresponds with the embryonal carcinoma in Dixon and Moore's classification.

Malignant Teratoma Trophoblastic (M.T.T.) This is distinguished by containing true trophoblastic tissues disposed in a papillary or villous manner.

Malignant Teratoma Intermediate Type B (M.T.I.B.) This differs from M.T.A. in having some early differentiation, epithelial and mesenchymal, but being without mature tissue or organoid structure.

Malignant Teratoma Intermediate Type A(M.T.I.A.) This shows some mature tissue or organoid structures.

Recently Melicow (1965) has reviewed and correlated this classification with the American classification. His Table 3 is relevant in this respect.

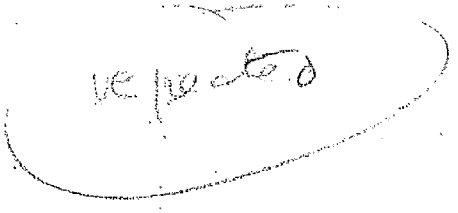


Table IX

Correlation of New British with United States Classification of Testicular Tumours.

(abridged from Table III of Melicow, 1965)

British Classification	Classification Popular in U.S.
A. Germinal Tumours	A. Germinal Tumours
I. Seminoma (S).	I. Seminoma
B. Tumours of unknown origin:	
II. Teratoma	II. Embryonal Tumours:
M.T.A.	Embryonal Carcinoma
M.T.I.	
(M.T.I.B.)	Embryonal Adenocarcinoma
(M.T.I.A.)	Teratocarcinoma
T.D.	Adult Teratoma
M.T.T.	III. Combined I and II
III. Combined I and II	IV. Gonadal Tumours in Intersexes
C. Uncommon Testicular Tumours	B. Non-germinal Tumours
Sertoli cell Tumour (S.C.T.)	Sertolioma
Interstitial cell Tumour (I.C.T)	Interstitioma
Orchioblastoma, etc.	Gynandroblastoma, etc.

In the present classification papillary adenocarcinoma like those illustrated in Fig. 30 are included in the category, embryonal carcinoma, as long as they show no differentiation beyond a primitive unspecialised epithelium. It seemed of doubtful value to separate these tumours from the more anaplastic carcinomas in this relatively small series. The Testicular Tumour Panel (Pugh and Smith, 1964) decided to separate the anaplastic tumours (malignant teratoma anaplastic) from those showing recognisably epithelial cells of cubical or columnar form with regular arrangement (malignant teratoma, intermediate B). All these separations at the present time are rather arbitrary and their justification must await further experience. Melicow (1956 and 1965) considered that these epithelial formations were endodermal in origin and that these tumours should be called embryonal adenocarcinomas. The Testicular Tumour Panel classify individual teratomas into the "most highly differentiated of the malignant categories that the histological appearances warrant however large or small the better differentiated areas may be". Exception is made of chorionepithelioma which they call "malignant teratoma trophoblastic". Three rigid histological criteria are considered necessary for this diagnosis. Firstly, there must be recognisable syncytiotrophoblast; secondly cytotrophoblast must be identified; thirdly, the cells must be arranged in definite papillae or villi. If these are fulfilled then the Panel designated such tumours as malignant teratoma trophoblastic".

In the classification used by the author the presence of different degrees of differentiation is shown by compound designations embryonal carcinoma and teratoma etc. In this way some indication is given about the most malignant and rapidly growing part of the particular neoplasm.

Friedman and Rienzo (1963) however considered that the embryonal carcinomas were derived from trophoblasts and were really trophocarcinomas or malignant placental tumours. These they classified as:-

(1) Undifferentiated trophocarcinoma.

(2) Trophoadenocarcinoma.

(3) Papillary trophocarcinoma.

(4) Choriopapillary trophocarcinoma.

(5) Chorio-epithelioma.

Using the classification already described (Chapter I) the 59 teratomas in the present series were divided into sub-groups as follows:-

Fully Differentiated Teratoma.	3
Partially Differentiated Teratoma.	20
Embryonal Carcinoma.	10
Embryonal Carcinoma + Teratoma.	21
Teratoma + Chorionepithelioma.	1
Embryonal Carcinoma + Chorionepithelioma	1
Teratoma + Embryonal Carcinoma + Chorionepithelioma.	3
Total	59

A further 10 patients with teratomas also had seminoma on the same side (6 per cent of the total). These are described in the next chapter. Among the 59 cases here described, two showed intratubular seminoma only.

Frequency among Testicular Tumours.

Dixon and Moore (1953) found that 61 per cent of their 990 cases of testicular tumour from the U.S. Army were teratomas, teratocarcinomas or embryonal carcinomas. This compares with the British Testicular Tumour Panel's figure of 32 per cent for teratomas and 14 per cent for combined teratoma and seminomas (Collins and Pugh, 1964). Dixon and Moore's series was from rather a selected young age group, the United States Armed Forces, and as the peak incidence of teratomas occurs a decade earlier than seminoma (Fig. 1) this might explain the higher incidence (61 per cent) of teratoma in their series. In a Swedish series of 355 malignant testicular tumours 39 per cent were teratomas or embryonal carcinomas (Notter and Ranudd, 1964). In the present series the teratoma group comprises 37 per cent of the tumours (Table II).

Age Incidence.

The ages at orchidectomy of patients with teratoma have already been compared with patients with seminoma (Table III and Fig.1). As seen in Table III the ages of patients at time of orchidectomy for teratoma range from 1 to 68 years. The average is 31.6 years as compared with an average age of 37.8 years for seminoma. As seen in Fig. 1 the peak incidence for teratoma is the third decade of life, a decade earlier than for seminoma.

Similar age incidence has been experienced in other series. The British Testicular Tumour Panel found that 85 per cent of their 322 patients with teratomas were between 20 and 44 years at operation and that 28 per cent were in the 25 - 29 quinquennium. (Pugh and Smith, 1964).

Laterality.

Unlike the seminomas, the teratomas in this present series show a preference for the left testis, (Table IV), 16 occurring in the right testis, 31 in the left and 12 with laterality unknown. The British Testicular Tumour Panel found that 169 of their teratomas were right-sided and 133 left-sided with 16 instances of unknown laterality (Pugh and Smith, 1964). Although they comment that this proportion of right-sided to left-sided teratomas is the same as for the whole series of testicular tumours they draw attention to the high proportion of left-sided growths in the small groups of malignant teratoma anaplastic and trophoblastic. No bilateral tumours of the teratoma group occurred in this series. Out of the Testicular Tumour Panel's 322 teratomas, 3 were bilateral (Pugh and Smith, 1964).

Multiple Malignant Tumours.

Unlike the patients surviving removal of seminomas, none of the survivors of the teratoma group died from other forms of malignancy.

Hormonal Effects.

Mammary enlargement was noted pre-operatively in four patients, two with partially differentiated teratomas, one with embryonal

carcinoma and one with teratoma and embryonal carcinoma. In two cases the enlargement was bilateral and in one of these it was painful. In two of these four patients the urine gave a positive Friedman test for pregnancy gonadotrophins at 1 in 20 dilution. Apart from these patients with mammary enlargement three patients, one with partially differentiated teratoma, one with embryonal carcinoma and one with teratoma and chorionepithelioma all had positive Friedman tests. One patient with teratoma and embryonal carcinoma and intratubular seminoma had a negative male toad test. In the remaining cases no pregnancy tests were recorded.

Aetiology.

Genetic Factors.

None of the 59 patients with tumours of the teratoma group gave a familial history of testicular tumour.

Trauma.

A history of trauma was given by 7 patients, a proportion of 12 per cent, a figure close to the 11 per cent found by the Testicular Tumour Panel (Pugh and Smith, 1964).

The time relationships of trauma, onset of symptoms and orchidectomy are set out in Table X.

Table X

The Time Relationship of Trauma, First Symptom and Orchidectomy.

Case	Interval (months) Trauma/Orchidectomy	Interval (months) First Symptom/Orchidectomy
P.	2	2
H.B.	3	2½
W.E.H.	5	4
S.S.	12	3
W.G.	15	13
J.E.	120	3
J.H.	96	2

It is quite impossible to assess the significance of trauma in these cases. The percentage with this history is less than with seminomas, where there was a traumatic history in 18 per cent.

Undescended Testis.

Two of the 59 teratomas (3.4 per cent) arose in inguinal testes. In one of these the neoplasm arose in the unilateral undescended testis; in the other left and right orchidopexies had been done at 8 and 10 years respectively and the tumour became apparent in the left testis at 16 years. As in other series seminomas are commoner than teratomas in undescended testis.

Previous Testicular Pathology.

Apart from the relationship to maldescent, less definite than with seminomas, nothing is known of the human testicular

pathology preceding growth of the teratomatous neoplasms. Unlike seminomas there have been no reports of teratoma following mumps orchitis. Interstitial scars with areas of tubular atrophy are not infrequently found close to teratomas, but their aetiological relationship to the tumour is not clear in human material. Such areas may in some cases be the result of tumour growth. Similar problems have arisen with bronchial carcinomas found associated with pulmonary scars (Raeburn and Spencer, 1957 and Kitagawa, 1965).

Clinical Presentation.

This is set out in Table XI.

Table XI.

Clinical Presentation and Fatality of Teratoma Group.

Presenting Feature.	No. of cases.	No. dead within 5 years.
Painless Swelling.	31	19
Swelling with pain or tenderness.	13	9
Pain only.	1	0
Found at Routine Examination.	1	0
Symptoms of Metastatic Disease.	3	3

Fifty-three per cent of those with known history presented with painless swelling and 27 per cent with swelling accompanied by pain or tenderness. The total of 80 per cent presenting with swelling either painless or painful is identical to the proportion so presenting with seminoma. Rather more patients with teratoma

(27 per cent) had an initial complaint of pain accompanying swelling than those with seminoma (12 per cent) and the relationship of this to prognosis is discussed later.

Naked Eye Appearances.

Externally the testis is usually moderately enlarged and nodular and in the case of the fully and partially differentiated teratomas, cysts of varying size near the capsular surface may have bluish translucent walls and be clearly recognisable as cysts on palpation.

In 20 cases the weight of the teratoma and surrounding testis was known and ranged from 20 to 1000 grammes. In 50 cases including 15 of the weighed specimens gross dimensions of the testis bearing the teratoma were noted. In eight of these where the teratoma was small the measurements of the contained teratoma were noted.

All the fully and partially differentiated teratomas had resulted in testicular enlargement at time of operation and this also applied to when they were associated with embryonal carcinoma.

Out of the 12 cases with embryonal carcinoma alone or associated with chorionepithelioma, five had definite testicular enlargement, with measurements in excess of 6 cms. in long diameter and with testis up to 145 grammes in weight; five cases on the other hand had testes within the normal size although in four the tumour caused localised nodularity or distension. No record of size or weight was present in two cases.

Section reveals the characteristic partly cystic and partly solid structure of the fully differentiated teratomas. The cysts

usually predominate, but hair and nodules of bone are common (Fig. 23). In the partially differentiated teratomas cysts of varying shape up to about 2 cms. in diameter contain clear or mucinous fluid (Fig. 24). The solid tissue is yellowish or white with sometimes areas of haemorrhage. Translucent nodules of cartilage and bony spicules may cause difficulty in sectioning. Caseous nodules are due to keratin in epidermal cysts (Fig. 25).

The embryonal carcinomas seldom produce such testicular enlargement as the other members of the group. They usually present a rather dirty white sectioned surface (Fig. 26) with variable amount of haemorrhage. The smaller embryonal carcinoma are usually spherical, rather soft in consistency with frequent central necrosis. The edge is not usually so well defined as the seminoma and is softer in consistency. The chorionepithelioma seldom large is rather similar in appearance, but more typically haemorrhagic (Fig. 37). None of the tumours in the present series consists exclusively of chorionepithelioma.

Histology.

The more complete the examination of tumours in general the less uniformity there is to be found in tumours even of highly specialised tissues. This is increasingly so with the ever varying parameters in which tumour growth is studied. The variety of growth is seen especially in teratomas where variety of tissues is considered an essential characteristic of the tumour. Although

histological sampling of teratomas, such as the usual examination of up to a dozen small blocks of tissue, shows the presence or preponderance of a particular tissue or combination of tissues in any particular teratoma at a particular point in time this has not so far provided a basis for classification. Many of the partially differentiated teratomas show such a variety of tissue and organoid structures when examined in serial blocks that this laborious method of examination would be necessary and a quantitative assessment would have to be made. Indeed the prospect of correlating the type of tissue formed with aetiological factors or prognosis in human teratomas seems to have been dismal enough to deter investigators so far. Nevertheless in his studies of experimental teratomas, Falin (1941) noted an absence of nerve cells and fibres in teratomas induced by zinc nitrate instead of zinc sulphate or chloride.

Most histological classifications have used the degree of differentiation or anaplasia and the different histological features will be described under the divisions adopted by the author.

Fully Differentiated Teratoma.

In this tumour the mixture consists of tissues of mature type, usually arranged in organoid fashion. Mitotic figures are rarely seen and no atypical epithelial structures or embryonic elements are present. Almost by definition it is benign, but incompleteness of examination may place an individual tumour in this category instead of the less differentiated category

of partially differentiated teratoma or embryonal carcinoma. Three fully differentiated teratomas are included in the present series; a Hindu boy of one year, an English boy of nine years and a Scottish school teacher of 25 years. The first consists mainly of an epidermal cyst containing hair arising from a boney eminence (Fig. 25). Underlying this eminence is bone with haemopoietic marrow, neurones and neuroglia. Elsewhere cartilage, skeletal muscle and adipose tissue predominate. In its epidermal cysts and hair it bears a close resemblance to the so-called "ovarian dermoids", which on careful search are frequently found to have tissues other than skin, dermal appendages and teeth. The other two are predominantly mesenchymal, with cartilage and bone and simple epithelial structures in the boy of nine years and entirely mesenchymal, cartilage and smooth muscle in the young adult.

Partially Differentiated Teratoma.

Here there is a variety of tissues many of which are haphazardly arranged and incompletely differentiated. The mesenchyme resembles embryonic mesenchyme and frequently islands of cartilage are seen in process of development (Fig. 27).

Primitive neural epithelium is also characteristic (Fig. 28). The tissues but not the particular arrangements are in many cases those seen at different stages of embryonic development. The atypical arrangement of the epithelial tubules or acini and their mitotic activity suggest malignancy. There seems little point in enumerating

all the tissues found, as these are legion and of various juxtapositions. The only tissue consistently absent is the germinal tissue of the gonads. Endocrine glands are rarely represented. Only thyroid glandular tissue which was present in one tumour is seen in the present collection. Cysts or channels lined by stratified squamous epithelium, frequently showing excellent differentiation and keratinization (Fig. 29) or by respiratory or intestinal epithelium with goblet cells are common (Fig. 30). The juxtaposition of cartilage to respiratory epithelium may mimic bronchial wall. Twenty-two partially differentiated teratomas are included in this series.

Embryonal Carcinoma.

As defined in Chapter I, this includes anaplastic carcinomas with cells growing in solid masses (the M.T.A. of the British Testicular Tumour Panel) and the growths in which tubular or papillary structures of similar cell type occur exclusively or in combination with the above (M.T.I.D. of the above mentioned Panel). Examples of the former are seen in Figs. 31a and 31b where the growth is confined in this area to the seminiferous tubules. The orientation of the embryonal carcinoma cells into clefts and primitive tubules (Fig. 32) is not infrequently seen even in tumours which fit the M.T.A. definition, when these tumours are extensively examined both in their primary foci and metastases. Therefore a division on the basis of tubule formation seems undesirable. A papillary adenocarcinoma considered to belong to the

teratoma group is illustrated in Fig. 33, but if examination of these papillary adenocarcinomas is confined to the primary tumour, distinction from the papillary adenocarcinoma of the rete may be difficult.

Embryonal Carcinoma with Teratoma.

In an embryonal carcinoma as defined above the presence of epithelial structure or arrangement of sufficient differentiation to resemble surface, glandular or ductal epithelium or of developing mesenchyme (Fig. 34) justifies the designation embryonal carcinoma with teratoma. Twenty-one examples of this are included in this study.

An embryonal carcinoma with teratoma in the present series contains structures resembling the human blastocyst. One of these is illustrated (Fig. 35). A large mass of cells is attached at one pole of the blastocyst-like structure. The cyst wall consists of large trophoblastic cells and in the cyst floating cells are present. A large mass of cells resembling the inner cell mass is attached at one pole and within this, where the amniotic cavity would be expected to develop, the early formation of a cavity is detectable.

These embryoid bodies were first described by Peyron and Limousin (1936). Further reports came from several authors, the most recent being from Evans (1957) and Marin-Padilla (1965). The latter describes them in considerable detail and compares them with the normal human embryo in the varying stages of their development.

Chorionepithelioma.

Six chorionepitheliomas in all are included in this series. One of these is associated with seminoma and is described in the next chapter. The other five occur in combination with the following:- Embryonal Carcinoma - 1, Partially Differentiated Teratoma - 1, Embryonal Carcinoma with Teratoma - 3.

In all these cases cells resembling both syncytiotrophoblast and cytotrophoblast are arranged in columns or villi infiltrating or surrounding blood spaces. Smaller areas resembling chorionic tissue are detected in two other tumours. In the five cases justifying the designation of chorionepithelioma, blood spaces lined by syncytial cells are also conspicuous (Fig. 36). Of the two cases in the collection from St. Mary's Hospital London, one T.W. (Fig. 37) was reported by the late Mr. R.M. Handfield-Jones with the assistance of Dr. W.D. Newcomb (1926).

Nuclear Sexing.

Shortly after the discovery of a nuclear chromatin body in the female cat by Barr and Bertram (1949) and the extension of this finding to other mammals, tumours were examined for possible discrepancies between the normal tissues of the bearer and the tissues of the tumour. Hunter and Lennox (1954) found that 4 out of 8 differentiated testicular teratomas in males had a female sex chromatin body. Later, Lennox (1960) pointed out that one of these, a pineal teratoma was from a boy with sex chromatin positive Klinefelter's syndrome. The earlier enthusiasm for this

finding has since been dampened by the finding of sex chromatin in parts of teratomas and not in other parts (Myers, 1959).

In the three fully differentiated teratomas of the present series bodies resembling the sex chromatin are seen in all three, but in two the sex chromatin is present in less than 10 per cent of nuclei with variation from one tissue component to another. In the case with the highest percentage it is seen at the nuclear membrane in epidermal nuclei and in 70 per cent of the cells, but in other tissues the percentage is less. Fibroblasts and smooth muscle cells show lower percentages. In the two fully differentiated teratomas with sufficient surrounding tissue, no sex chromatin can be seen in non-neoplastic tissues for example, Leydig cells, but this is an extremely small sample of the host's tissues.

In the partially differentiated teratomas, an occasional sex chromatin body is seen in cubical epithelium of respiratory or intestinal type and in the embryonic type of mesenchyme, but no constant pattern or geographical localisation is evident.

In the embryonal carcinomas of the present series no sex chromatin body is recognisable, although large nuclei occasionally contain two or three rather similar bodies. This also applies to the cytotrophoblast of chorionepithelioma. Squash preparations made from solid particles of testicular tumours, pre-treated with hypotonic-solutions appear to show more sex chromatin bodies than sections of the same tumour.

It seems that nuclear sexing alone will not be of value at present in elucidating histogenesis in this complex group of tumours.

Further information along these lines must await detailed chromosome studies of the tumours and their hosts.

Stromal Reaction.

Unlike the seminoma with its characteristic lymphocytic stroma the teratoma excites no particular cellular reaction. A scanty exudate of lymphocytes or plasma cells does occur especially in embryonal carcinoma (Fig. 33). Fibrous reaction as such is inconspicuous except as a sequel to necrosis of parts of the tumour. Tuberculoid foci as seen in seminomas (Fig. 10) have not been found, although occasionally in embryonal carcinoma confined to the tubules a multinucleated giant cell with small central and peripheral nuclei has been found close to the basement membrane. (Fig. 38).

Other changes in the Testis.

Seminiferous Tubules.

Apart from the 10 cases of coexistent seminoma and teratoma, evidence of intratubular seminoma or seminoma-in-situ is found on microscopy in two cases, one of teratoma and one of teratoma plus embryonal carcinoma. The latter K.R. aged 19 years shows somewhat depressed spermatogenesis and in situ seminoma arising at different points close to and around the embryonal carcinoma (Figs. 39 a and b). In neither case do the naked eye appearances suggest independent seminoma nodules and study of serial sections of the surrounding testis does not reveal evidence of invasion. This would suggest that these early in situ seminomas arise either as a sequel to teratomatous

growth, or as a delayed response to the same carcinogenetic stimulus.

Out of the 59 teratomas 20 show either no surrounding testis or only a narrow rim less than 0.5 cms. in depth in the material available. Of the remaining 39 teratomas 14 (36 per cent) show spermatogenesis in tubules slightly removed from the growth. In some of these spermatogenesis appears slightly depressed. One of these patients A.M.D. aged 25 years presented with a complaint of infertility and although spermatocytes are seen in division no spermatozoa are present in the tubules. Immediately surrounding the tumour compressed and hyalinized seminiferous tubules are almost invariable with teratoma, although with the more rapidly growing embryonal carcinoma almost normal seminiferous tubules are in process of invasion by embryonal carcinoma. In 22 cases (56 per cent) seminiferous tubules even beyond 0.5 cms. from the edge of the tumour show atrophy and hyalinization. In three cases (8 per cent) the surrounding tubules are prepubertal in type. Two of these were in boys, 1 year and 8 years of age. The other was in a youth of 16 years, who had previously undergone bilateral orchidopexies for undescended testes. In view of the effects of the growing tumour on the tubules, the condition of the seminiferous tubules in the other testis might be more indicative of the pre-cancerous state of the tubules.

Interstitial Cells of Leydig.

Thirty-nine specimens have sufficient surrounding testis for

study of the Leydig cell population. Ten tumours of the teratoma group (26 per cent) composed of five partially differentiated teratomas and five teratomas with embryonal carcinoma show definite interstitial-cell hyperplasia. Twenty tumours (52 per cent) show normal numbers of interstitial cells in the surrounding interstitium and nine (22 per cent) slight to moderate reduction in numbers.

Spread of the Teratoma Group.

Local Spread.

Locally embryonal carcinoma and seminoma appear to spread in similar manner within seminiferous and occasionally rete tubules. In the latter however, a papillary adenocarcinoma without teratoid differentiation may merit more a diagnosis of adenocarcinoma of the rete testis. The growing edge of an embryonal carcinoma is usually less well defined than that of a seminoma and discrete satellites seen so frequently with seminoma are absent. The differentiated teratomas seem to grow as a solid mass with fairly well defined edges and even a peripheral fibrous encapsulation.

Lymphatic and Venous Invasion.

The more malignant components of this group especially embryonal carcinoma undoubtedly infiltrate the lymphatic and venous channels within the testis and under the capsule.

Metastases.

Regional Lymph Nodes.

Although malignant testicular tumours spread by the normal

lymphatic drainage of the testis and epididymis to the para-aortic lymph nodes near the terminations of the testicular veins occasional metastases develop in the ipsolateral inguinal nodes. This occurred with three of the 59 tumours of the teratoma group. In one patient the inguinal growth was present before operation for a teratoma of a scrotal testis. In the other two it followed operation. In none of these cases was there scrotal involvement. None of the cases with inguinal metastases occurred in undescended testes or had exploration prior to orchidectomy. The true incidence of metastases to the para-aortic lymph glands is not known; 39 per cent of the patients with teratomas or embryonal carcinomas had courses of therapy with X-Rays or more recently with cobalt 60 directed to the common iliac and para-aortic areas. Although these tumours require high dosage microscopic metastases may have been arrested. Post-mortem findings in the fatal cases are described later.

Palpable masses in the abdomen not obviously in the liver are usually assumed to be metastases in para-aortic or common iliac glands, although rarely the growth may be in the wall of the alimentary tract. In one case, D.H., the stomach was diffusely infiltrated by embryonal carcinoma (Fig. 40). On the right side lymph glands near the hilum of the right kidney are frequently involved. Involvement of the common iliac lymph glands is probably by retrograde spread.

Distant Metastases.

Nine patients (15 per cent) had evidence, clinical or radiological of metastases beyond the regional lymph glands at or prior to operation.

Metastases were present in the lungs in two patients; in the vertebral bodies in one and in cervical lymph nodes in two. One of the last mentioned had the diagnosis confirmed by biopsy. The other four patients had high abdominal masses. Eight of the nine patients died within 7 months of operation. One with a papillary adenocarcinoma survived 10 years and the high epigastric mass has receded.

Eighteen patients showed evidence of distant metastases after operation. Twelve of these had pulmonary deposits. One showed a cervical lymph glandular deposit 10 years after operation. Two had spinal metastases and three had high epigastric and hepatic metastases. One with a teratomatous pulmonary deposit removed by lobectomy was lost trace of 5 years after orchidectomy. All the others died within one year of operation.

Post-mortem Findings.

Ten of the 39 patients who died of tumours of the teratoma group had post-mortem examinations. The distribution of the metastases is indicated in Table XII.

Pituitary Gland.

In three cases the pituitary gland was available for examination. It showed in all three cases some increase in numbers of the P.A.S. positive delta cells as found in one of the cases of seminoma (Fig. 22). In two of the three cases the other testis had been examined. One showed some increase in interstitial cells and hyaline basement membrane thickening of

Table XII Age at Death and Distribution of Metastases in 10 Fatal Testicular Tumours of Teratoma Group

Case Ref.	Age at death (yrs)	Tumour type	Metastases								
			Abd. LN	Lungs	Liver	Pancreas	Kidneys	Brain	Bones	Skin	Adrenals
B.W.	25	EC	EC	T + EC	EC	EC	0	0	0	0	EC
J.McF.	28	T + CE	CE	CE	CE	0	0	0	0	0	0
R.McD.	38	EC	EC	EC	0	0	0	0	0	0	0
T.B.	40	EC	EC	EC	0	0	0	0	EC	0	0
T.T.	34	T + EC	EC	EC	0	0	0	0	0	0	0
T.W.	41	CE + T + EC	EC	CE	CE	0	0	0	0	0	0
R.M.W.	29	EC	EC	EC	0	0	0	0	0	0	0
D.H.	27	CE + T + EC	0	CE	CE + EC	0	CE	0	EC	CE	0
M.A.	28	EC	EC	EC	EC	0	EC	EC	0	0	0
D.H.	28	T + EC	T + EC	0	EC	T + EC	0	0	0	0	0

T = Teratoma; EC = Embryonal carcinoma; CE = Chorionepithelioma; Abd. LN = Abdominal lymph nodes.

tubules, which showed atrophy of the spermatogenic elements. In the other there was depressed spermatogenesis with only occasional deformed spermatozoa in short segments of tubules and otherwise tubules lined by Sertoli cells only. Interstitial cells were normal in numbers.

In two other cases in which the pituitary gland was not available for examination, the other testis showed atrophic changes in the seminiferous tubules.

Treatment.

This consisted of orchidectomy and removal of spermatic cord up to level of internal abdominal ring. Twenty-three patients (39 per cent) received just over 3,000 Roentgen units (R) to the para-aortic and common iliac lymph glands over several weeks. Of these 13 (56.5 per cent) died of their tumours. Three patients received general body bath irradiation in palliative doses and all died within 15 months from the effects of metastases. Thirty-three received no irradiation treatment, and of these 18 (56.2 per cent) died from metastases. Radiation in these doses would appear to have no effect on the fatality rate. None of the cases included had received 60 cobalt therapy or X irradiation from supervoltage machines. The radiotherapy will not be discussed here. It has been dealt with recently by Smithers and Wallace (1962) and Notter and Ranudd (1964).

In this series no dissection and removal of para-aortic lymph glands was carried out, but post-operative removal of inguinal

glands was carried out in two cases and the removal of a large glandular mass, involving pancreas and spleen was carried out in D.H., two years after orchidectomy (see Table XII). In one remarkable case W.E.H., a chorionepitheliomatous metastasis was removed from the neck 10 years after orchidectomy for embryonal carcinoma. This patient died shortly afterwards, but without post-mortem examination and so the possibility of a new testicular growth in the remaining testis could not be excluded.

Two patients at the stage of multiple metastases in abdomen and chest received oral cyclophosphamide, but without benefit. Both died within two months of starting this form of therapy.

Prognosis.

Thirty-nine patients died from metastases of a tumour of the teratoma group. Apart from one case, W.E.H., mentioned above, all the deaths resulting from the spread of teratoma group tumours occurred within 4 years of orchidectomy and of the 39 deaths, 28 (72 per cent) occurred within the first year, and 35 (90 per cent) within the first two years. The corrected survival rates are shown in Table XIII. The percentage surviving at five years after orchidectomy is 32.4 per cent which compares with a figure of 73.8 per cent for seminoma.

The numbers of cases in each sub-division of the teratoma group is too small for the compilation of survival tables, but some idea of mortality can be obtained. Thus out of 10 patients with embryonal carcinoma seven died within one year, two have so far

Table XIII Life Table Survival Rates: Percentage Survivors of Patients with Teratoma Group Tumours

Year after orchidectomy	Alive at beginning of year	Lost sight during year	Dying from causes other than testicular tumour	Observed for only part of year	Exposed to risk of dying during year	Dying from testicular tumour during year No.	Dying from testicular tumour during year %	Surviving the year %	Surviving from orchidectomy to end of each year %
1	58	3	0	0	56.5	28	49.6	50.4	50.4
2	27	0	0	0	27	7	25.9	74.1	37.3
3	20	0	0	2	19	2	10.5	89.5	33.4
4	16	0	0	0	16	1	6.3	93.7	32.4
5	15	1	0	1	14	0	0	100	32.4
6	13	0	0	1	12.5	0	0	100	32.4
7	12	0	0	1	12.5	0	0	100	32.4
8	12	0	0	1	11.5	0	0	100	32.4
9	11	0	0	1	10.5	0	0	100	32.4
10	10	0	0	1	10.5	0	0	100	32.4
11	9	0	0	0	9	1	11.1	88.9	28.8

survived 12 and 10 years since orchidectomy and one has not been traced.

Seven of the 20 patients with partially differentiated teratoma have died, whereas 16 of the 21 patients with partially differentiated teratoma + embryonal carcinoma have died. All four patients with chorionepithelioma as part of their original tumour died within nine months.

Relationship of Various Factors to Prognosis.

Method of Presentation.

No conclusion can be drawn from Table XI as to the prognostic value of the method of presentation of the primary tumour. The presence of metastases however at time of operation carried a hopeless prognosis in this small series. Nine cases showing either local or distant metastases were all dead within 13 months.

Lymphatic Invasion.

Nine cases showed infiltration of the growth into lymphatic channels. In six, the veins were also invaded. Two of the three cases showing lymphatic permeation only died of metastases. One has survived nine years. The numbers are too small for statistical analysis.

Venous Invasion.

Invasion of the walls and lumina of veins in the testis or spermatic cord was found in 10 cases. Nine died of their tumour. One could not be traced.

None of the other factors studied, presence of necrosis, state of interstitial cells or stromal reaction appeared to have any relationship to prognosis, but the numbers are too few for statistical analysis.

Chapter IV

Coexistence of Seminoma with Teratoma, Embryonal Carcinoma or Chorionepithelioma.

The occurrence of seminoma confined to the tubules, semino-in-situ, in two cases of teratoma has been described in the last chapter. It is therefore not surprising that seminoma as a distinct tumour should coexist with a tumour of the teratoma group. The ten cases described in this chapter consist of unequivocal double tumours in the same testis and are not merely seminoma-like areas in a teratoma.

Classification.

Coexisting with seminomas were the following tumours:-

Embryonal Carcinoma.	2
Partially Differentiated Teratoma, and Embryonal Carcinoma.	3
Partially Differentiated Teratoma.	3
Fully Differentiated Teratoma	1
Chorionepithelioma	1
	10

In all ten cases the seminoma was a distinctive white tumour, in eight cases clearly separated from the other tumour and in two intermingled with it. Only tumours with distinctly seminomatous areas outwith the teratoid tumour have been included. The main features are tabulated in Table XIV.

Table XIV

Main Features of Coexistent Seminoma and Teratoma Group Tumours.

Case	Age at Orch. (yrs.)	Initial Symptom	Pre-orch Hist. (months)	Post-orch. Survival (yrs.)	Teratomatous Component.
R.J.	40	Swelling	8	0.9 (D)	E.C.
H1014/27	45	Swelling	0 found at exam.	4 (to 1931)	E.C.
C V→W	32	Painful Swelling	3	0.4 (D)	P.D.T. + E.C.
L.B.	43	Swelling	10	3 (to 1965)	P.D.T. + E.C.
M.C.	22	Painful Swelling	5	0.4 (D)	P.D.T. + E.C.
91 9/20	19	Swelling	18	Unknown	P.D.T.
J.D.N.	30	Swelling	7	Unknown	P.D.T.
A.N.	44	Swelling	3	1.5 (D)	P.D.T.
F.F.	37	Backache	5	1.2 (D)	C.E.
J.G.	33	Swelling	6	13 (to 1965)	F.D.T.

Abbreviations: P.D.T. - Partially Differentiated Teratoma.

F.D.T. - Fully Differentiated Teratoma.

E.C. - Embryonal Carcinoma.

C.E. - Chorionepithelioma.

(D) - Died from tumour.

orch. - orchidectomy. yrs. - years.

Frequency.

Out of the total of 158 testicular tumours in the present series, 10 (6 per cent) are combined seminoma and teratoma group tumours in the same testis. In the British Testicular Tumour Panel's large series of 995 tumours of the testis (Collins and Pugh, 1964) 14 per cent are described as combined tumours, i.e., teratoma in combination with seminoma. They found that no single type of teratoma was more likely than any other to have a seminoma associated with it. (Pugh and Thackray, 1964).

Age Incidence.

The ages of the ten patients at orchidectomy range from 19 years to 45 years with an average of 34.5 years. Although the number of cases of coexistence of seminoma with teratoma group tumour is small this average age falls between the average of 37.8 years for seminoma and 31.6 years for the teratoma group.

Laterality.

Five are right-sided, three are left-sided and in two the laterality is unknown.

Multiple Malignancy.

In view of the small number of cases and the relatively short post-operative survival (see Table XIV) it is not surprising that none developed a further malignant tumour.

Hormonal Effects.

One patient, J.D.N., aged 30 years had unilateral mammary enlargement and another F.F., aged 37 years had bilateral mammary

enlargement before orchidectomy. Both had positive Friedmon tests for progmancy gonadotrophins. The former had combination of seminoma and partially differentiated teratoma and after radiotherapy for abdominal metastases disappeared in 1945. The latter who had seminoma with chorionepithelioma died at home 14 months after orchidectomy and had persistent painful mammary enlargement.

Aetiology.

Genetic Factors.

No familial history has been obtained. It will be recalled that only one patient with seminoma gave a history of familial involvement and none of the patients with teratoma had a familial history of testicular tumour.

Trauma.

Two patients (20 per cent) had a definite history of injury to the affected testis shortly before the onset of swelling.

Undescended Testis.

None of the patients in this group had undescended testes or previous orchidopexies.

Previous Testicular Pathology.

The study of this group of mixed tumours revealed no association with previous testicular disease.

Clinical Presentation.

As can be seen from Table XIV nine of the ten cases presented with swelling of the testis, in two of these accompanied by pain and one with lumbar back-ache. One mixed tumour was found

at a routine medical examination. The pre-operative duration of symptoms in the other cases ranged from 3 to 18 months with an average of 7.2 months.

Naked Eye Appearances.

Each component of these double tumours has its characteristic appearances. The seminomatous component is uniform whitish in colour, usually well demarcated from the surrounding testis and from the teratomatous component, which can be as variable as any tumour of this group. The clear separation and distinct appearance of the two tumours are seen in Fig. 41. In one case J.G., aged 33 years a fully differentiated teratomatous nodule was removed from the rete testis and three months later a slightly enlarged seminomatous testis was removed. Seven showed slight or moderate enlargement with nodular testicular surface but in one R.J., the testis measured 10 X 7 X 6 cms. Two showed no enlargement. In all cases except L.B. (Fig. 41) the seminomatous component was the smaller.

Histology.

The ten cases of coexistence of seminoma with a tumour of the teratoma group show as might be expected the features of the individual tumour components. Of special interest is the boundary zone between the tumour. Two cases show intratubular seminoma and one showed intratubular embryonal carcinoma.

Intermingling of the two tumours occurs in two cases and this is illustrated in Fig. 42, where the highly malignant growth

of an embryonal carcinoma appears to be infiltrating into the seminoma. On the other hand, a fibrous zone may separate the two (Fig. 43).

Stromal Reaction.

The seminomatous component shows similar reaction to seminoma occurring alone. Tuberculoid foci are not seen in this small number of cases. Like teratomas occurring alone, the teratomatous components show little or no reaction, usually a few lymphocytes and occasionally slight fibrous encapsulation.

Other Changes in the Testis.

Two cases, J.G., and F.F., show persisting but slightly depressed spermatogenesis away from the immediate vicinity of the tumours and perhaps unexpectedly they also show some increase in the interstitial cells of Leydig, in one forming distinct microscopic nodules. The other eight cases show atrophic seminiferous tubules with intratubular seminoma in two and intratubular embryonal carcinoma in one.

Spread.

Infiltration of rete and epididymal tubules by seminoma occurs in one case M.C., where there is also infiltration of lymphatic channels by embryonal carcinoma. Other two cases L.B., and C.V., show infiltration of lymphatic vessels by seminoma and one case A.N., by teratoma. In another case J.D.N., there is infiltration of the lumina of small veins by teratoid carcinoma. Sections of the upper end of the resected spermatic cord are free

of tumour in all cases.

Metastases.

Two patients F.F., and J.D.N., had epigastric masses before operation and one patient C.V., had radiological evidence pre-operatively of pulmonary metastases.
Enlarged lumbar glands were detected after operation in one patient, M.1014/27, who had a recorded survival of four years following radium treatment.

Three patients without evidence of metastases pre-operatively developed clinical or radiological evidence of metastases post-operatively. Two of these R.J., and A.N., had pulmonary metastases and one M.C., had extensive intra-abdominal growth and paraplegia due to spinal metastases.

Five patients died of metastases from their tumours. In one case, F.F., with inguinal and distant metastases, biopsy of the inguinal metastases showed chorionepithelioma. In the others no biopsies of metastases or post-mortem examinations were carried out and in none of the other fatal cases was the nature of the metastases established. Contact with two other patients including one with distant metastases was lost shortly after operation.

Treatment.

In all ten patients the surgical treatment consisted of orchidectomy and removal of the spermatic cord up to the internal ring. Seven patients had post-operative X irradiation to the common iliac and para-aortic areas and one had similar treatment by

insertion of radium needles into lumbar glandular masses detected some time after operation. One patient C.V., had X irradiation of pulmonary metastases without improvement and another had cyclophosphamide orally for pulmonary and hepatic metastases. This chemotherapy produced temporary improvement with diminution of size of the liver.

Prognosis.

These ten cases of course form too small a group for statistical comparison with seminoma and teratoma group tumours occurring alone. Five had died from the effects of metastatic growth within 18 months and another with extensive metastases could not be traced. Another with epididymal invasion by teratoma could not be traced beyond post-operative convalescence. This would suggest a prognosis closer to the teratoma group than that of the seminoma, but of course no firm general conclusion can be drawn. The British Testicular Tumour Panel's study of 136 cases of combined tumour suggested that the survival rate of patients with combined tumour is very slightly better than those with teratoma and distinctly worse than those with seminoma. (Pugh and Thackray, 1964).

Of the five fatal cases four showed lymphatic permeation three by seminoma and one by partially differentiated teratoma. Of the other cases, L.B. has survived 2½ years up to the present time despite infiltration of lymphatic channels by the seminomatous component. Only J.D.N., had infiltration of venous channels in the testis by partially differentiated teratoma, but the duration

of his survival is unknown. No conclusions can be drawn from the stromal reaction, state of the Leydig cells and seminiferous epithelium. Of the ten cases only one J.G., still surviving 10 years after orchidectomy showed absence of necrosis.

The presence of metastases before orchidectomy carried a bad prognosis. Of the three cases with distant metastases, two died within 14 months of operation and the other J.D.N., could not be traced in the Registrar General's records.

Chapter V.

Malignant Lymphoma.

The term "Malignant Lymphoma" is used here to include all malignant tumours of lymphocytes or reticulum cells. The ten cases collected here complained of symptoms usually swelling referable to the testis. It is difficult to be certain that the lymphomatous process originated in the testis, but this problem of site of origin applies to lymphoid neoplasms in general and need not be debated here. It has been discussed by Stout (1951) and by Willis (1960).

The author uses in general the terminology employed by Willis (1960) viz.,

A. Follicular lymphoma and lymphosarcoma.

B. Lymphosarcoma with or without leukaemia.

C. Hodgkin's Disease.

D. Reticulum cell sarcoma.

In the present small group of ten cases no examples of follicular lymphoma (Brill-Symmers' disease) or Hodgkin's disease occurred. The particulars are set out in the following table.

Table XV

Main Features of Malignant Lymphoma of Testis.

Name	Type	Age (yrs.)	Presenting site	Pre-op. symptoms (months)	Post-op. survival (months)
D.McI.	L.S.	23	Testis	8	2
C.H.	R.S.	74	Testis	1	13
T.B.	R.S.	36	Cervical lymph nodes.	2	12
D.M.	R.S.	60	Testis	1	3
J.M.	R.S.	50	Testis	3	8
P.B.	R.S.	72	Testis	5	5
J.P.	R.S.	69	Testis	12	8
N.S.	R.S.	70	Testis	24	6
W.D.	R.S.	79	Testis	3	4
W.T.	R.S.	71	Testis	2	6

No operation. Figures refer to institution of radiotherapy.

op.- operative.

R.S. - reticulum cell sarcoma; L.S. - lymphosarcoma.

The diagnoses entered in Table XV were based on examination of sections stained by Ehrlich's haematoxylin and aqueous eosin and Gordon and Sweet's method for reticulin. In four cases C.H., T.B., D.H., and N.S., sections from tissues removed post-mortem were also available.

Frequency.

In the present series, the ten malignant lymphomas of the testis constituted 6 per cent of the total number of testicular tumours. In the Testicular Tumour Panel's large series, malignant lymphomas constituted 7 per cent of the total (Collins and Pugh, 1964).

Age Incidence.

Malignant lymphoma of the testis as can be seen from Table III is a disease with maximum incidence in the seventh and eighth decades of life. Survey of the literature shows that it does occur at all ages and Waddell (1961) in reporting a case of lymphoma of the testis in a boy aged eight years comments on seven recorded cases of primary and secondary lymphoma of the testis in children.

Laterality.

Four lymphomas affected the right testis, five the left and in one the side was not recorded. None of the ten cases had clinical evidence of involvement of both testes and in the four cases in which post-mortem examinations were carried out, three showed no tumour in the remaining testis. The condition of the

remaining testis was not recorded in the fourth case.

Multiple Malignancy.

None of the cases of malignant lymphoma suffered from the other types of malignant tumour. Lymphoma is not recorded as having occurred in association with other types of testicular tumour.

Hormonal Effects.

As with lymphomas in general no hormonal effects have been found in association with lymphomas.

Aetiology.

Genetic Factors.

No familial history has been recorded in the present series or in the larger series of testicular tumours in respect of malignant lymphomas.

Trauma.

Two cases gave a history of injury, one involving both testes eleven years previously and the other affecting one testis shortly before the onset of swelling.

Undescended Testis.

All ten cases of testicular lymphoma occurred in scrotal testes with no history of previous maldescent.

Previous Testicular Pathology.

Nothing is known of the condition of the testis prior to development of lymphoma.

Naked Eye Appearances.

The testis is usually uniformly enlarged and firm with a

fairly smooth capsular surface. Section shows a whitish or pinkish tumour with blurred margins involving the body of the testis. Occasionally some lobulation is present. Small areas of necrosis and haemorrhage are sometimes present near the centre of the growth. Sometimes a little surrounding testicular tissue is present (Fig. 44).

Histology.

In one case D.McI., the testis shows an extensive growth of small round cells of lymphocytic type. This is lymphosarcoma. In parts of the growth, surviving testicular tubules are lined by Sertoli cells and spermatogenesis is not seen. In the other cases the intertubular growth consists of larger round cells with scanty ill defined cytoplasm and round or oval nuclei containing dense chromatin masses (Fig. 45). Mitotic figures are frequent. In three cases the cellular pattern shows uniformity, but in six there are varying degrees of pleomorphism. The reticulin pattern is variable. A branching network of fine fibres is commonly present, but this is nowhere pericellular in distribution (Fig. 46). These are designated reticulum cell sarcoma, but the cell line is debatable.

Stromal Reaction.

As reticulum cells can produce fine reticulin fibre, this cannot be considered as part of a stromal reaction. A few lymphocytes accompany the proliferation of reticulum cells, but their role in the neoplasm has not been defined.

Changes in Other Parts of the Testis.

Seminiferous Tubules.

In all ten cases, including D.McI., aged 23 years, the

spermatogenic cells have undergone atrophy. In the older age group affected by malignant lymphoma this is not surprising; the natural involution would be accentuated by pressure effects and invasiveness of the neoplasm. The tubules appear more widely separated than in seminoma. Gowing (1964) draws attention to the differing reticulin pattern of the testicular lymphoma and seminoma. The reticulin is condensed around the seminiferous tubules in the seminoma, but is more open around these tubules in the lymphoma owing to the penetration of the fibres ensheathing the tubules by the lymphomatous cells. This does not appear to be invariably so in the present small series. The reticulin shows slight peri-tubular condensation in two of reticulum cell sarcomas (Fig 47a) and in a seminoma shows a light framework with no peri-tubular condensation. (Fig. 47b).

Extension of the lymphomas into tubules surrounded by the growth is not uncommon, but intratubular spread outwards from the periphery of the tumour is not seen.

Interstitial Cells of Leydig.

None of the cases shows any increase in numbers of Leydig cells. Only isolated Leydig cells are present in nine of the testes; in one D.McI., aged 23 years, the Leydig cells were normal in number.

Spread.

Malignant lymphoid neoplasms infiltrate into lymphatic and venous channels. All ten cases show this involvement. The infiltration of the smooth muscle of a venous wall by reticulum cell sarcoma

here as in other sites leads to separation of the smooth muscle fibres and is well illustrated in Fig. 48. It contrasts with the more focal infiltration and formation of intimal tumour plaques by seminoma (Fig. 13).

Involvement of other Organs.

As with lymphoid neoplasms in general, lymph nodes and organs containing lymphoid tissue are not infrequently involved in the spread of the lymphomatous process. It seems uncertain whether all these multiple foci are metastases in the usual sense or are part of a widespread initiation of neoplasia. Although reticulum cell sarcoma and even lymphosarcoma may appear to arise and remain confined for some time to a particular organ or group of lymph glands, involvement of other lymph glands and organs sooner or later occurs in the vast majority of cases. Without exception all ten cases here died of malignant lymphoma and post-mortem examinations in four showed extensive involvement of internal organs and lymph glands. Para-aortic lymph glands contained growth in all four, the kidneys in two and the liver and adrenal glands in one. The case with lymphosarcoma showed infiltration of the cerebellum and the soft palate and also extensive skin and osseous involvement. This association of lymphosarcoma of skin and testis has been described by Altman and Winkelmann (1960).

In one case T.B., aged 36 years, the initial manifestation was swelling of a group of cervical lymph nodes which were removed and on examination proved to be reticulum cell sarcoma.

Testicular swelling appeared two years later. This patient had extensive deposits of reticulum cell sarcoma at necropsy one year after orchidectomy.

Haematology.

None of the patients had a record of a leukaemic blood picture.

Treatment.

In nine cases this consisted of orchidectomy and the removal of the spermatic cord up to the internal inguinal rimg. All cases except P.B., aged 72 years had X irradiation applied to the common iliac and para-aortic lymph glands. Although these tumours are usually very sensitive to X irradiation, high dosages were employed and involvement of other lymph glandular groups was followed by radiotherapy. One of these cases J.M., aged 50 years, a native of Goa, developed massive enlargement of liver and thyroid. He was treated with cyclophosphamide with only limited improvement.

Prognosis.

All ten patients had died within a year of commencing treatment. Long survival of a patient diagnosed as suffering from malignant lymphoma of the testis should suggest a critical review of the histology.

Chapter VI

Leydig Cell Tumours.

Definition.

This is a neoplasm of identifiable interstitial cells of Leydig. In its early stages its distinction from simple hyperplasia cannot be made with certainty. It is a rare tumour and is usually benign.

Frequency among Testicular Tumours.

Only three of this series of 156 testicular tumours (1.9 per cent) can be classified as interstitial-cell tumours. This compares with the Testicular Tumour Panel's figure of 1.4 per cent (Collins and Cameron, 1964).

Age Incidence.

The ages of the three cases are 22, 29 and 68 years, but although the literature shows examples at all ages the majority occur in adult life. Dalgaard and Hesselberg (1957) report 23 examples in boys under 15 years of age.

Laterality.

Two tumours arose in the right testis and one in the left. No particular preference for either side is noted in the literature.

Hormonal Effects.

In one case R.K., aged 22 years the 17 keto-steroid output was estimated on three occasions, twice before and after orchidectomy and was found to be within normal limits. This young man had gynaecomastia and testicular swelling. The other two

showed no clinical evidence of hormonal upset.

Aetiology.

Little has been discovered about aetiological factors from the study of human Leydig-cell tumours. There are no reports of a familial incidence, nor is there a special relationship to trauma or to undescended testis. All three tumours in this series arose in the scrotal testis and there had been no history of previous orchidopexy. Nor was there a history of trauma.

The preceding testicular pathology can only be surmised from the history of previous testicular abnormality and from the condition of the testis at operation. None of these three cases gave a history of previous orchitis, but one, R.K., aged 22 years had a history of sterility and rather small testes. In this patient and in B.B., aged 29 years the surrounding testis showed marked depression of spermatogenesis. In the case of W.L., aged 69 years no surrounding tubules were present in the biopsy.

Clinical Presentation.

One patient R.K., complained initially of sterility and was found to have gynaecomastia, an enlarged right and atrophic left testis. The other two complained of testicular swelling of 3 and 4 months' duration.

Naked Eye Appearances.

Leydig-cell tumours are characterised by a yellow or orange colouration with a well demarcated boundary sometimes accentuated by a fibrous capsule, which may extend into the tumour as fibrous septae.

Areas of necrosis are rare, but small haemorrhages and cystic change are seen occasionally.

The Leydig-cell tumour in patient R.K., measured 2.5 X 2.0 X 2.0 cms., and was encapsulated (Fig. 49). In the case of B.B., the tumour was similar in size, but in W.L., the testis was enlarged to 8 cms. in longest diameter and only a biopsy was taken from a large tumour containing areas of haemorrhage.

Histology.

These tumours can usually be distinguished at a glance from the other human testicular tumours. The cells are typically polygonal with large amount of eosinophilic cytoplasm, granular or foamy in appearance and are arranged in solid masses or cords with a fine reticulin network supporting a rich capillary bed. The nuclei are roughly spherical with a well marked membrane and in the smaller cells a reticulated chromatin pattern with one or two nucleoli. The larger granular and foamy cells usually show a dark rather pycnotic nucleus (Fig. 50). Frozen sections of formalin fixed tumour show in cases R.K., and B.B., numerous drops of lipid stainable by the Sudan dyes and Oil Red O. Mitotic figures are sometimes present in moderate numbers and in case W.L., the biopsy had numerous mitoses and spindle-shaped cells. The experience of this small group of three cases is of course quite inadequate to assess possible criteria of malignancy and this difficulty seems to have frequently occurred in the assessment of individual cases, although in retrospect the vast majority pursue a benign course.

Stromal Reaction.

There is little stromal reaction apart from minimal fibrosis and encapsulation by collagen.

Other Changes in the Testis.

In only two cases, R.K., and B.B., was surrounding testis available for examination. In both cases spermatogenesis is severely depressed.

Spread and Metastases.

In two of the cases the Leydig-cell tumours were benign and neither reached the limits of the body of the testis. Both grew as solid tumours with fibrous capsules and showed no infiltration. The other case was the patient, W.L., aged 68 years who died 6 months after biopsy with multiple intra-abdominal masses, but no post-mortem examination was carried out and the malignant status of his Leydig-cell tumour must remain uncertain.

Treatment.

This consists of orchidectomy. In the two cases in which orchidectomy was possible, the spermatic cord was removed up to the internal inguinal ring.

Prognosis.

As indicated above, one patient died within 6 months but the cause of his death and the nature of his metastases were unestablished. The other two R.K., and B.B., have survived seven and six years up to the present date without evidence of recurrence. Both appear to have remained sterile. In a recent

report Short and Coe (1963) have described a malignant interstitial-cell tumour and in a review of the 12 reported cases, they accepted only six as being proved malignant. Warren and Olshausen (1943) go as far as to state that no definite criteria for malignancy can be established except for the presence of metastases. On the other hand, in a poorly differentiated interstitial-cell tumour it will be difficult to identify its origin from interstitial cells as the specialised features which alone distinguish the Leydig cells from fibroblasts are likely to be inconspicuous or completely absent.

Chapter VII

Miscellaneous Human Testicular Tumours.

Orchioblastoma.

Definition.

Orchioblastoma is a tubular and papillary adenocarcinoma, often mucin-secreting and arising in the testis in infancy or early childhood.

Frequency.

It is undoubtedly a rare tumour, although five occurred in the present series, two from the files of the Western Infirmary, Glasgow (1907 - 1953) and three from the files of St. Mary's Hospital, London, (1895 - 1964). This represents 3.2 per cent of the present combined series of 158 testicular tumours and contrasts with the Testicular Tumour Panel's percentage of 0.8 (Brown, 1964).

Age Incidence.

In this study the ages were 8, 11, 21, 22 and 30 months, a range from 8 months to 2½ years.

Laterality.

Three were left-sided and in two the side was unknown.

Hormonal Effects.

No endocrine effects were recorded.

Aetiology.

There is no record of any of the five tumours arising in undescended testis, but this is only stated in three cases. No history of trauma is recorded. A familial incidence has not been found.

Clinical Presentation.

In all cases a swelling of the affected testis was noticed by the child's parents, usually the mother. The swelling usually increased rapidly, but apparently without discomfort in the early stages.

Naked Eye Appearances.

The tumour is usually whitish or yellowish white, rather soft and friable with fairly well-defined margin and small cystic areas sometimes containing mucin (Fig. 51). Three of the orchioblastomas have been available as specimens in the museum of the Pathology Department of St.Mary's Hospital, London and only one of these shows small areas of haemorrhage. The measurements of the three museum specimens and one case from the Western Infirmary, Glasgow are:-

3.8 x 4.0 x 3.0 cms.

3.5 x 2.0 x 2.0 cms.

5.0 x 4.0 x 4.0 cms.

7.0 x 5.0 x 4.5 cms.

Histology.

This has been well described by Teoh, Steward and Willis (1960). Usually parts of the tumour are irregular tubular and papillary adenocarcinoma with more solid areas of vacuolated clear and more compact cells surrounding isolated infantile testicular tubules (Fig. 52). The mucoid vacuolation of the cuboidal or columnar cells lining the tubules is often distinctly basal,

forming in sections a mucinous zone between nuclei and basement membrane. In another form the cells are arranged in a loose mesh-work. Mitotic figures are fairly frequent and occasional giant nuclei are seen in the solid areas.

Sections from all five orchioblastomas were stained by alcian blue, muci-carmine and the periodic acid - Schiff (P.A.S.) method for mucin and by Best's carmine and P.A.S. after diastase and without diastase for glycogen. These special stains confirm the large mucinous content of certain vacuolated cells, tubules and parts of the stroma and reveal a variable glycogen content of the clear cells.

Stromal Reaction.

The stroma consists of fine reticulin and in places collagen fibres. Little or no cellular reaction is present.

Other Changes in the Testis.

The characteristic infantile testicular tubules consist of fairly uniform cells with spherical or ovoid nuclei and basally vacuolated cytoplasm. These are arranged in layers two or three cells deep on a basement membrane. These tubules surround the tumour and are also found within its substance virtually unchanged. (Fig. 52). Teoh Steward and Willis (1960) claim to see transitions between these tubules and the tubules of the orchioblastoma.

Spread and Metastases.

This does not appear to be different from that of other malignant testicular tumours in later life. The epididymis was

involved in one of the three fatal cases. The other two were known to have evidence of pulmonary involvement before death. One of these had also intra-abdominal metastases around the left kidney and the other bilateral enlargement of inguinal lymph glands.

Treatment.

All cases were treated by orchidectomy and removal of the spermatic cord up to the internal inguinal ring. None were treated by radiotherapy, but only one of the cases occurred within the last 30 years.

Prognosis.

Three out of the five patients with orchioblastoma died within one year of orchidectomy. The other two were only followed up for week after operation. Eight of the thirteen cases of Magner, Campbell and Wiglesworth (1956 and 1962) survived five years.

Adenocarcinoma of the Rete Testis.

Definition.

This is a papillary adenocarcinoma arising in the rete tubules.

Relative Frequency.

Only one case occurred in the present series of 158 testicular tumours. It is equally rare in all large series, but difficulty may arise in distinguishing it from the papillary adenocarcinoma of teratomatous origin or a Sertoli cell tumour. Cases have been reported among others by Scully and Parham (1948), Shillitoe (1952), and Willis (1960).

Age Incidence.

The present case, A.McL., was aged 70 years. The two cases reported by Willis (1960) were aged 31 and 59 years and these ages appear to be the lower and upper limits of the few cases reported by other authors.

Aetiology.

Maldescent, trauma or previous atrophy do not appear to be factors in the development of these tumours.

Clinical Features.

The present case presented with a painless swelling of the left testis of eight months duration. He died 15 months later with evidence of multiple pulmonary metastases, but without post-mortem examination. He had no gynaecomastia. Tests for urinary gonadotrophins were not carried out.

Naked Eye Appearances.

These have no characteristic appearance apart from their location. The present case is a fairly solid whitish tumour 3.5 cms., in diameter in the body of the testis, completely replacing the rete and growing into the epididymis.

Histology.

The typical appearance of this papillary adenocarcinoma growing in rete tubules is illustrated in Fig. 53. Full post-mortem examination of metastases as well as examination of serial blocks from the parent tumour may be necessary in some cases in order to distinguish adenocarcinoma of the rete testis from the

papillary type of embryonal carcinoma (see Chap. III). One would expect these tumours to have some affinity with Sertoli-cell tumours, as the Sertoli cells of the seminiferous tubules and the lining cells of the rete, straight and efferent tubules have many features in common. No Sertoli-cell tumours are included in the present series, but although numerous canine Sertoli-cell tumours are described in Part II, papillary adenocarcinomas of the region of the rete testis have not yet been recognised in the dog.

Other Changes in the Testis.

There is atrophy of the spermatogenic cells in the surrounding seminiferous tubules with surviving Sertoli cells and thickening of basement membrane.

Spread and Metastases.

Due to their site of origin these tumours should be prone to early epididymal spread. Examination of the orchidectomy specimen of the present case revealed invasion of the epididymis. Intra-abdominal metastases were present, but no post-mortem examination was carried out.

Treatment.

As the tumour is so rare there is no reliable assessment of the effects of radiotherapy. The present case had palliative dosage of X irradiation to the abdomen without improvement. Orchidectomy and removal of the spermatic cord up to the internal inguinal ring is the standard surgical treatment for malignant disease of the testis and the precise nature of these

carcinomas is only likely to be discovered on pathological examination.

Prognosis.

Death occurred in the case here described within 15 months of orchidectomy. One of the cases, two in number, reported by Willis (1960) died one month after operation. Scully and Parham's case (1948) had metastases before discovery of the testicular lesion and later died with multiple metastases.

Argentaffin Carcinoma, Carcinoid Tumour or Argentaffinoma of the Testis.

One occurred in the present series, and has been reported by Zachary Cope (1930). This was an argentaffin carcinoma of the right testis in a man of 50 years who had a resection eight years previously for an argentaffin carcinoma of the small bowel. He died six years after orchidectomy without evidence of recurrence. Re-examination of the material gives no indication whether the testicular tumour was a new primary or metastasis from the bowel. His further survival for six years after orchidectomy supports the former.

These are solid yellow tumours of characteristic polyhedral cells arranged in acini or solid islets with fine cytoplasmic granules which may reduce silver salts to metallic silver, (the argentaffin reaction) and stain brick-red with the alkaline diazonium reaction (Pearse, 1960). They closely resemble the argentaffin tumours of the alimentary tract and elsewhere (Willis, 1960). Stewart, Willis and De Saram (1939) described an argentaffin carcinoma arising from intestinal mucosa in an ovarian teratoma

and the likelihood of a similar process in testicular teratomas must be considered; nevertheless pure argentaffin cell tumours in the testis have been carefully examined and there is only one report of a teratomatous origin (Simon et al, 1954).

Secondary Tumours.

Many types of metastasising tumour can be found in the testis. The exact incidence of testicular involvement in disseminated malignancy is uncertain as the testis is not always examined post-mortem. The problem of lymphoma and the question of its primary or secondary nature in the testis has also already been discussed in the chapter on malignant lymphoma. Myeloma or plasmocytoma presents a similar problem. Interstitial leukaemic infiltration also occurs.

The other tumours are usually incidental findings at necropsy. In the author's experience the primaries have been carcinomas of the prostate, urinary bladder, bronchus and stomach and melanomas of the skin in descending order of frequency. Secondary tumours of the testis appear to be much less common than secondary tumours of the ovary. This could be explained by the intra-abdominal site of the latter and their susceptibility to transcoelomic and direct spread.

Tumours of Testicular Tunics and Appendages.

Two extra-testicular tumours were encountered during this study. They are briefly described here.

Adenomatoid Tumour of the Epididymis.

Definition.

This is a localised neoplasm of the epididymal region consisting of smooth muscle and fibrous tissue surrounding clefts or tubules lined by flattened or low cuboidal epithelium. A homologous tumour occurs in the female in the wall of the Fallopian tube.

Frequency.

This is a relatively rare intra-scrotal neoplasm, but is the commonest tumour of the epididymis. Rankin (1956) found 106 cases in the literature and added two of his own. These benign tumours have been variously regarded as adenomas, mesotheliomas, haemangiomas or lymphangiomas. One case is included in the present series.

Origin.

There have been various views on histogenesis, but recent publications have tended to support an origin in Mullerian vertiges (Sundarasivarao, 1953 and Jackson, 1958).

Age.

The reported cases have occurred from birth to old age.

Aetiology.

Nothing is known about aetiological factors and associated testicular pathology.

Clinical Features.

The presenting feature is usually a slowly enlarging

painless lump behind the testis. In the present case, D.S., aged 30 years, the swelling had first been noticed just before localised removal was carried out. No local trauma had been experienced and the patient was married with two children. Only an occasional dull ache was experienced. Both testes were fully descended and of normal size.

Naked Eye Appearances.

The patient described above had a spherical swelling 2 cms. in diameter in the lower pole of the epididymis. On section it was firm in texture with a yellowish and white cut surface somewhat whorled in appearance.

Histology.

The features noted in the definition are characteristic.

Prognosis.

This is generally considered to be a benign tumour but Soderstrom and Liedberg (1966) describe deposits in the tunica vaginalis in one case. Recurrence after complete removal has not yet been described.

Fibroma.

A pedunculated fibroma 2 cms., in diameter arose from the tunica albuginea of the left testis in a man aged 33 years (W.M.). It was first noticed one month before its resection and the patient remained well without recurrence seven years later. Fibroma, fibrosarcoma, rhabdomyosarcoma and other mesenchymal tumours are

described as paratesticular by Gowing and Morgan (1964). The rhabdomyosarcomas and embryonic sarcomas are well described in that paper and by Holtz and Abell (1963).

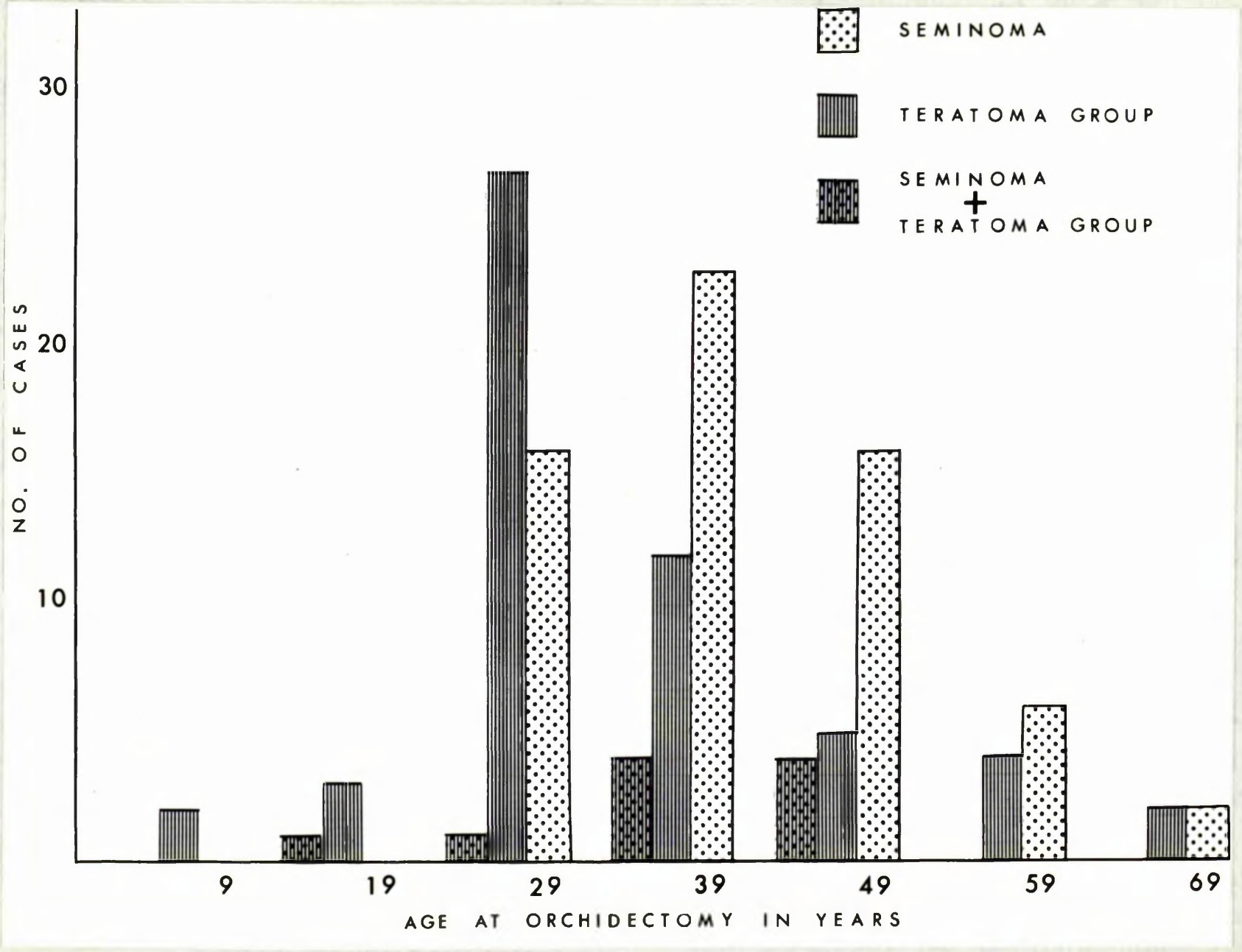
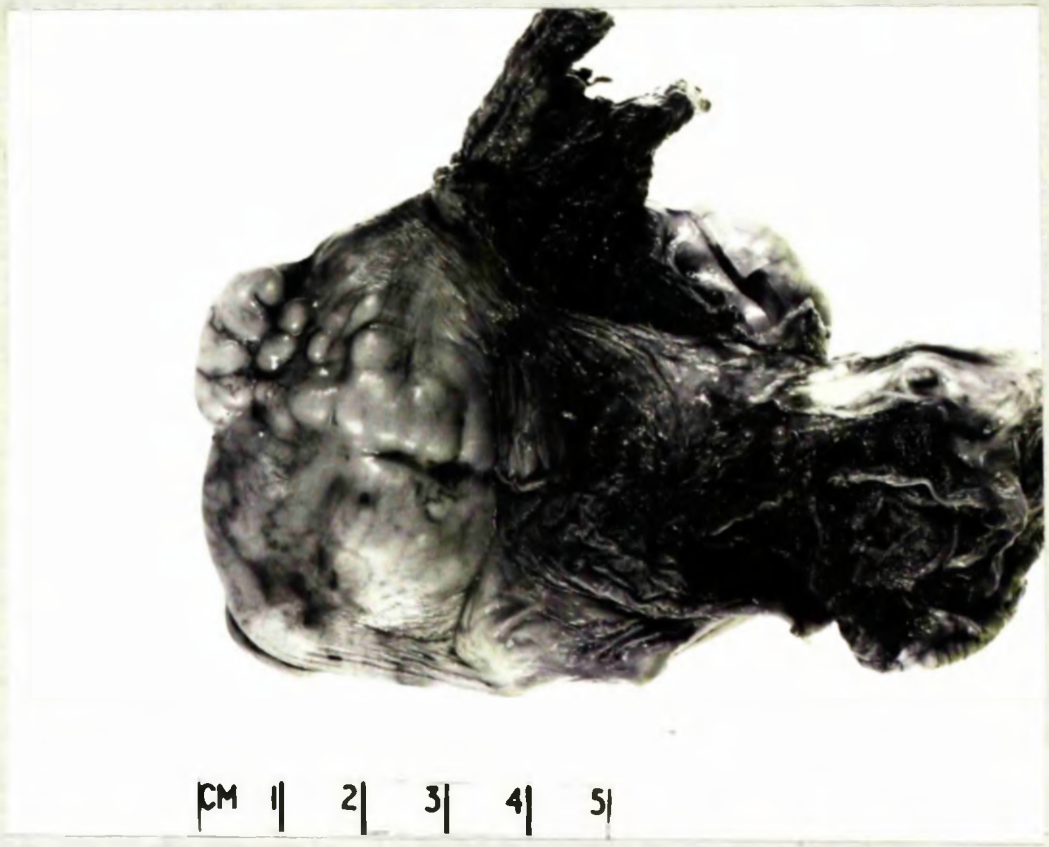
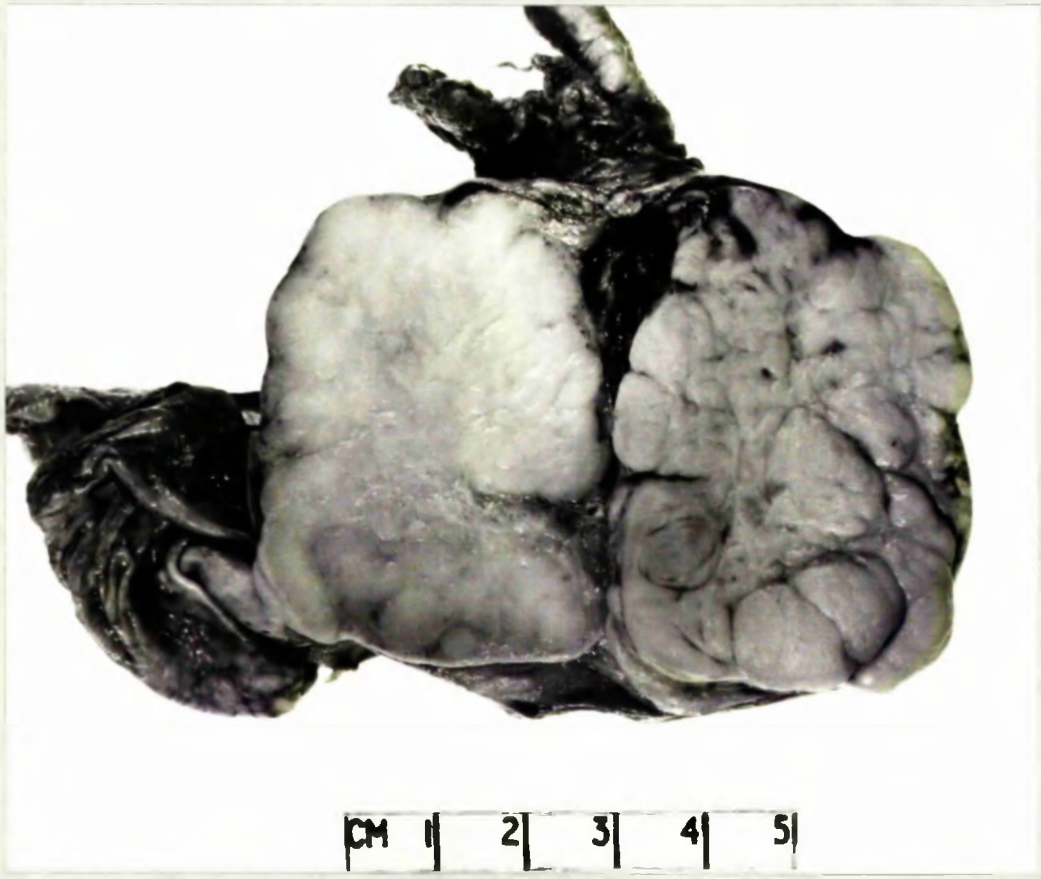


Fig. 1. Age distribution at orchidectomy of different types of human testicular tumour.



a



b

Fig. 2. Human seminoma showing in (a) the coarse nodularity of the serosal surface and in (b) the lobulated appearance of the cut surface.

Fig. 3. Human testis and epididymis showing roughly ovoid seminoma with a clear demarcation of its upper part which bulges out on the cut surface.

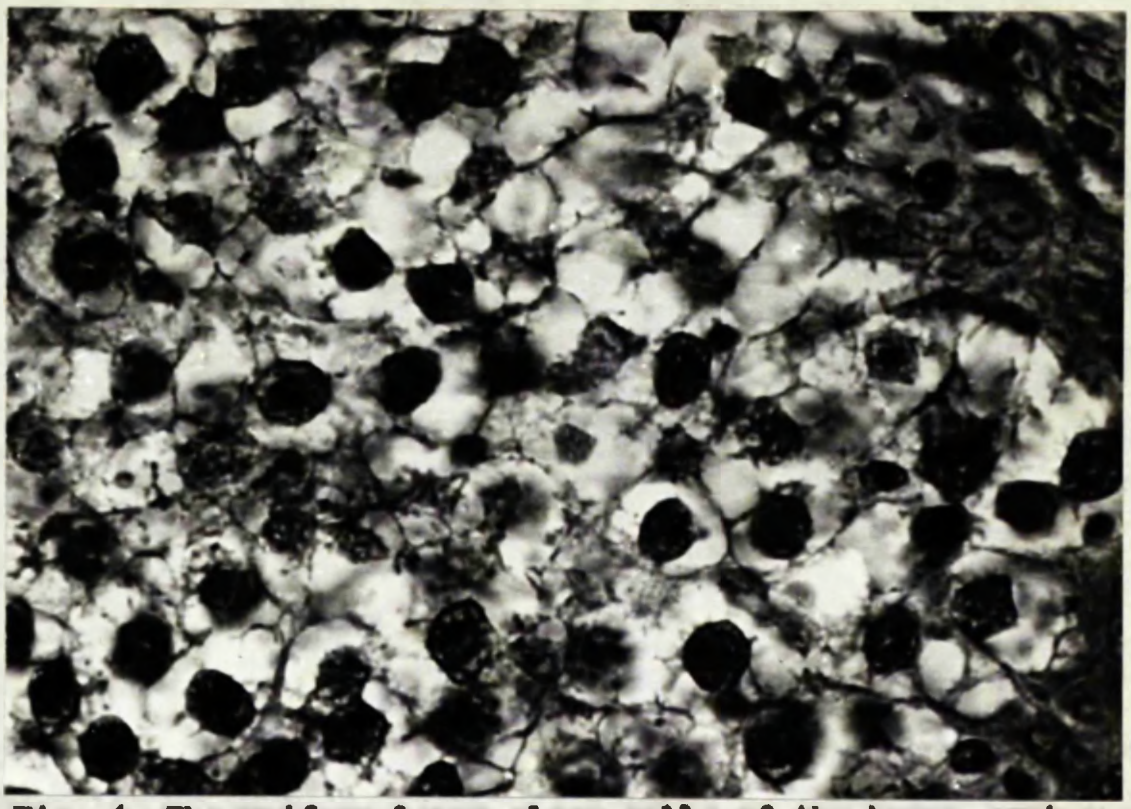


Fig. 4. The uniform large clear cells of the human seminoma. Note the distinct cell boundaries and the spherical nuclei with one or two distinct nucleoli. H & E X 800.

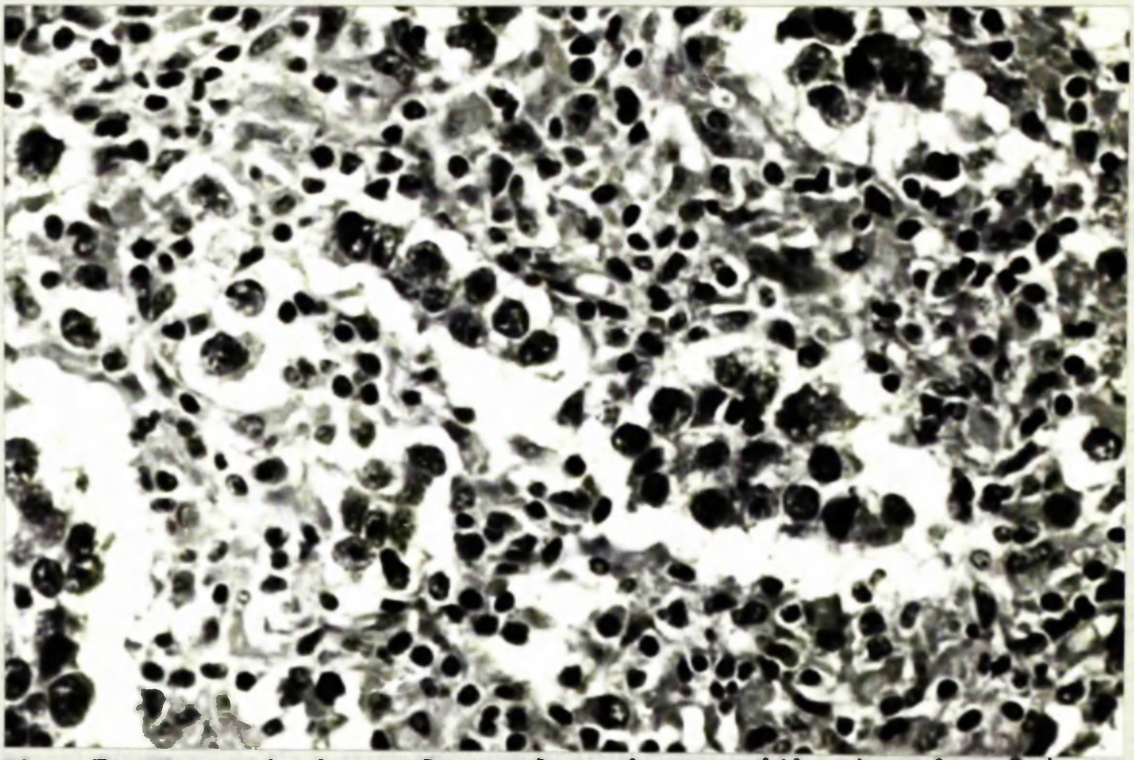


Fig. 5. The scirrhous form of seminoma with strands of tumour cells separated by fibrous stroma infiltrated by lymphocytes and plasma cells. H & E X 320.

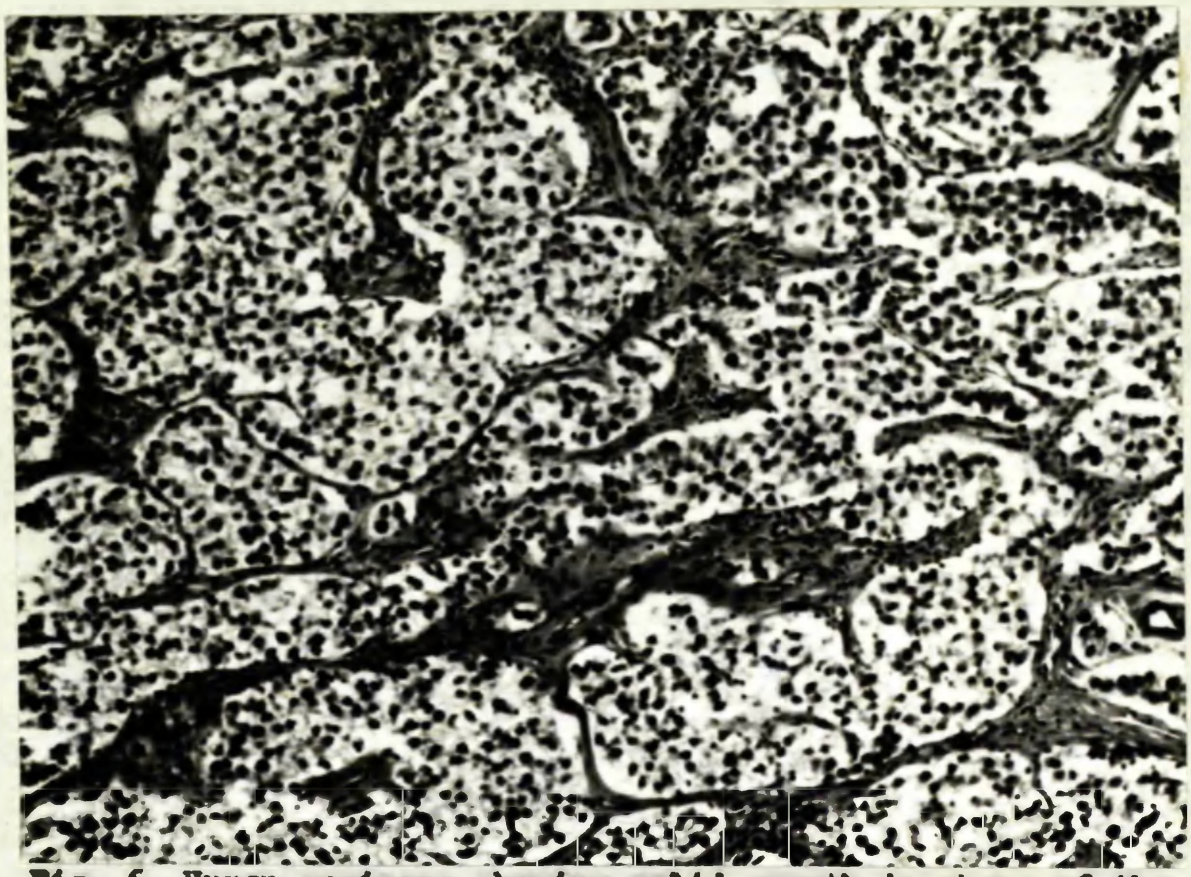


Fig. 6. Human seminoma showing solid growth in shape of the seminiferous tubules. H & E X 125.

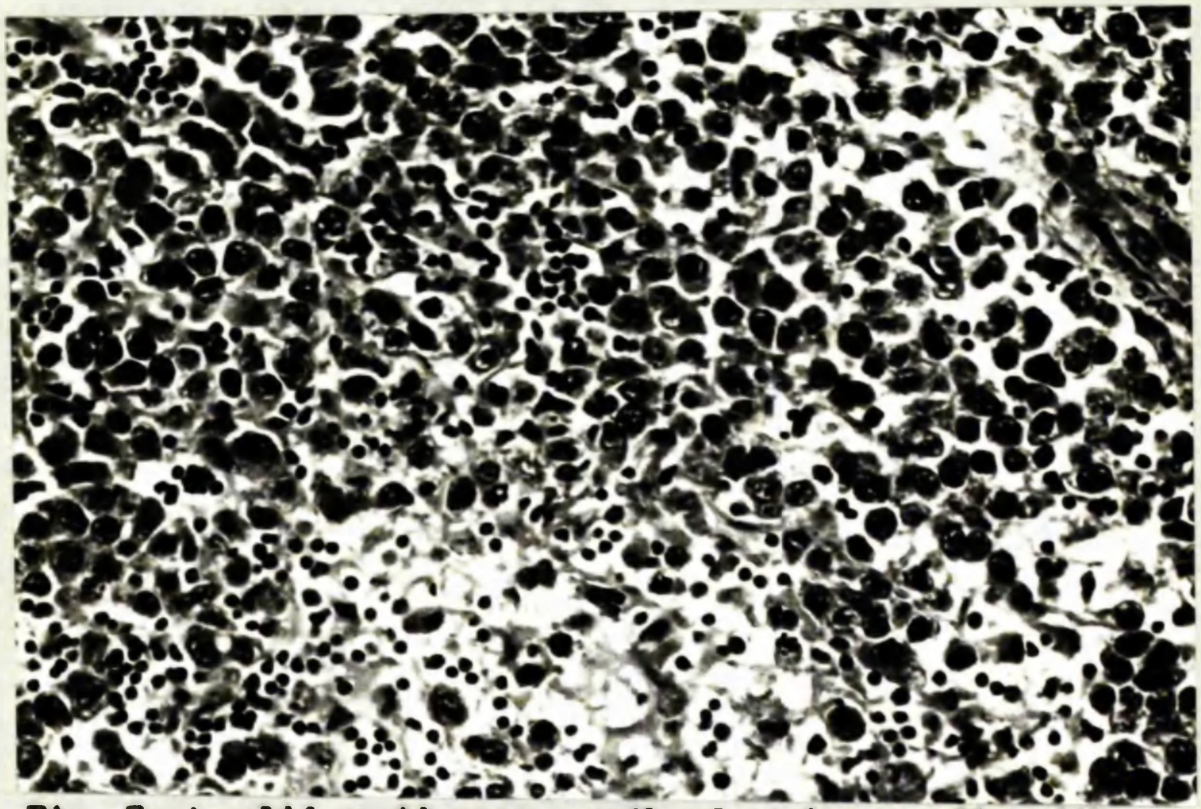


Fig. 7. A solid contiguous growth of seminoma cells with minimal stroma. H & E X 320.

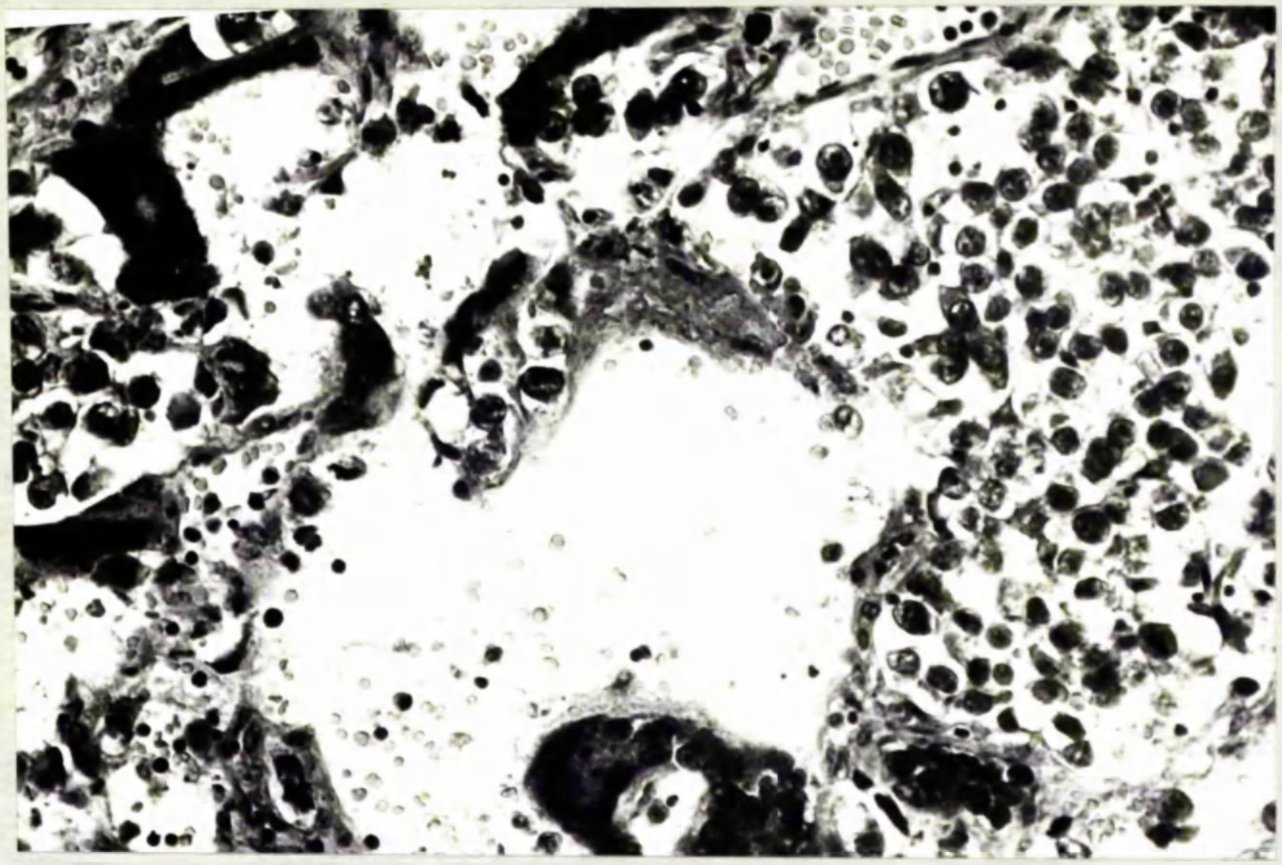


Fig. 8. Multinucleated tumour giant cells surrounding blood spaces in seminoma. H & E X 320.

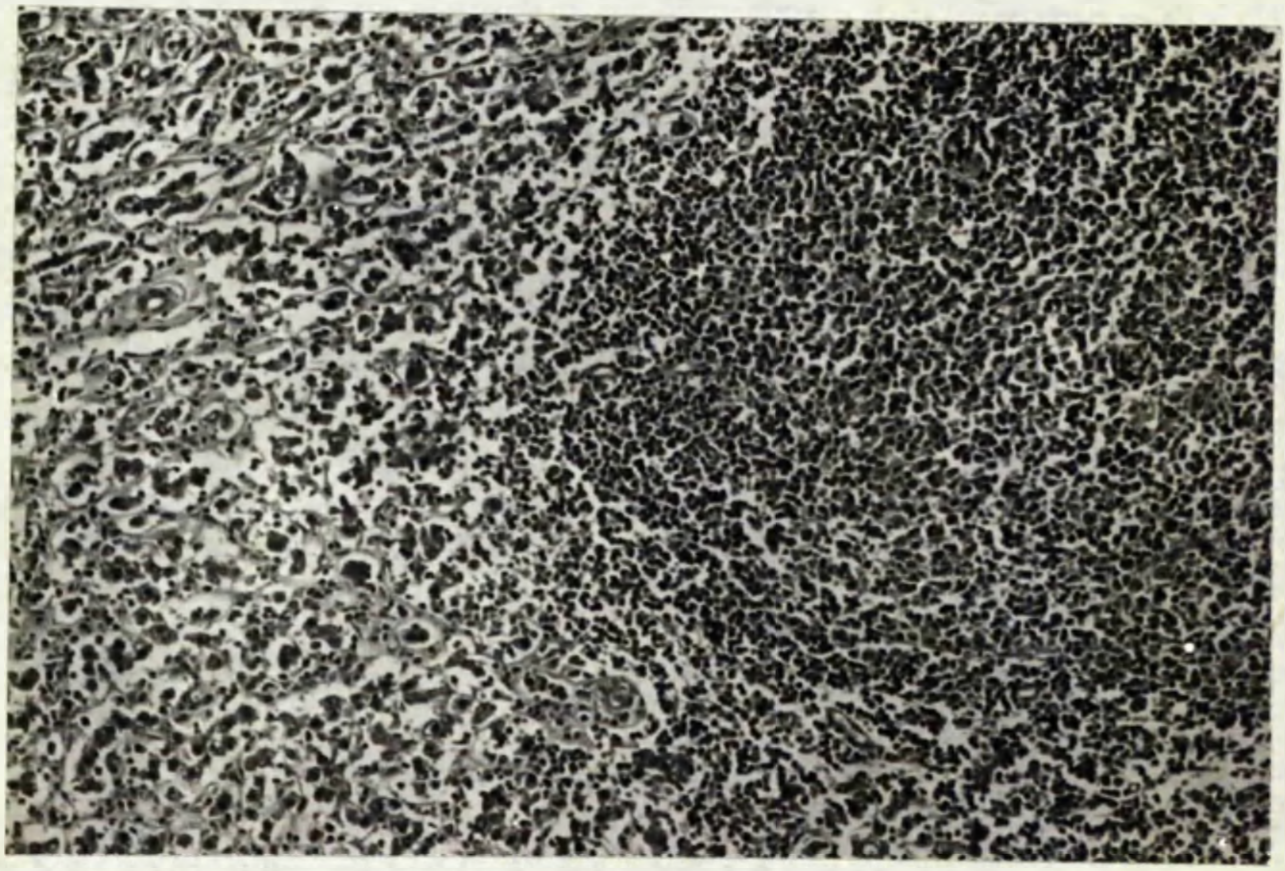


Fig. 9. Seminoma showing lymphoid focus at right. H & E X 125.

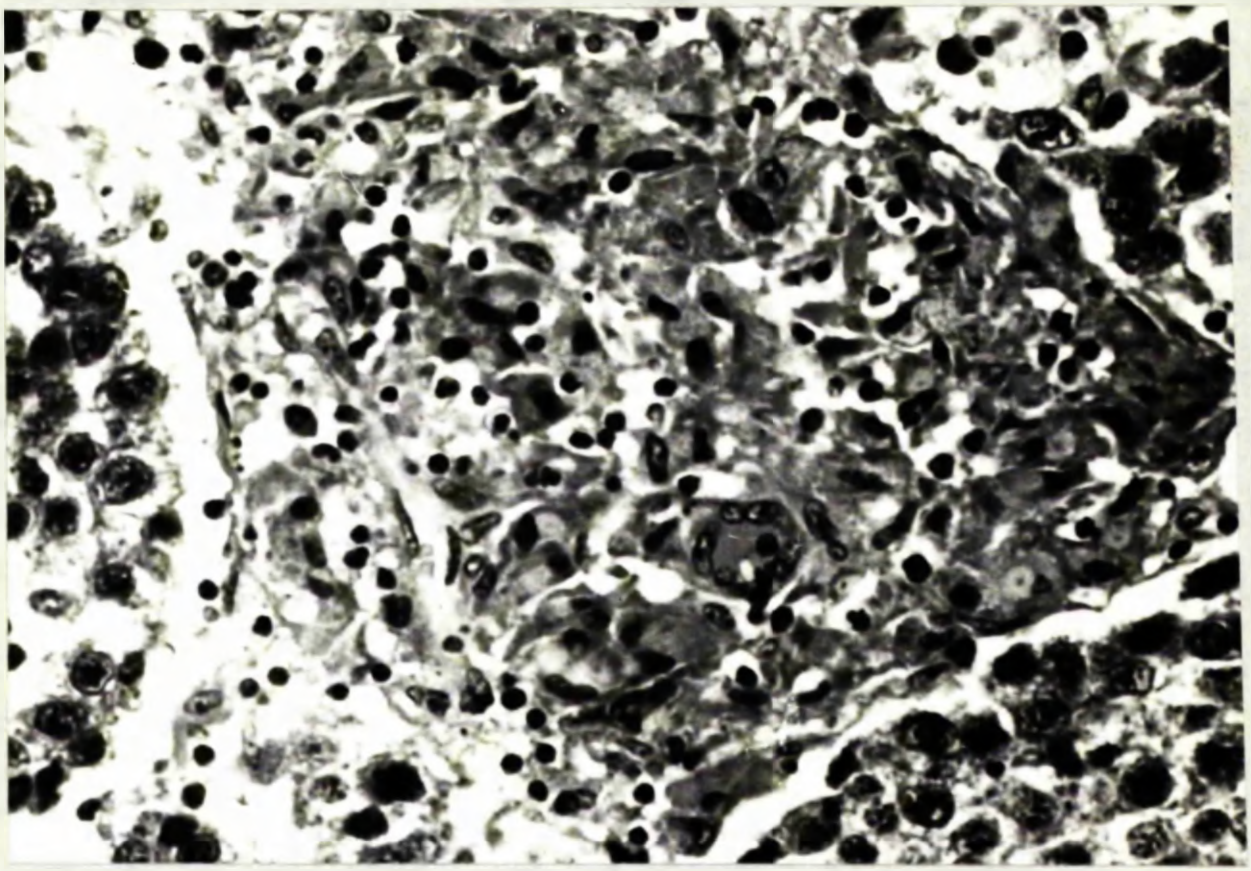


Fig. 10. Tuberculoid focus in seminoma. H & E X 320.

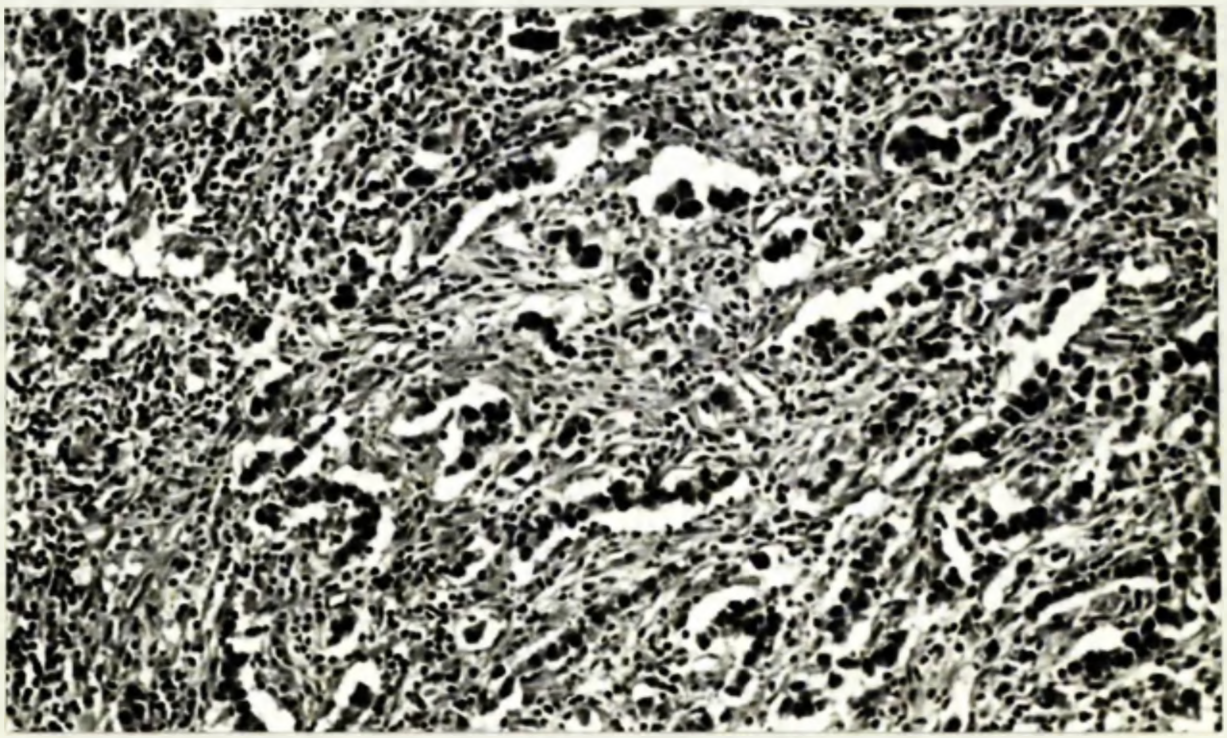


Fig. 11. Fibrous reaction separating strands of tumour cells in seminoma. Note also the diffuse lymphocyte reaction. H & E X 125.

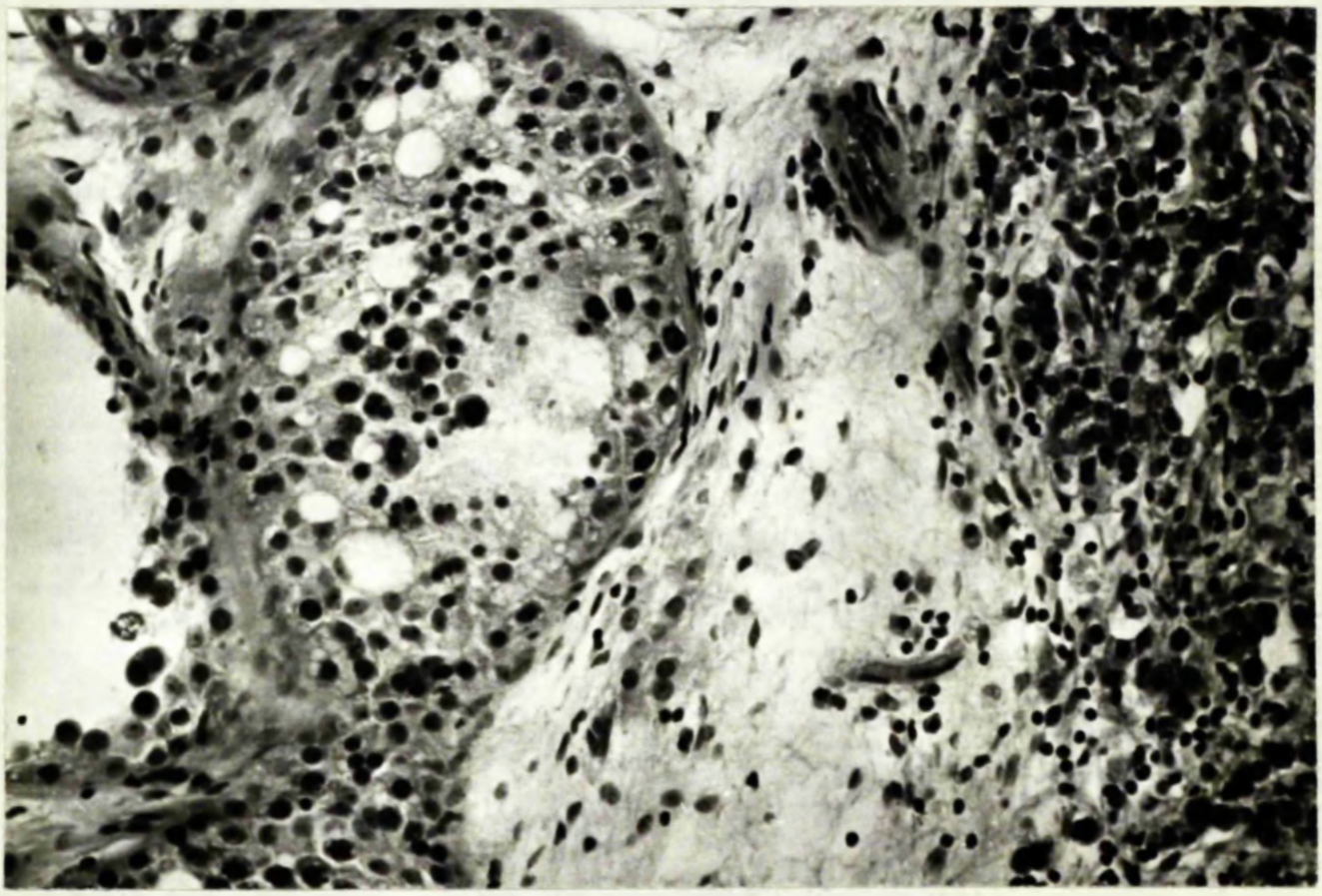


Fig. 12. Edge of human seminoma showing on the left depressed spermatogenesis in a tubule which contains a few large atypical cells. H & E X 320.

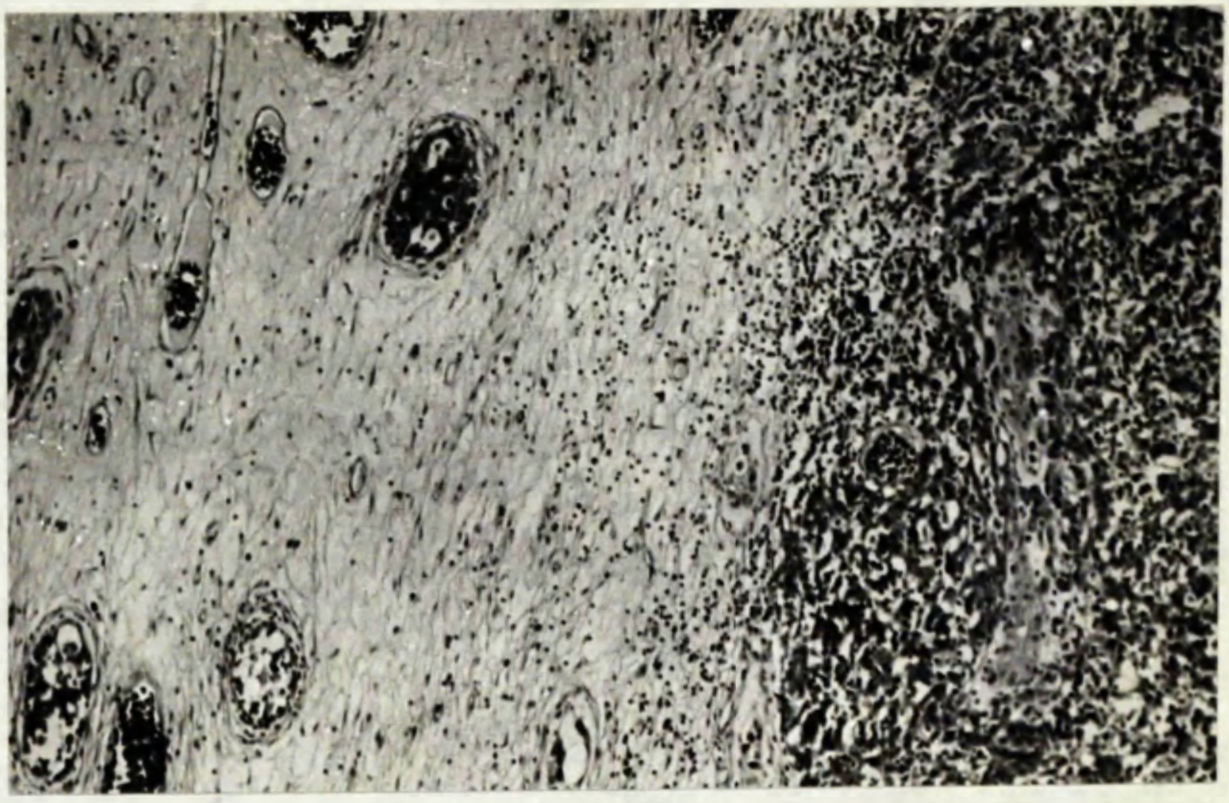


Fig. 13a. The left half of the illustration shows intratubular seminoma in small and atrophic tubules close to a seminomatous nodule. H & E X 125.

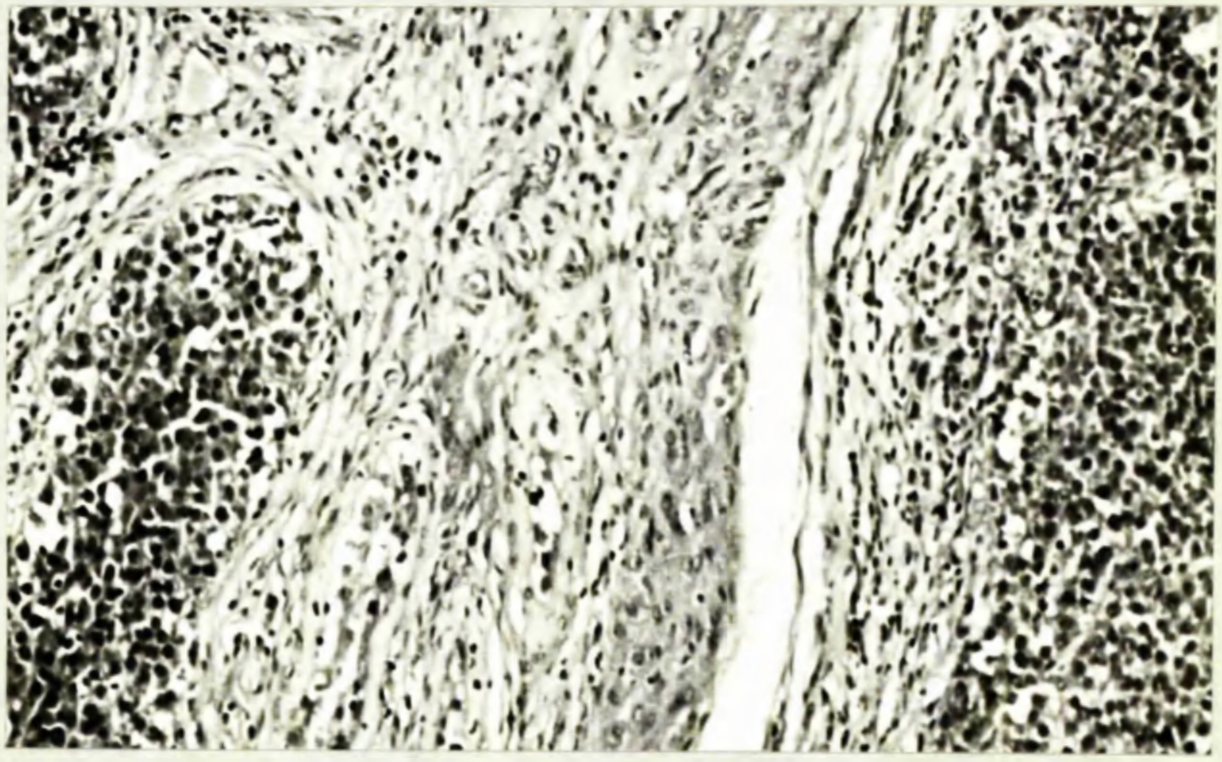


Fig. 13b. Large calibre tubules filled with intratubular seminoma on the left. The edge of a seminoma is on the right. H. & E X 160.

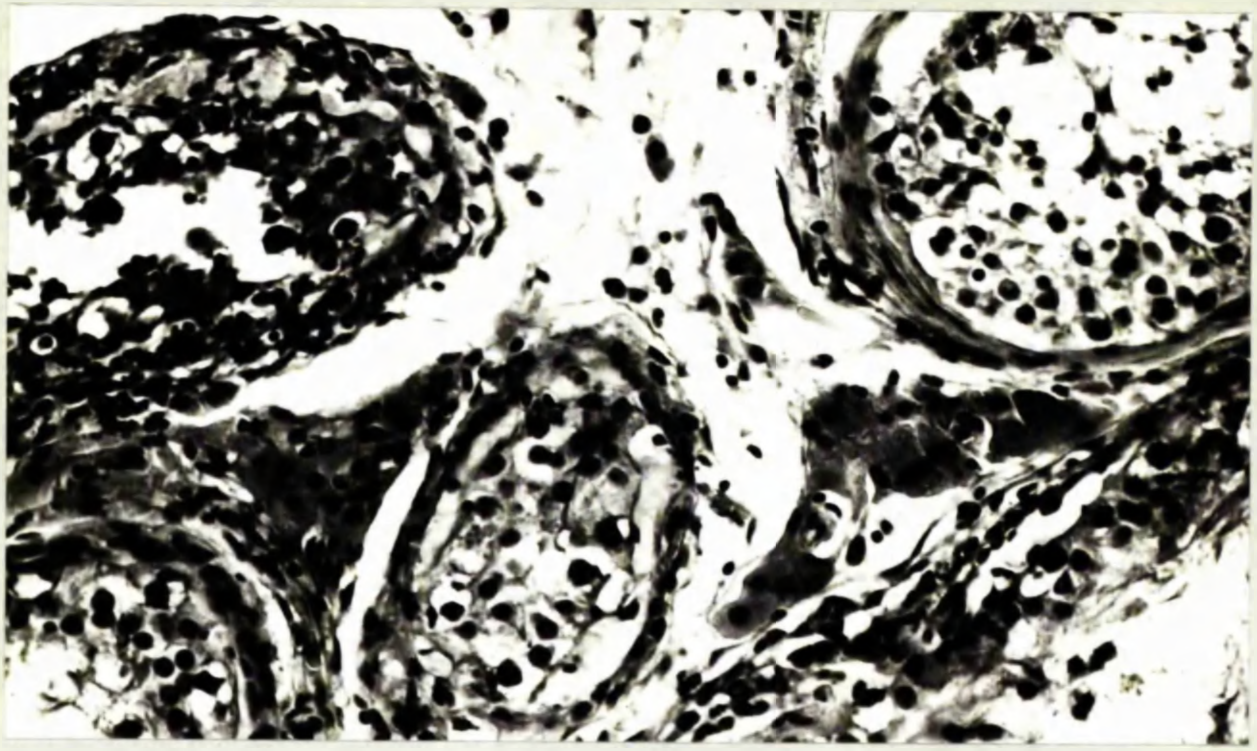


Fig. 14. Seminiferous tubules near a seminoma with at top left lymphocytic infiltration of a tubule containing atypical hyperchromatic cells. H & E X 320.

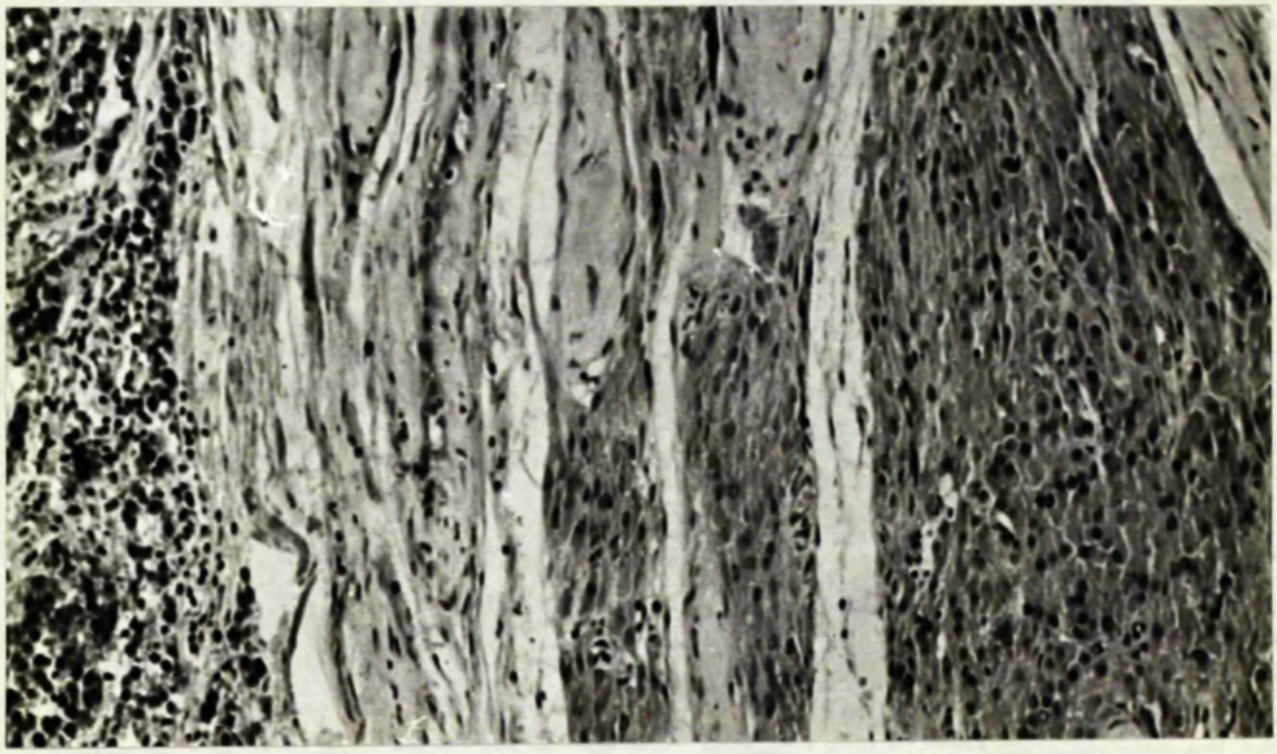


Fig. 15. Nodular proliferation of interstitial cells close to a seminoma, the edge of which is seen on the left. H & E X 125.

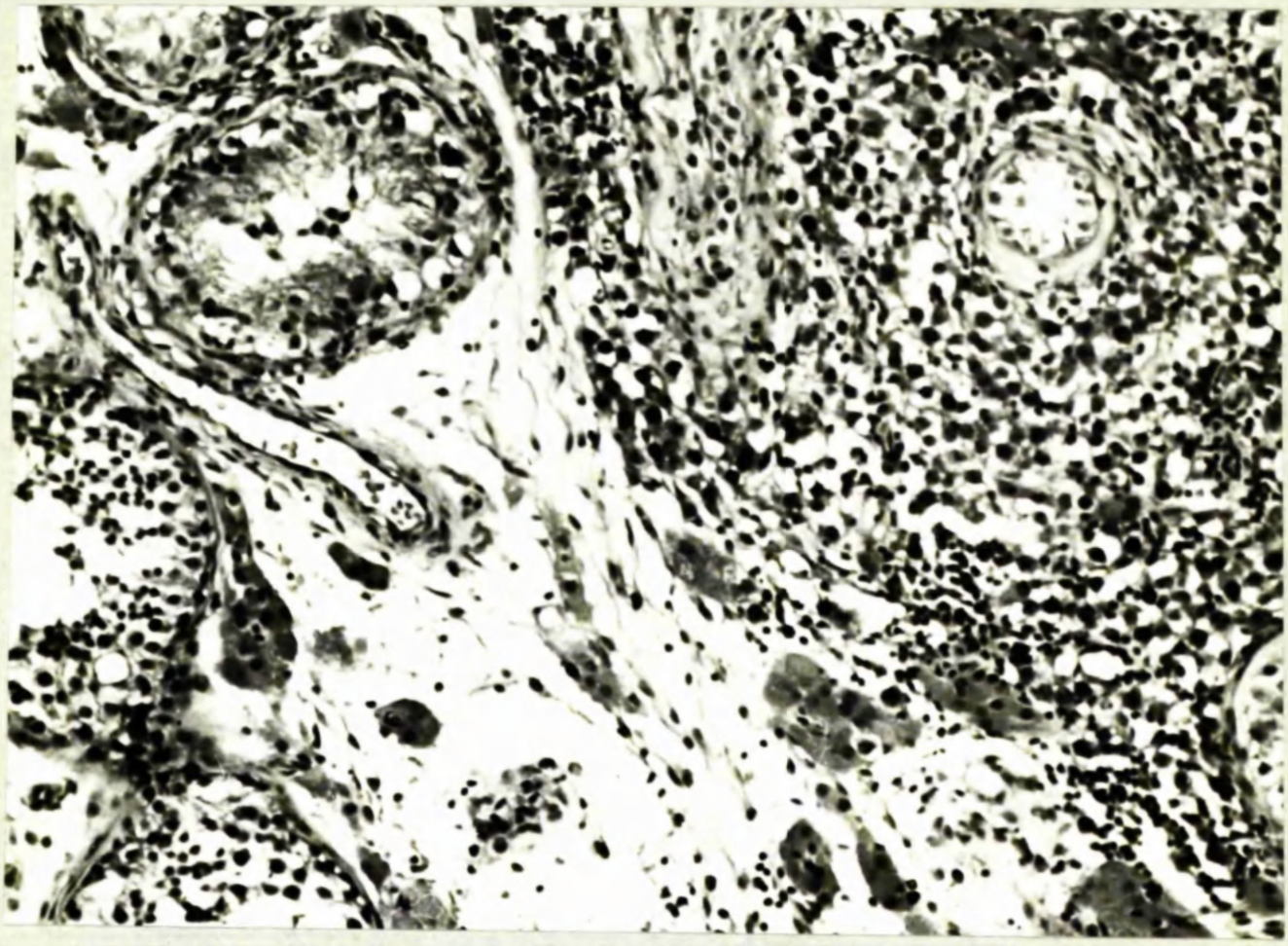


Fig. 16. Intertubular growth at edge of seminoma. Spermatogenesis is seen at the extreme left. H & E X 125.

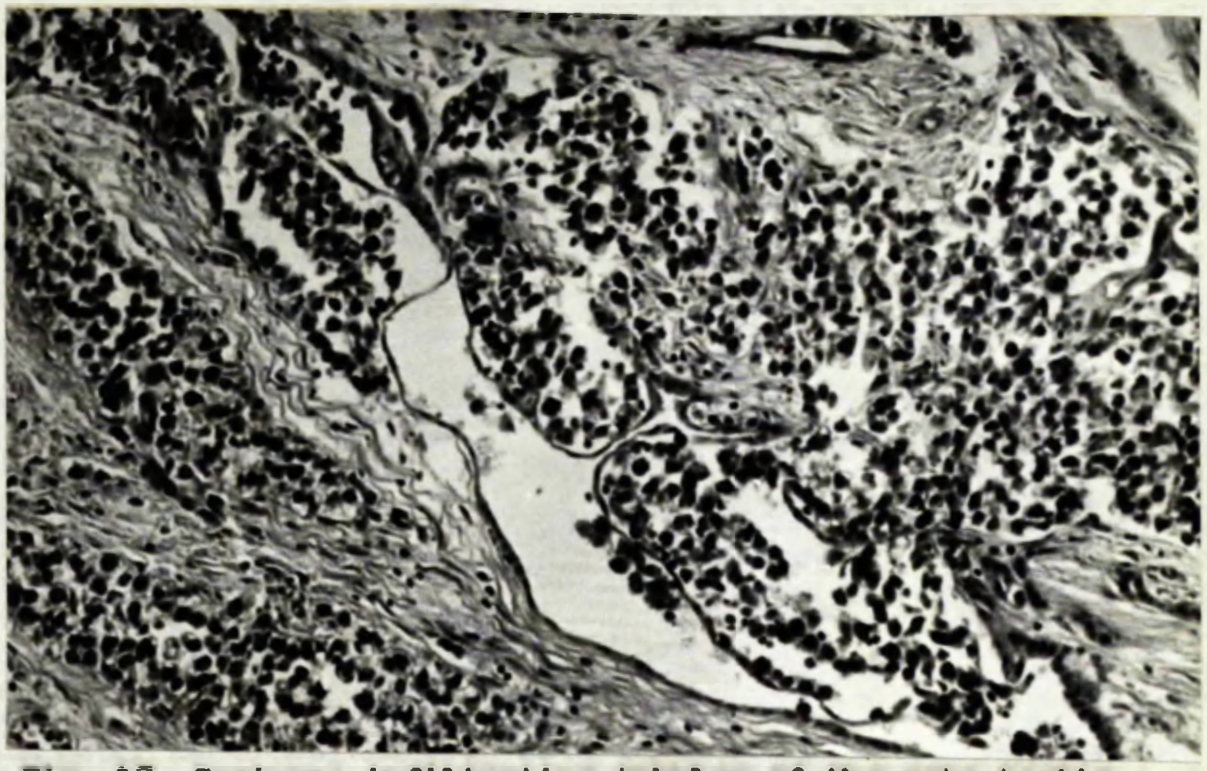


Fig. 17. Seminoma infiltrating tubules of the rete testis. H & E X 125.

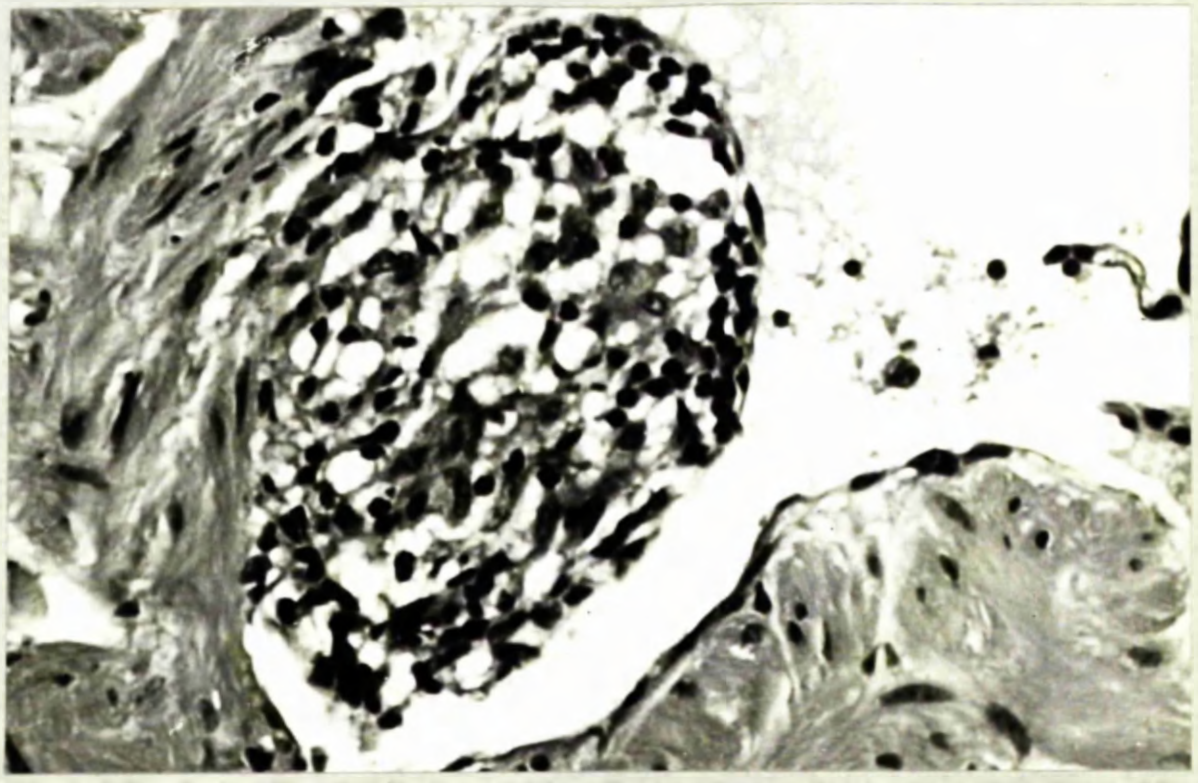


Fig. 18. Intraluminal deposit of seminoma in vein of spermatic cord. H & E X 320.

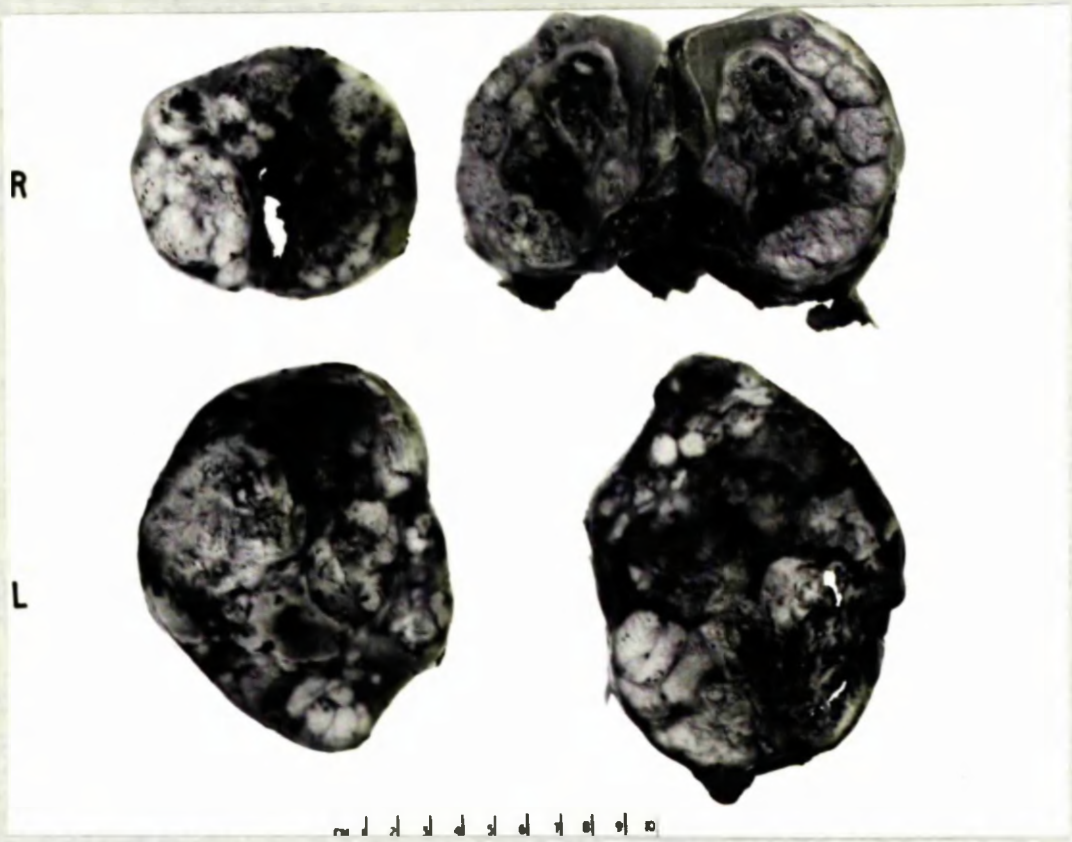


Fig. 19. Multicentric growth of spermatocytic seminoma in both testes.

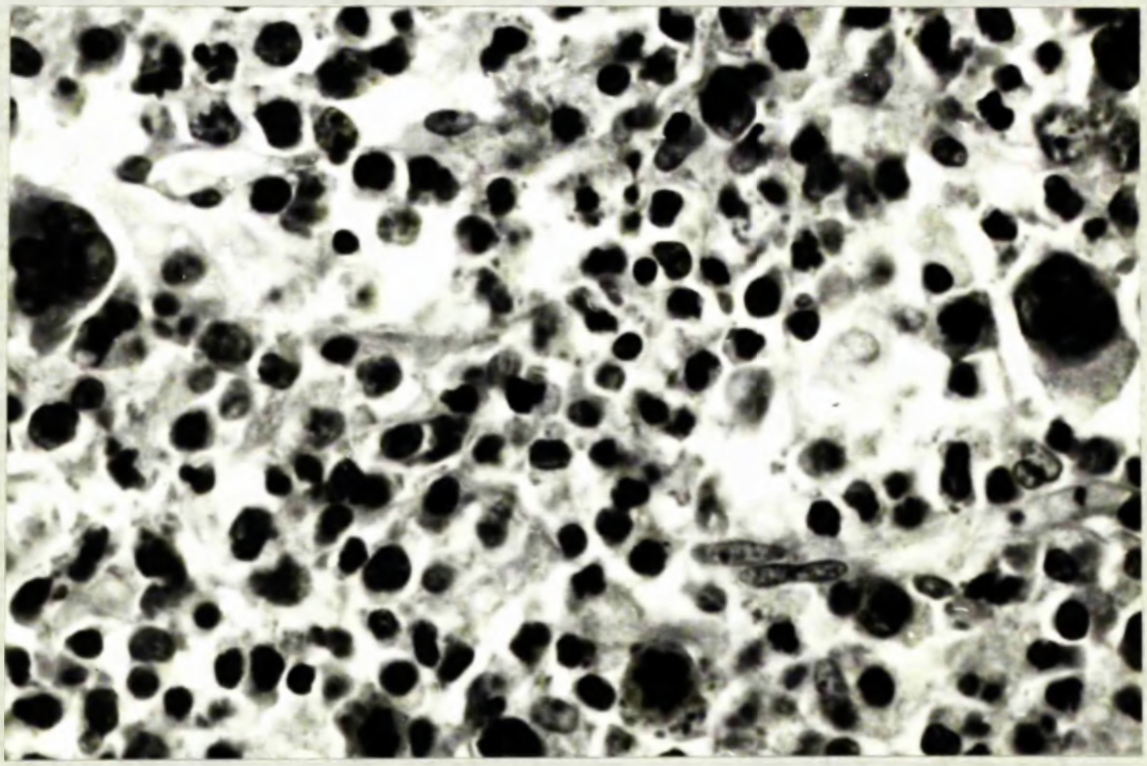


Fig. 20. Spermatocytic seminoma with its typical tumour giant cells containing three or four large central nuclei. H & E X 800.

Fig. 21. Seminomatous deposit in a para-aortic lymph gland. The wall of the inferior vena cava is on the left. H & E X 160.

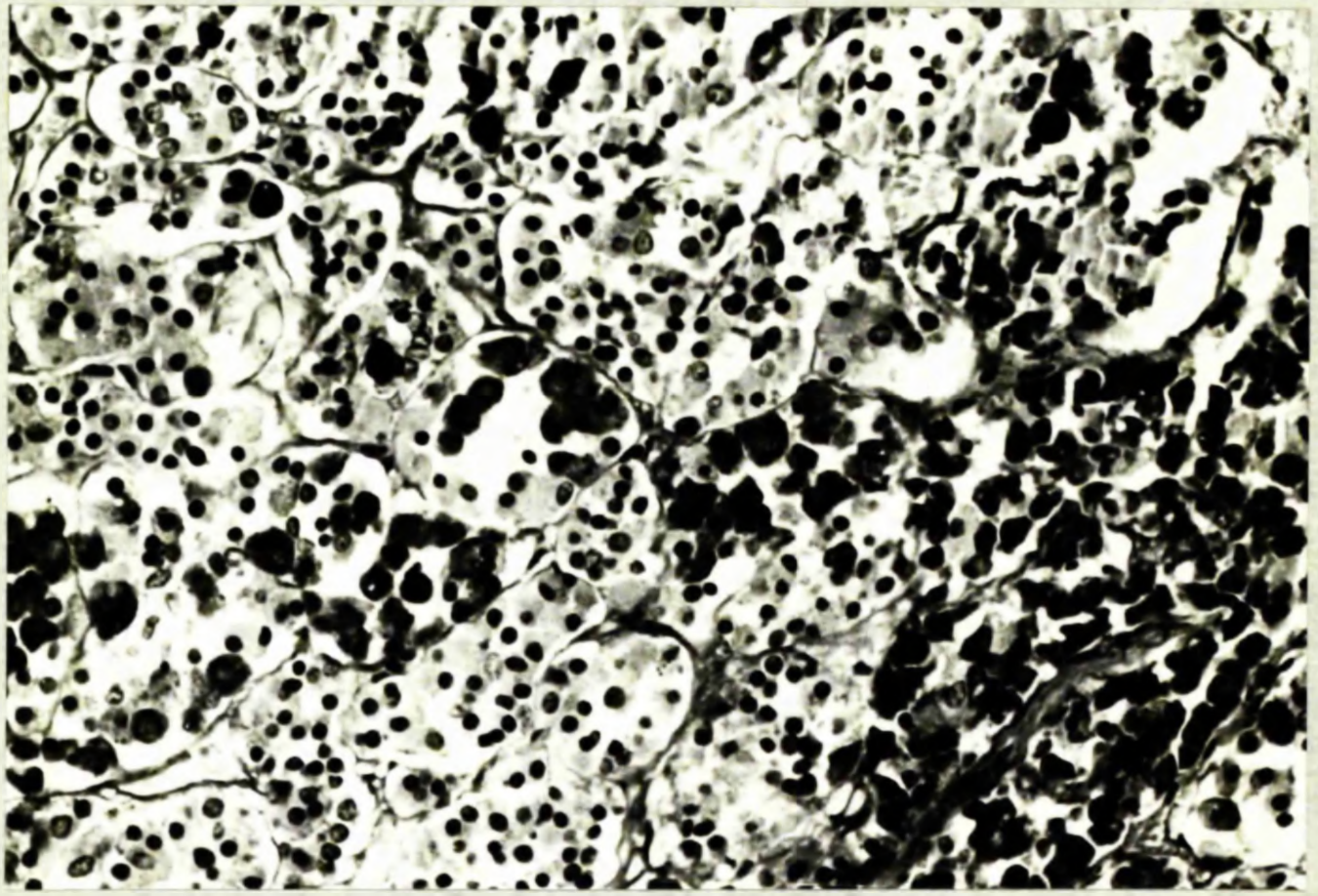


Fig. 22. Section from postero-lateral area of pars distalis of pituitary gland from man aged 53 years. In this usually predominantly alpha cell area the delta cells are markedly increased. They are seen as the dark granular cells in this P.A.S. Orange G preparation. An occasional one shows a vacuole. P.A.S. Orange G X320.

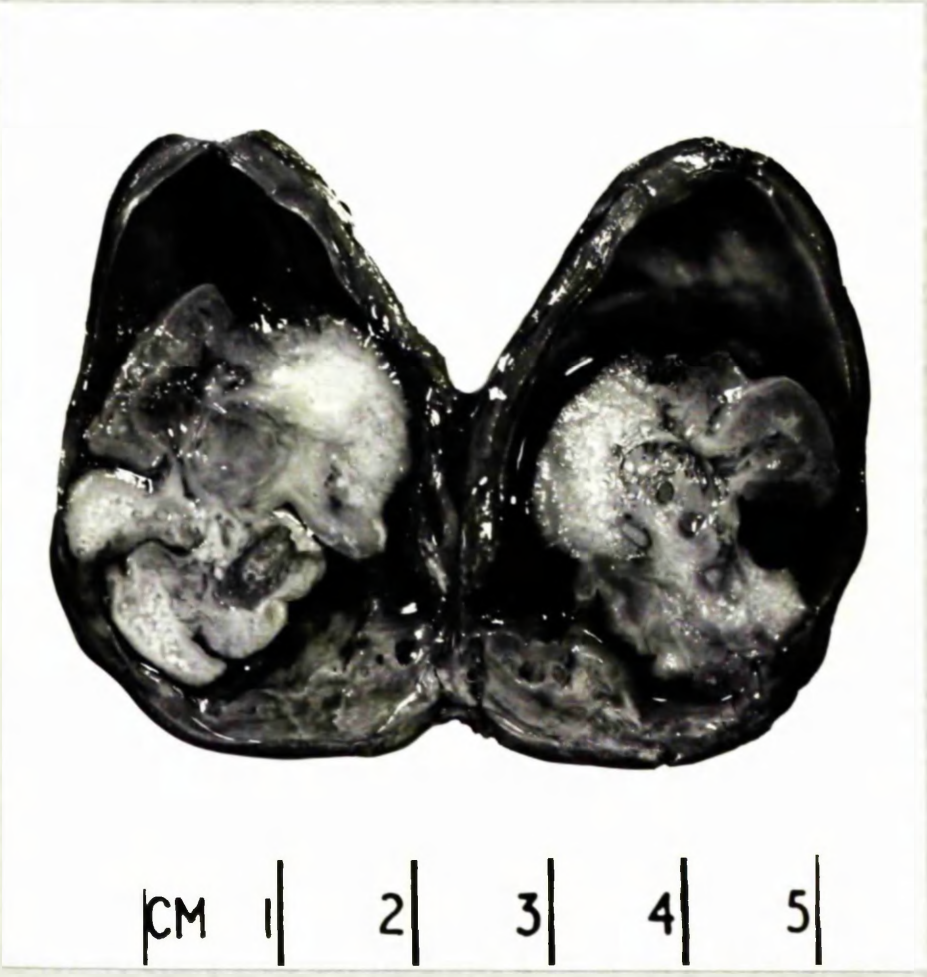


Fig. 23. Bisected teratoma of infant testis. The solid central area is seen to be surrounded by a cystic space. The convoluted tissue at the top of the solid area's lateral border is seen to be cerebral tissue on microscopy. Bone is present in its lower part.

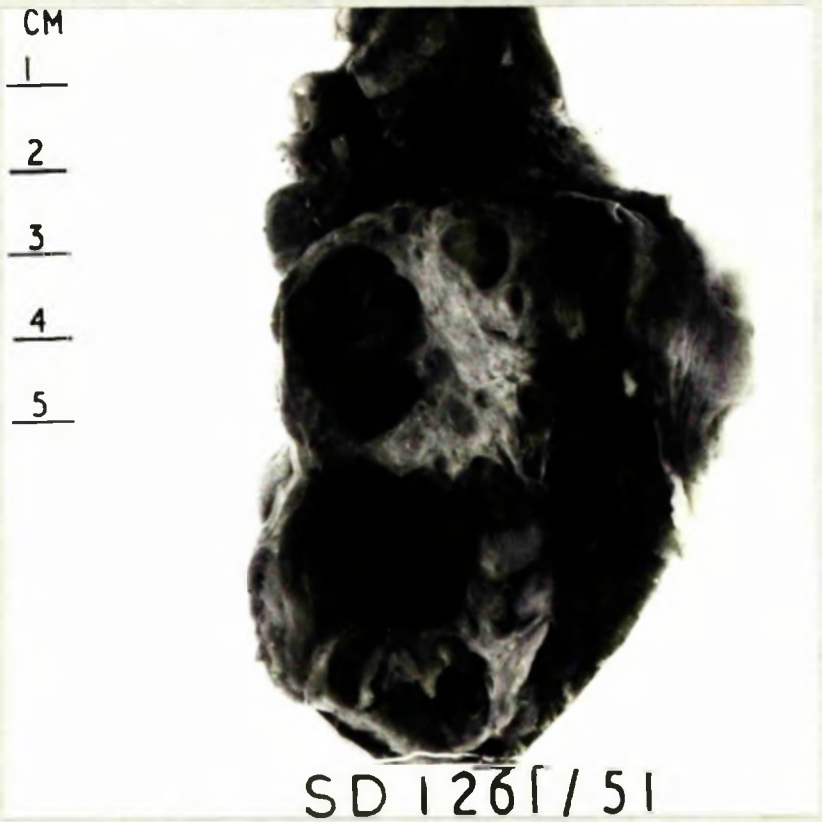


Fig. 24. Partly cystic and partly solid teratoma of human testis. Note varying shapes of the cysts.

Fig. 25. Predominantly solid teratoma with small opaque whitish areas due to keratin in horn cysts.

Fig. 26. An embryonal carcinoma producing little overall enlargement of the testis. The tumour has a whitish appearance with haemorrhage in its subcapsular part.

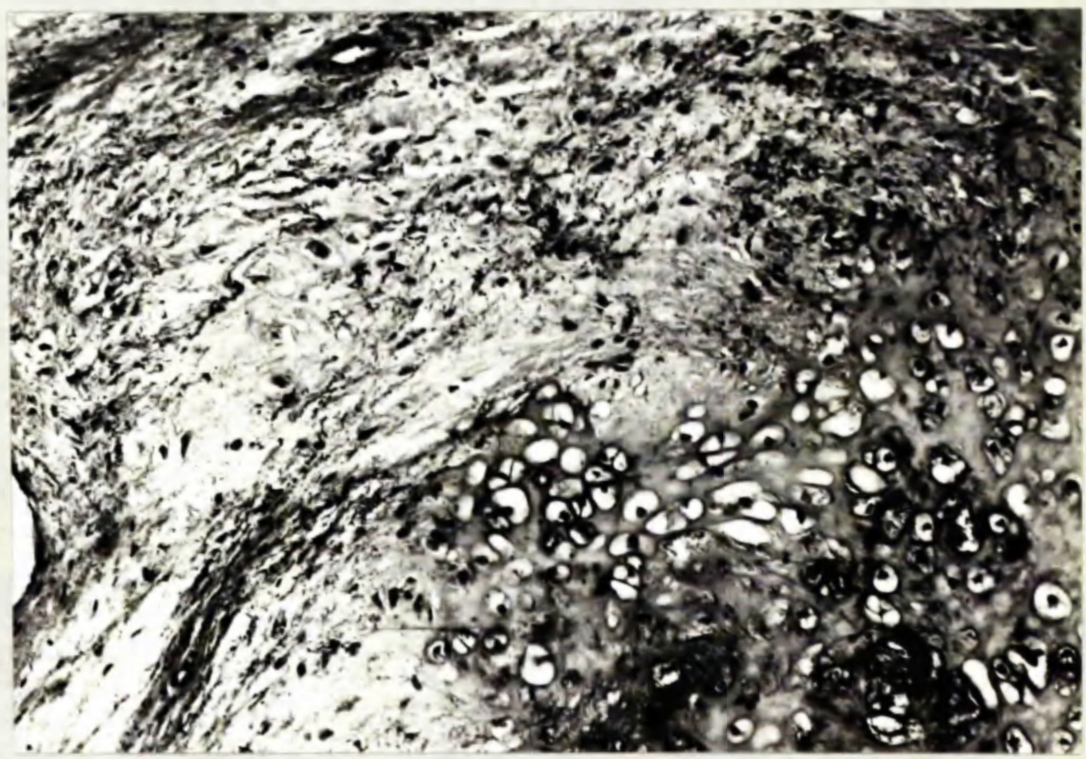


Fig. 27. Neoplastic mesenchyme with developing cartilage at bottom right in a partially differentiated teratoma. H & E X 130.

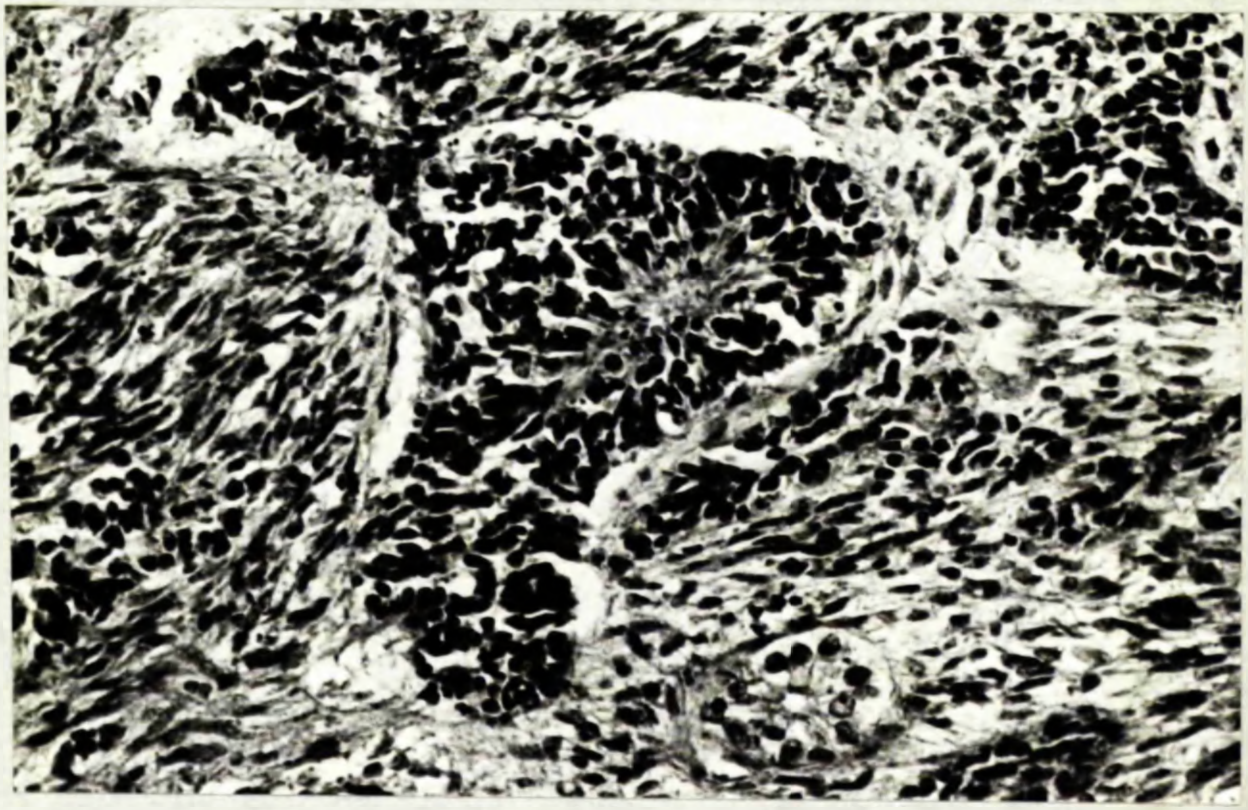


Fig. 28. Cells resembling neuroblasts in rosettes reminiscent of neuroblastoma from a partially differentiated teratoma. H & E X 320.

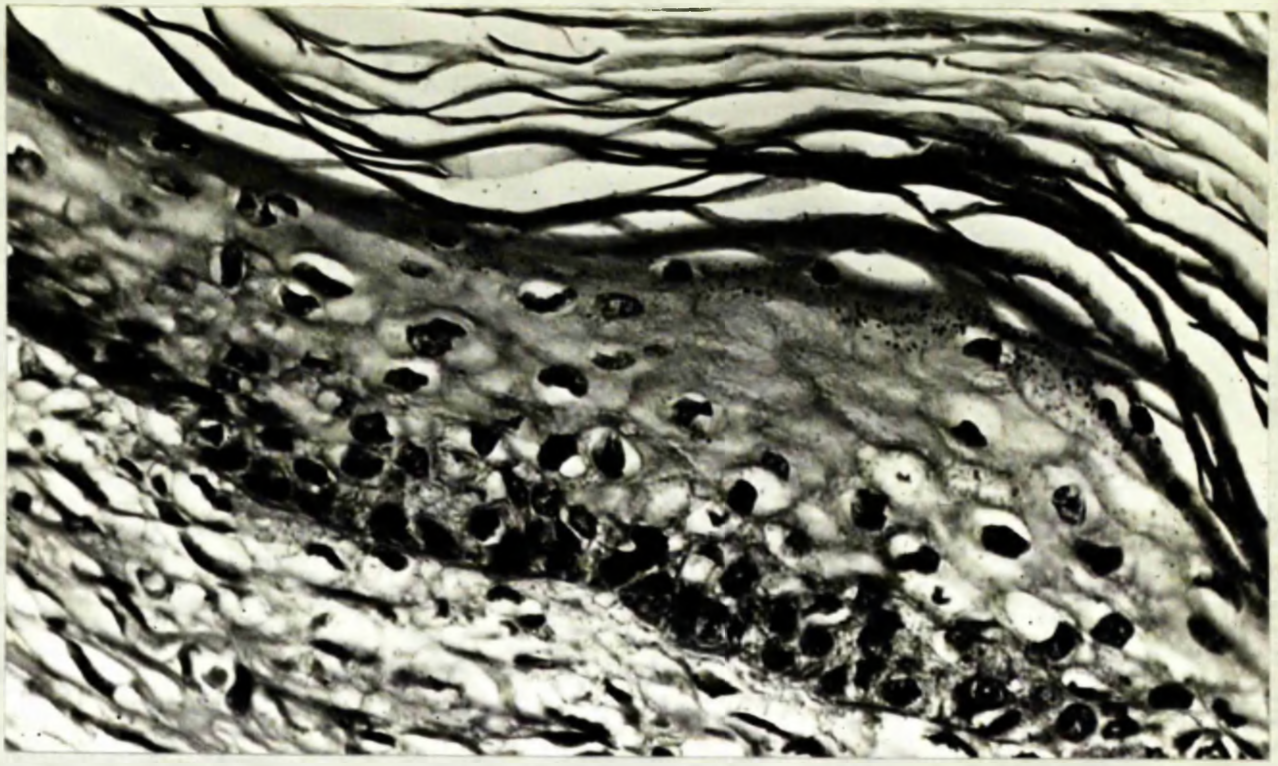


Fig. 29. Well differentiated epidermis from cyst in teratoma of human testis. H & E X 640.

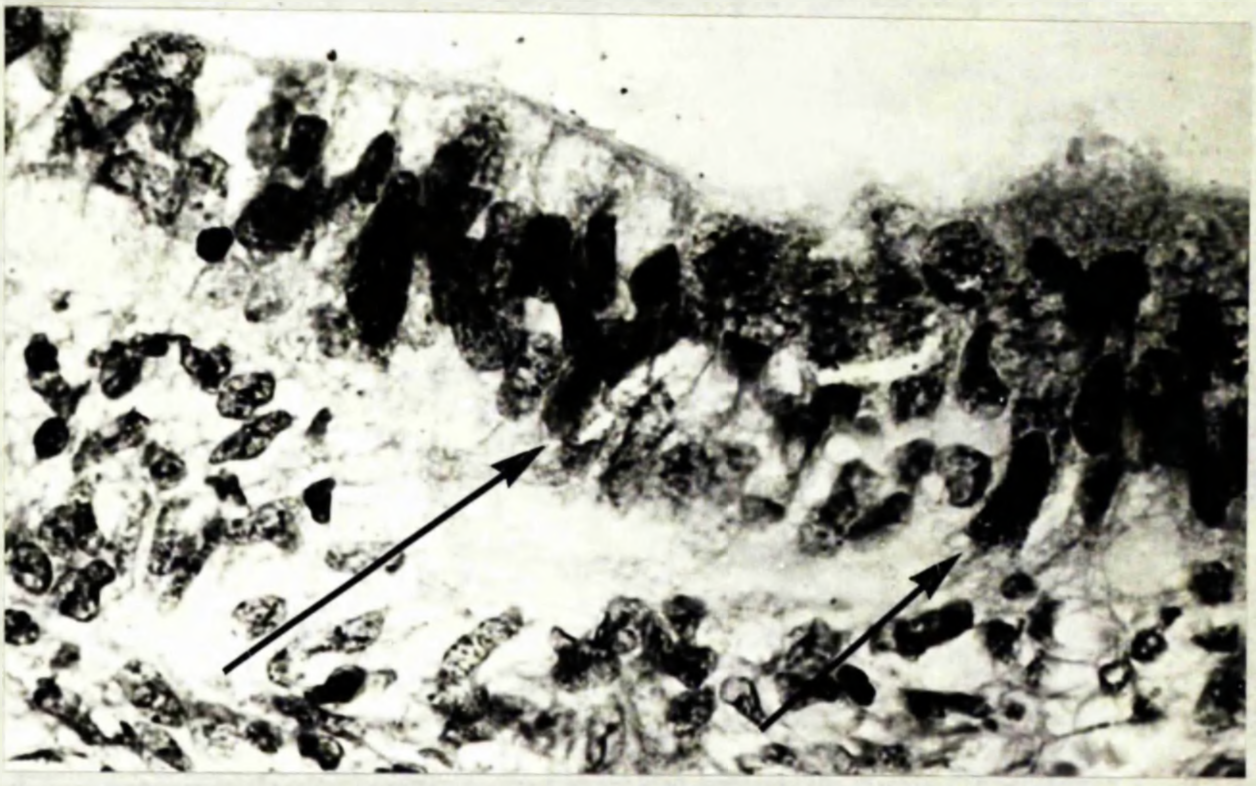


Fig. 30. Intestinal type of epithelium in human testicular teratoma of the partially differentiated variety. Numbers of goblet cells are seen and two argentaffin cells showing granules are indicated by arrows. Alkaline diazonium method. X 800.

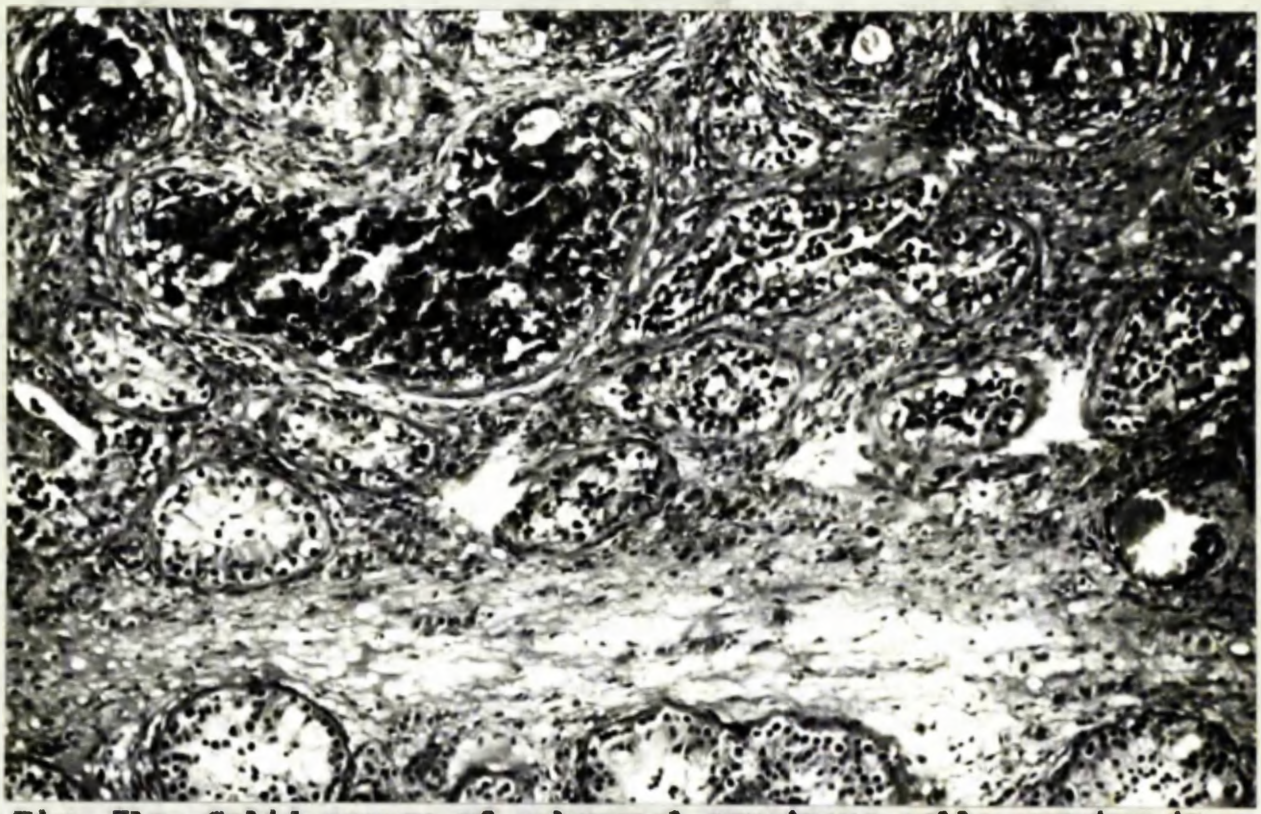


Fig. 31a. Solid masses of embryonal carcinoma cells growing in seminiferous tubules in upper part of picture. H & E X 125.

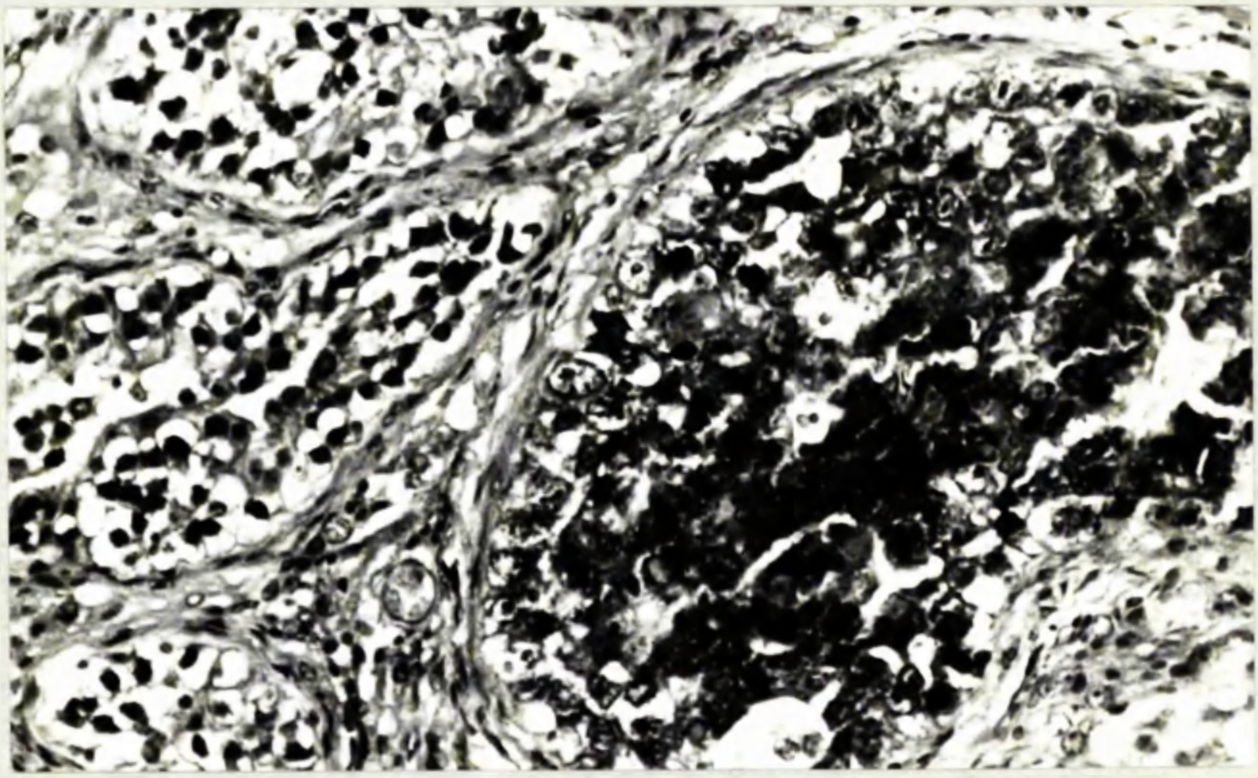


Fig. 31b. High power view of embryonal carcinoma depicted in Fig. 30. Here the embryonal carcinoma fills seminiferous tubules on the right. The tubules on the left show intratubular seminoma. H & E X 290.

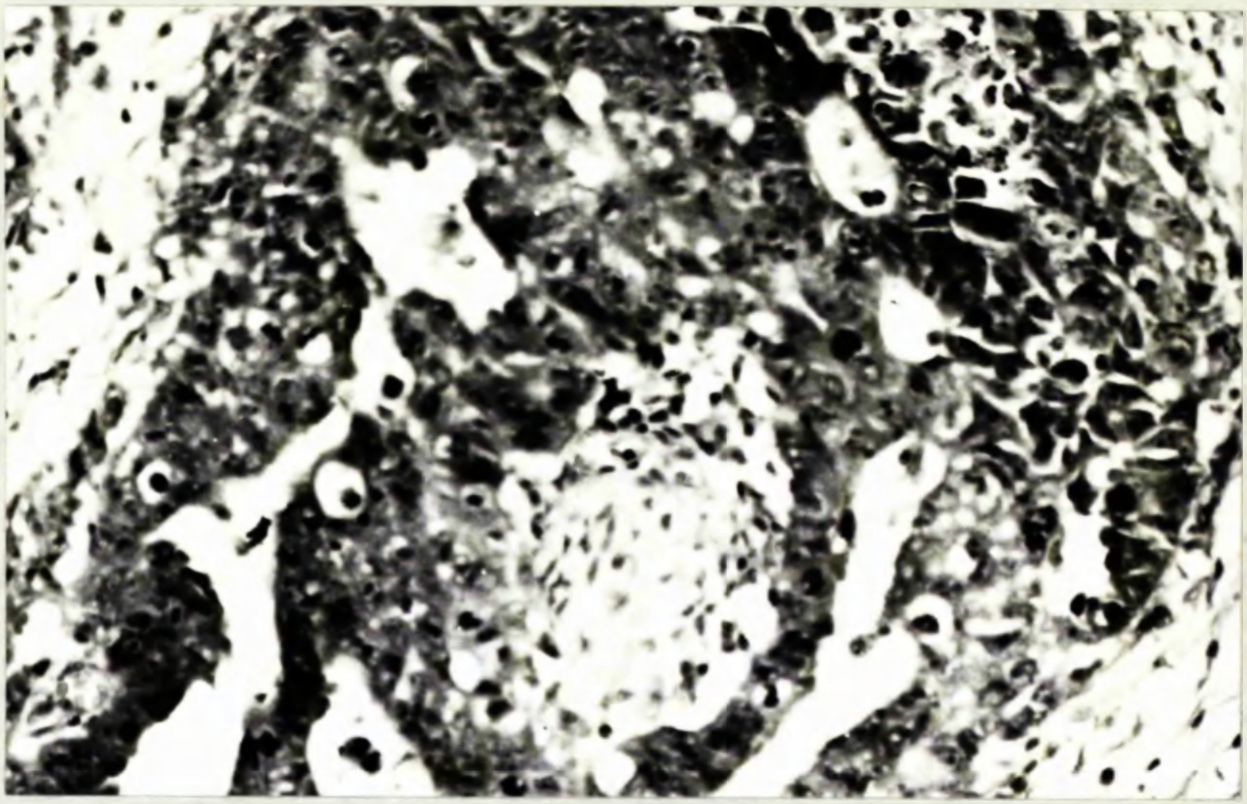


Fig. 32. Cleft formation in embryonal carcinoma. H & E X 320.

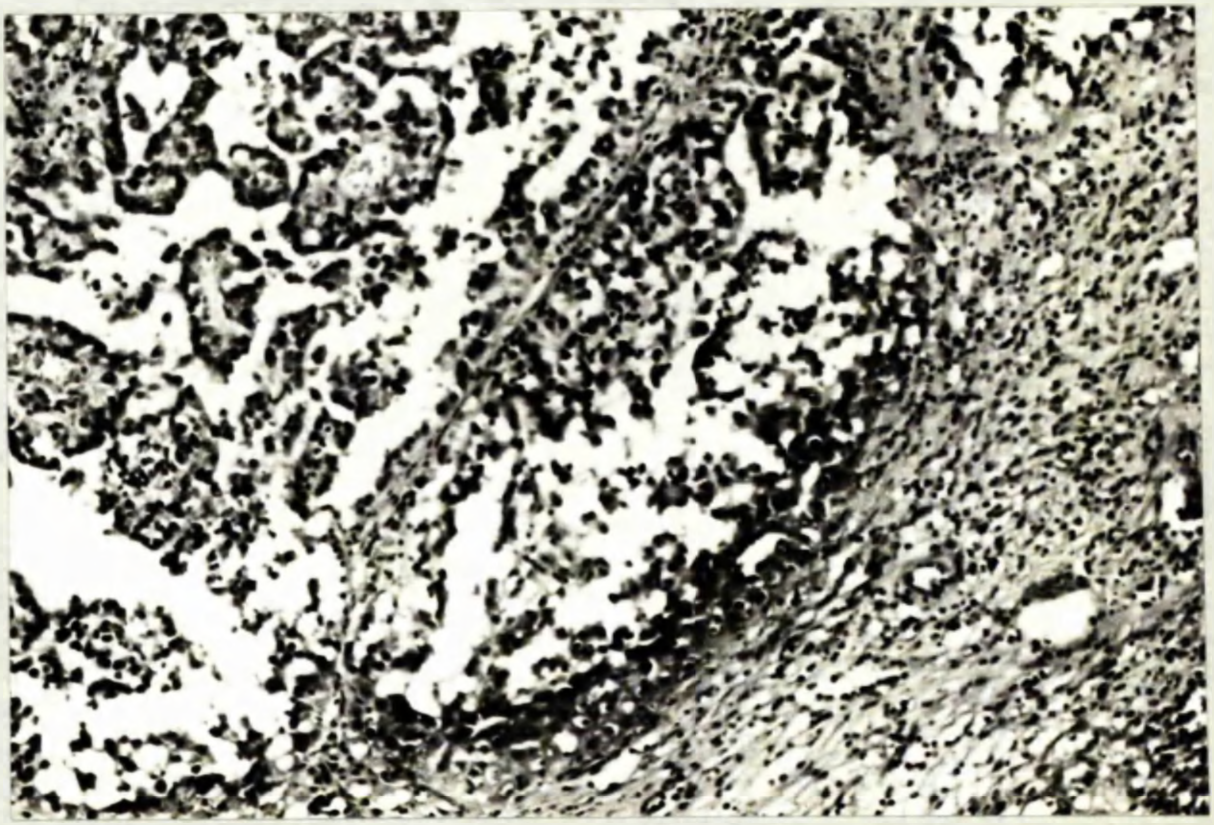


Fig. 33. A papillary part of an embryonal carcinoma. H & E 125.

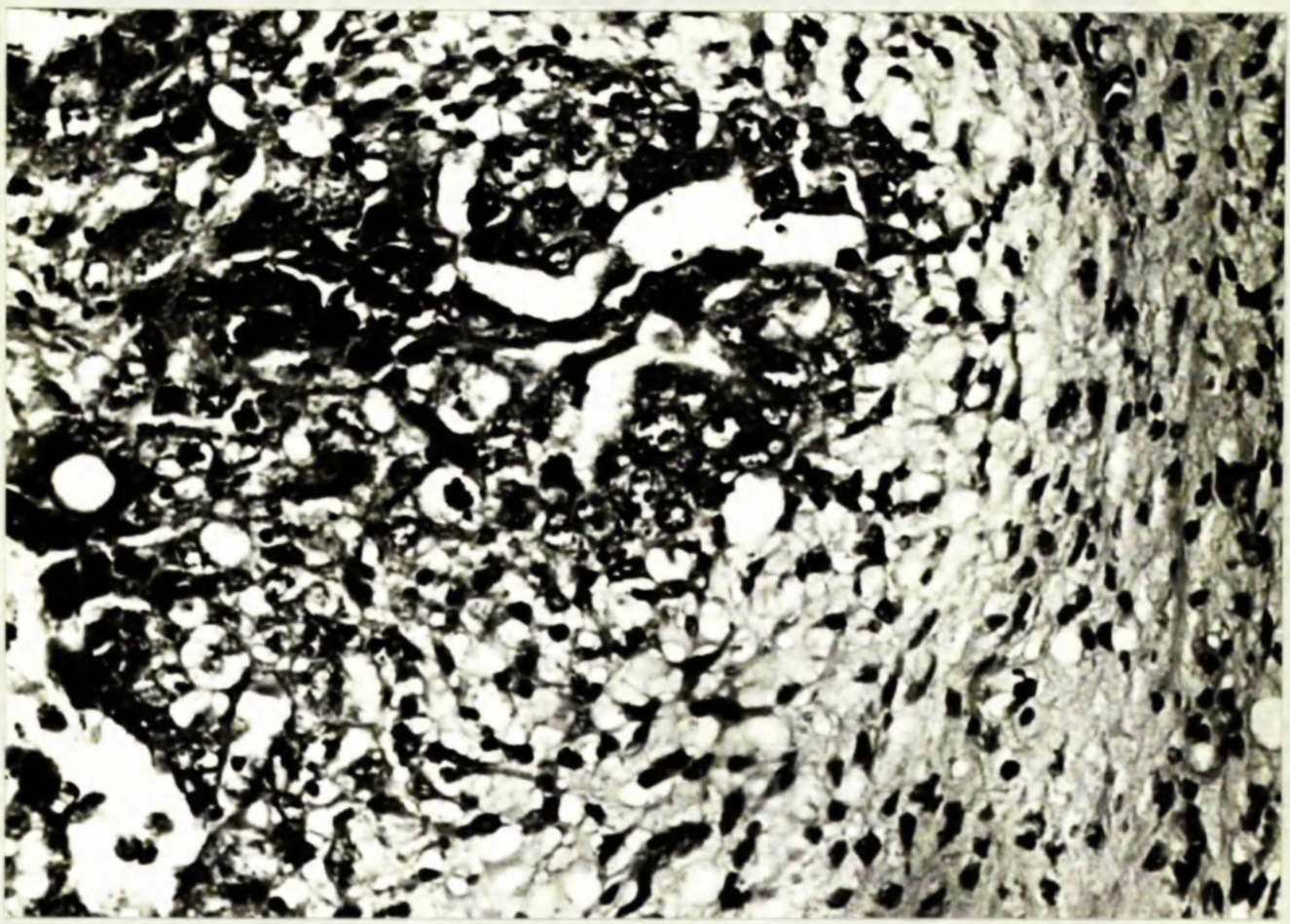


Fig. 34. Embryonal carcinoma + teratoma. The left of the picture shows embryonal carcinoma with tubule formation while on the right there is developing mesenchyme. H & E X 320.

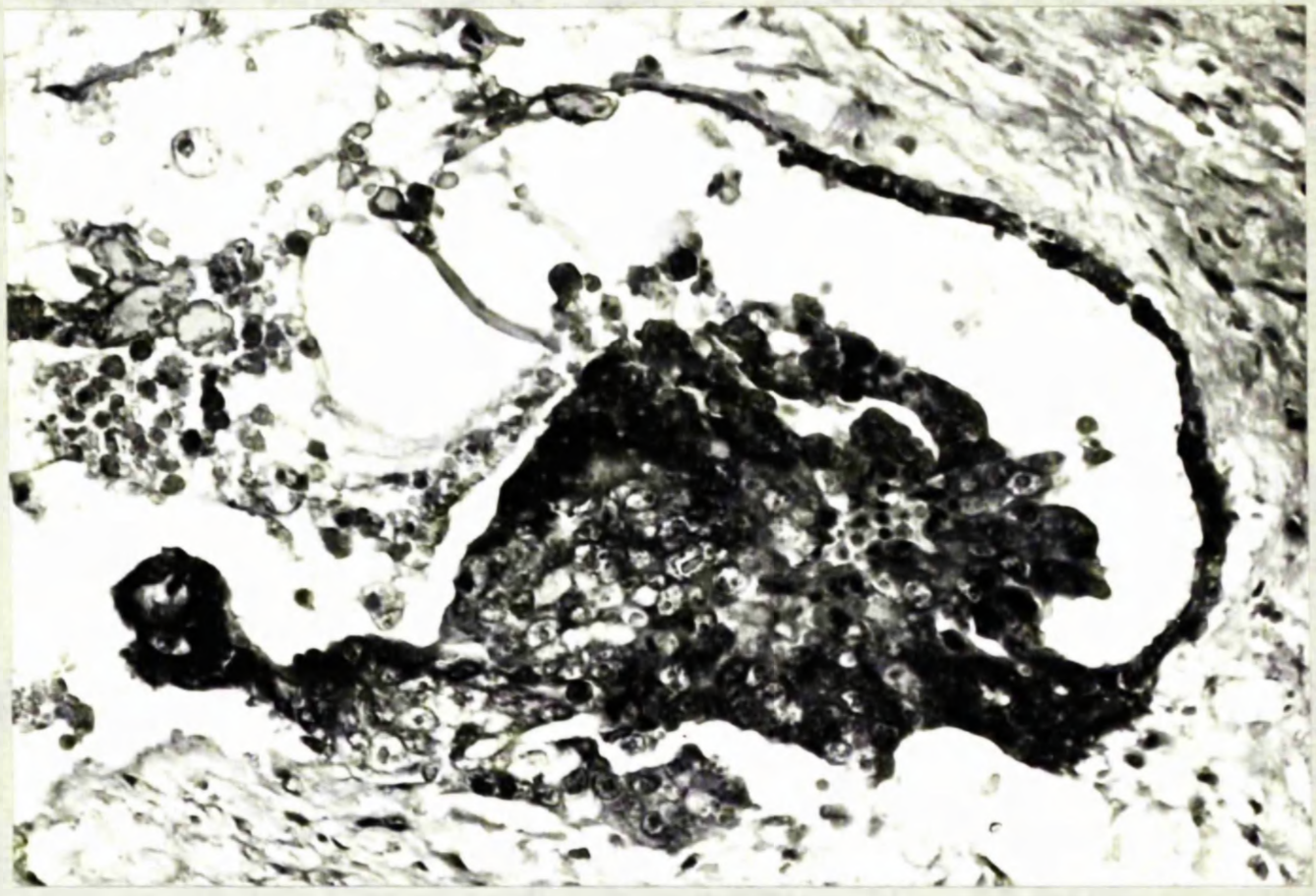


Fig. 35. "Embryoid body" resembling the human blastocyst in embryonal carcinoma of the testis. Note the large central mass of cells attached like an inner cell mass to one pole of the blastocyst-like structure, which is lined by large trophoblastic cells. A few floating cells are seen in the cavity. The early stages of a cavity are seen near the centre of the cell mass, where the amniotic cavity would be expected. H & E X 320.

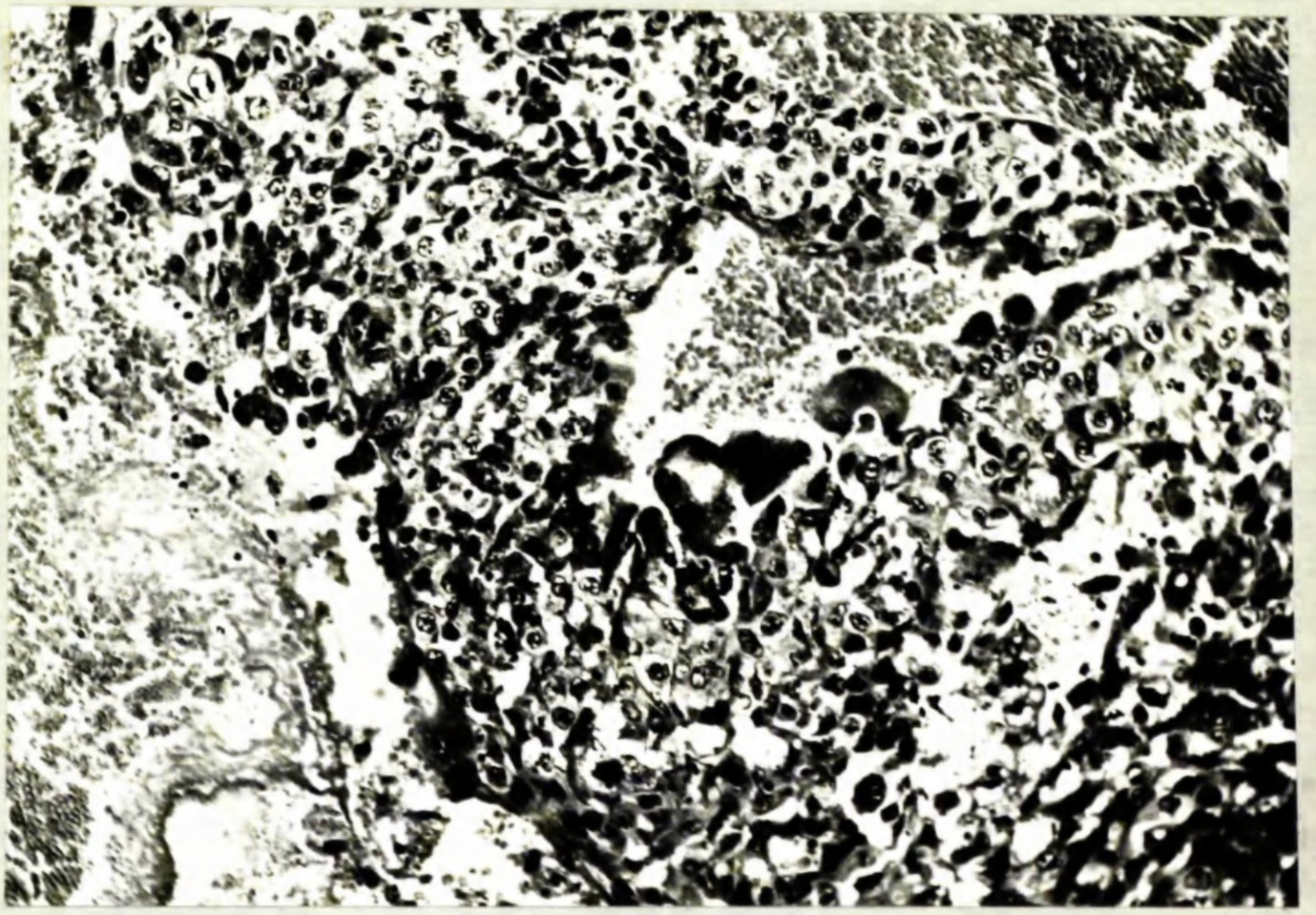


Fig. 36. Section of chorionepithelioma of the testis. The blood spaces are lined by cells resembling syncytiotrophoblast and outside these are large clear cells resembling the cytotrophoblast of the normal chorion. H & E 280.

Fig. 37. T.W. aged 41 years. Tumour of the teratoma group with haemorrhagic areas of chorionepithelioma.

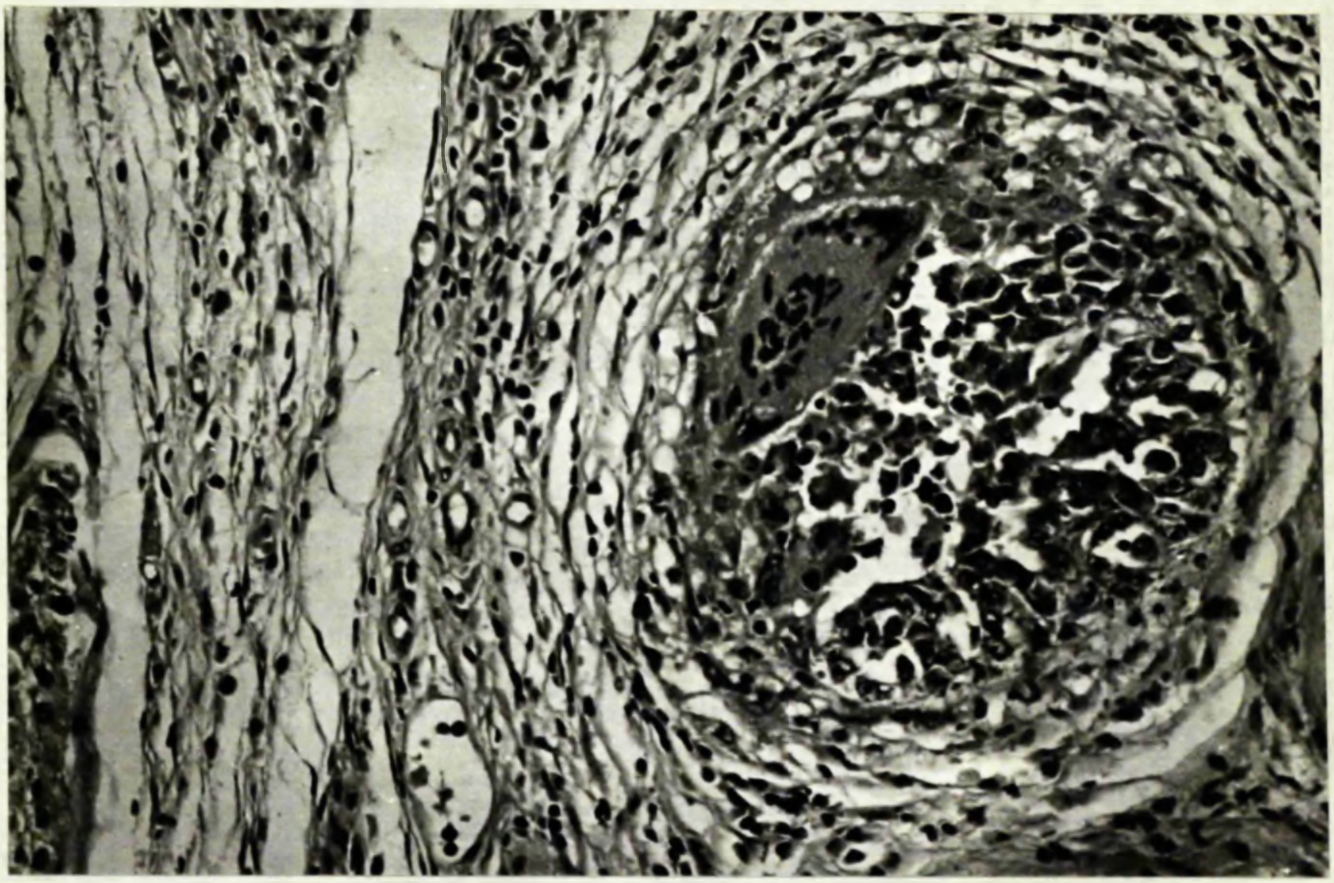


Fig. 38. Large multinucleated giant cell with both central and peripheral nuclei in wall of seminiferous tubule containing embryonal carcinoma. H & E X 300.

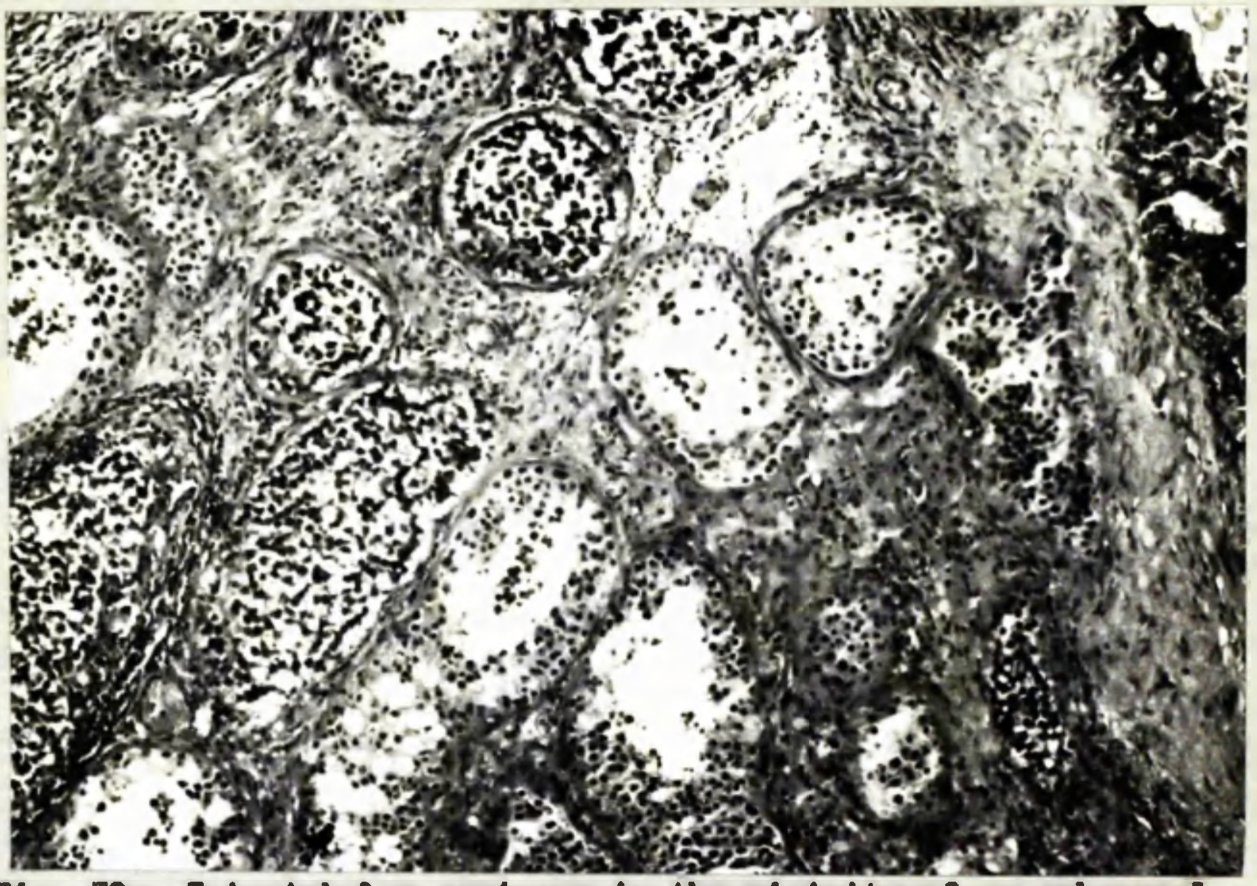


Fig. 39a. Intratubular seminoma in the vicinity of an embryonal carcinoma is seen in cross sections of a tubule extending from bottom left to the top middle of the photograph. H & E X 125.

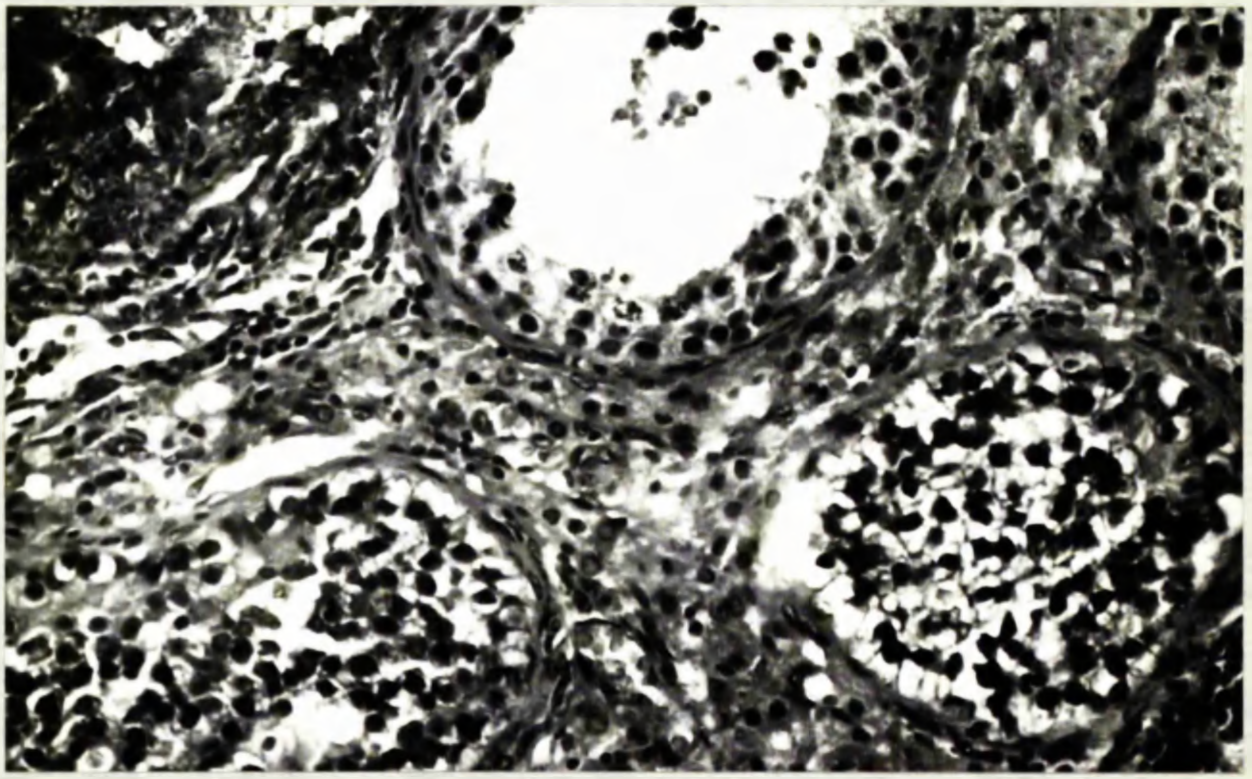


Fig. 39b. High power view of intratubular seminoma illustrated in Fig. 39a. The embryonal carcinoma is seen top left, intratubular seminoma at the bottom and some atrophy of the spermatogenic elements in tubule at top centre and right. H & E X 288.

Fig. 40. Diffuse nodular thickening of the gastric mucosa due to infiltration by metastatic embryonal carcinoma of the testis. X ½.

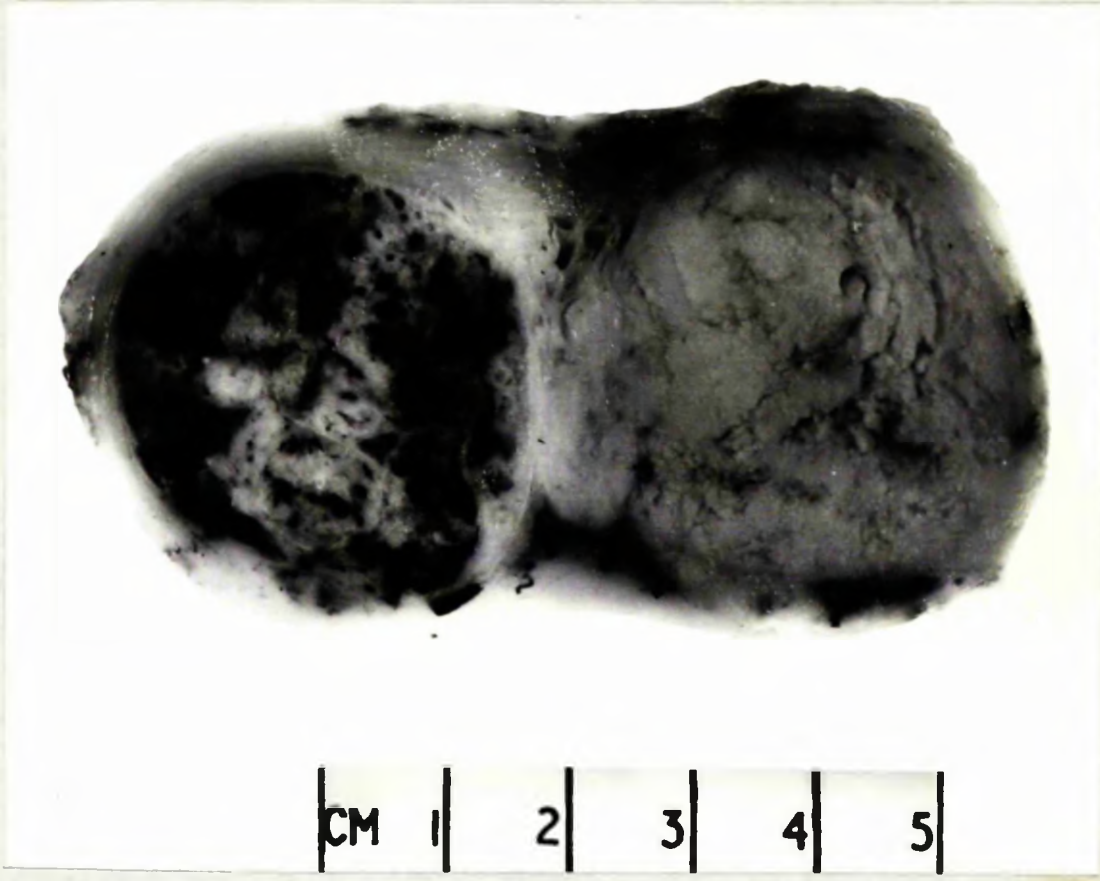


Fig. 41. Co-existant teratoma and seminoma. The partly solid and partly cystic tumour of the teratoma group on the left is clearly separated from the solid white seminoma on the right.

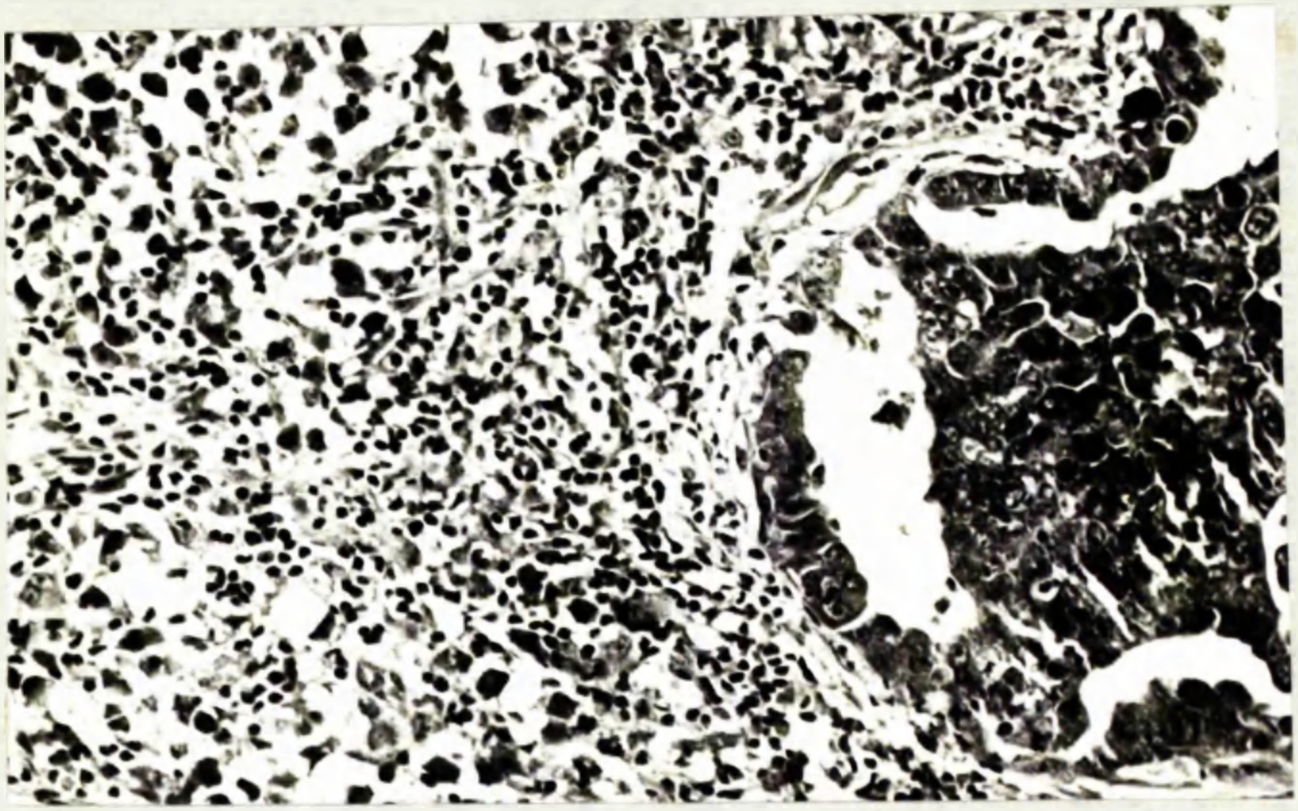


Fig. 42. Invasion of seminoma on the left by embryonal carcinoma on the right. H & E X 320.

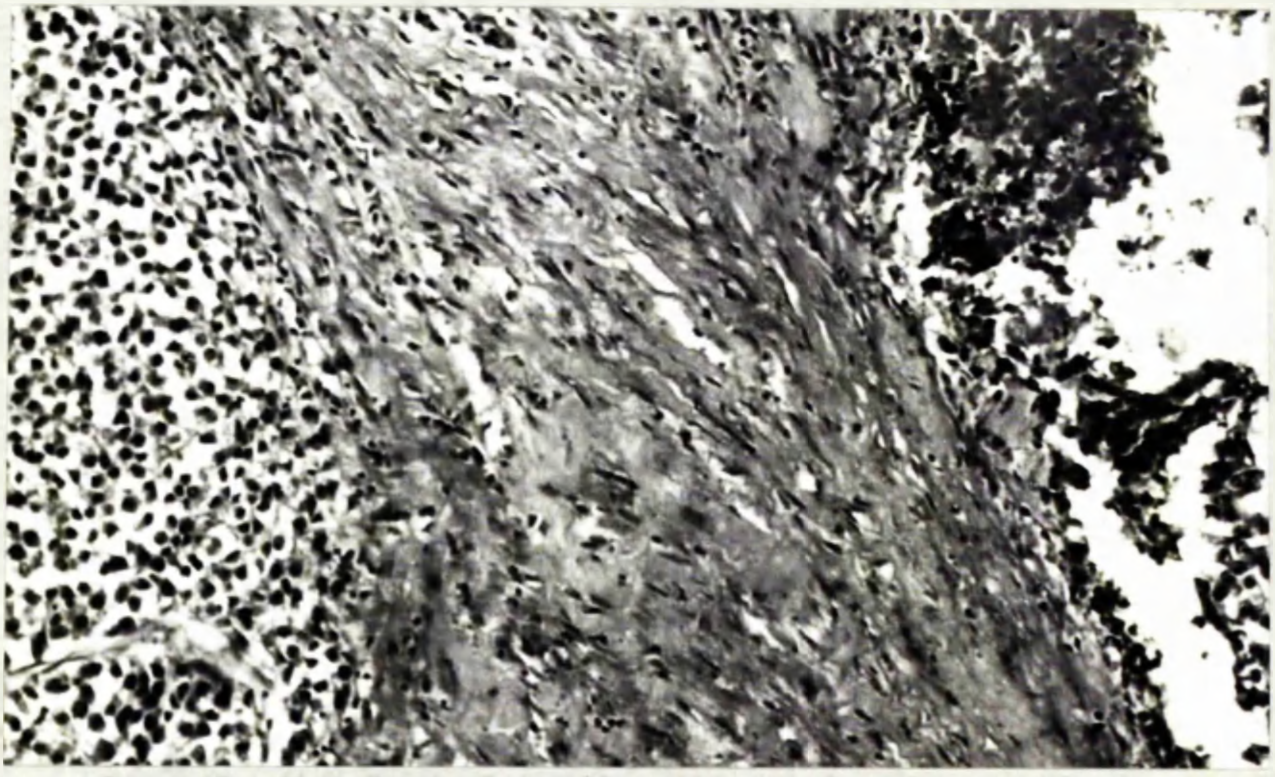


Fig. 43. Histological section through boundary zone between seminoma on the left and embryonal carcinoma on the right. H & E X 125.

Fig. 44. The uniform whitish appearance of a testis enlarged and replaced by reticulin cell sarcoma. 7/5

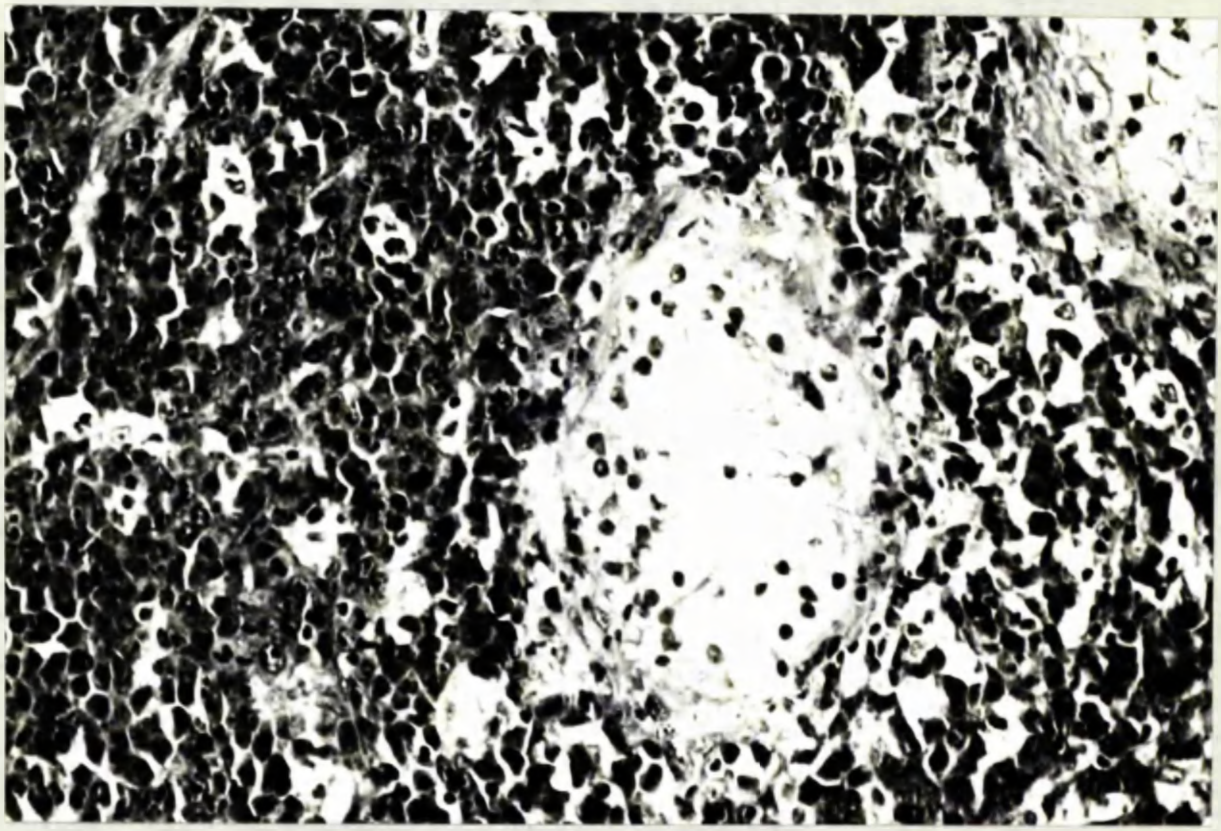


Fig. 45. Intertubular growth of reticulum cell sarcoma in the human testis. H & E X 320.

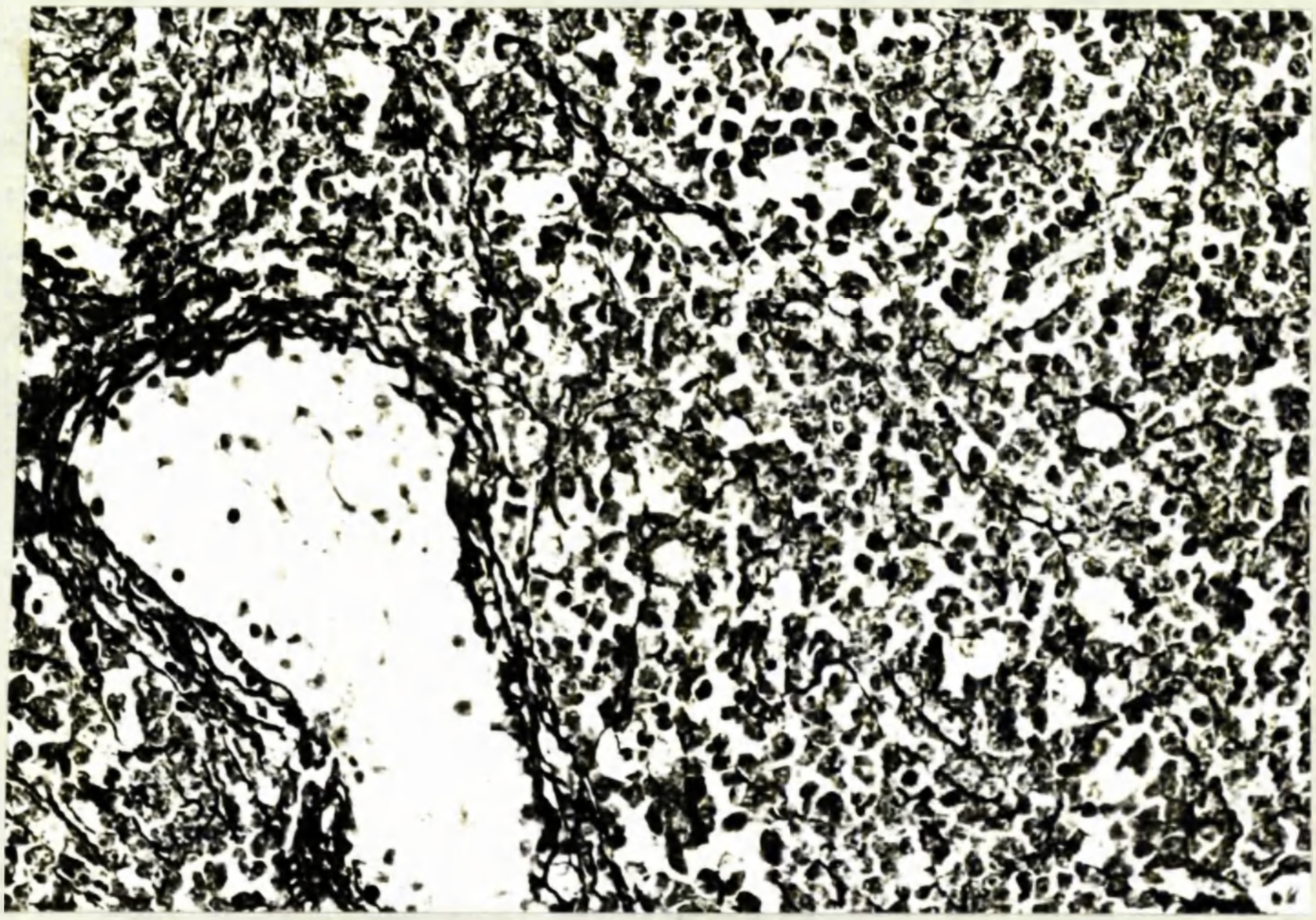


Fig. 46. The branching reticulin pattern of reticulum cell sarcoma. A seminiferous tubule is present on the left of the picture. Gordon and Sweet's reticulin stain X 320.

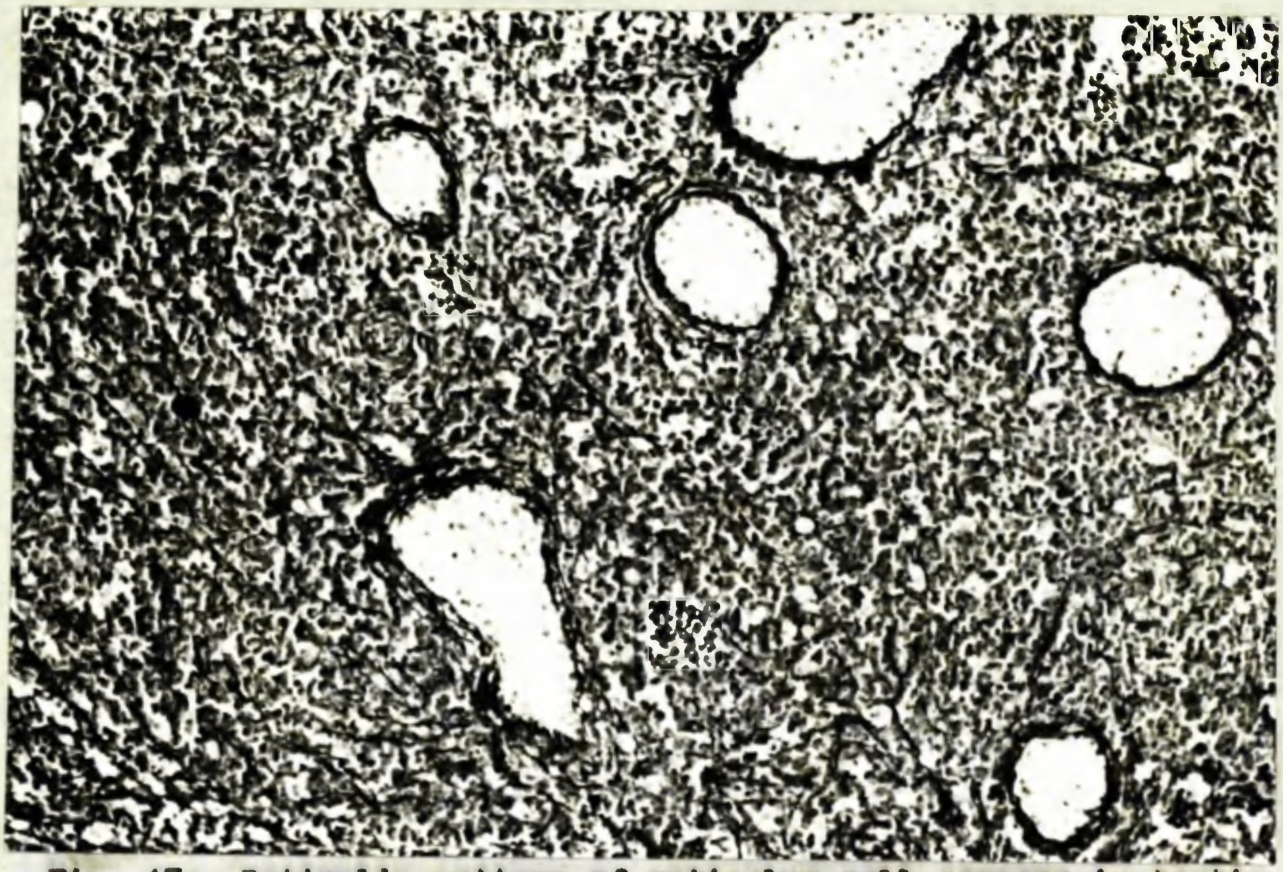


Fig. 47a. Reticulin pattern of reticulum cell sarcoma in testis. Note slight condensation around the seminiferous tubules. Gordon and Sweet's reticulin stain X 125.

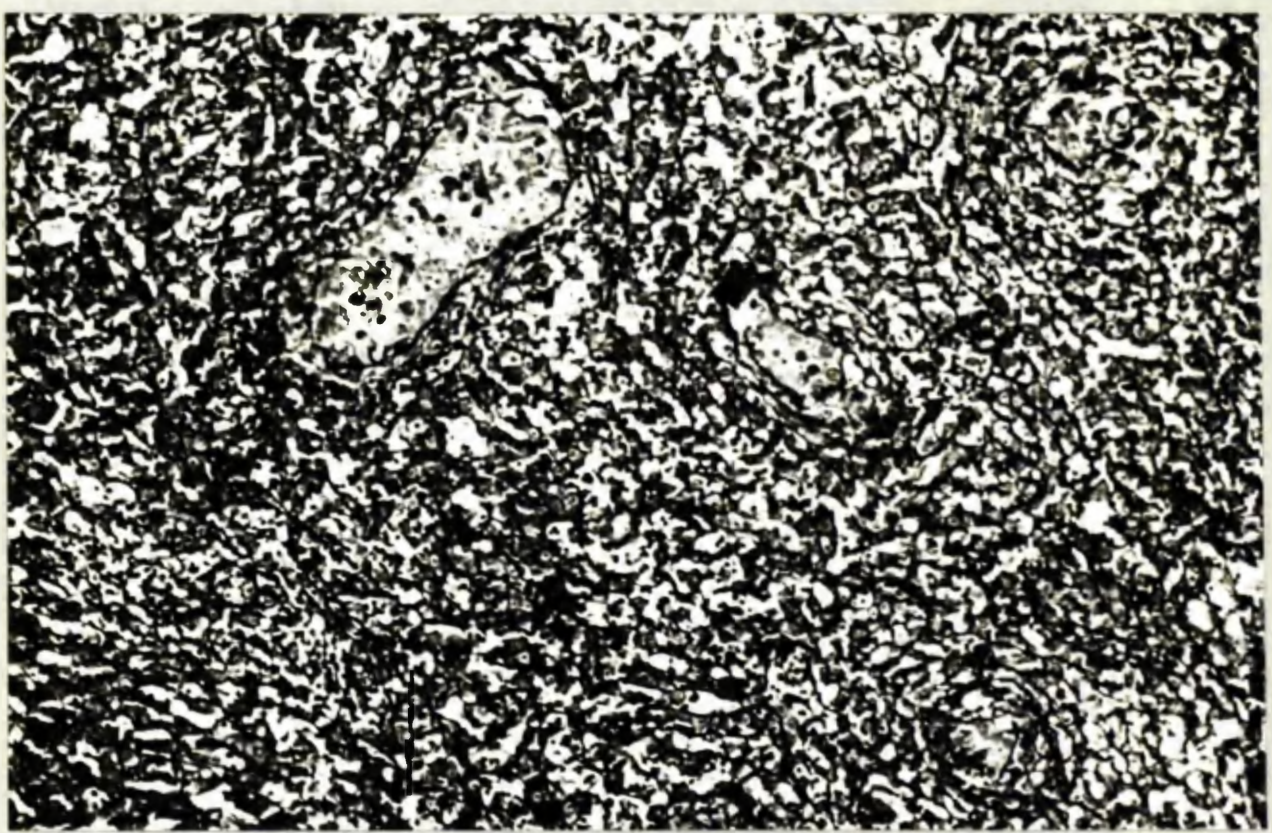


Fig. 47b. Reticulin pattern of seminoma in testis. Note heavier reticulin pattern than in Fig. 47a, but lack of peritubular condensation. Gordon and Sweet's reticulin stain X 125.

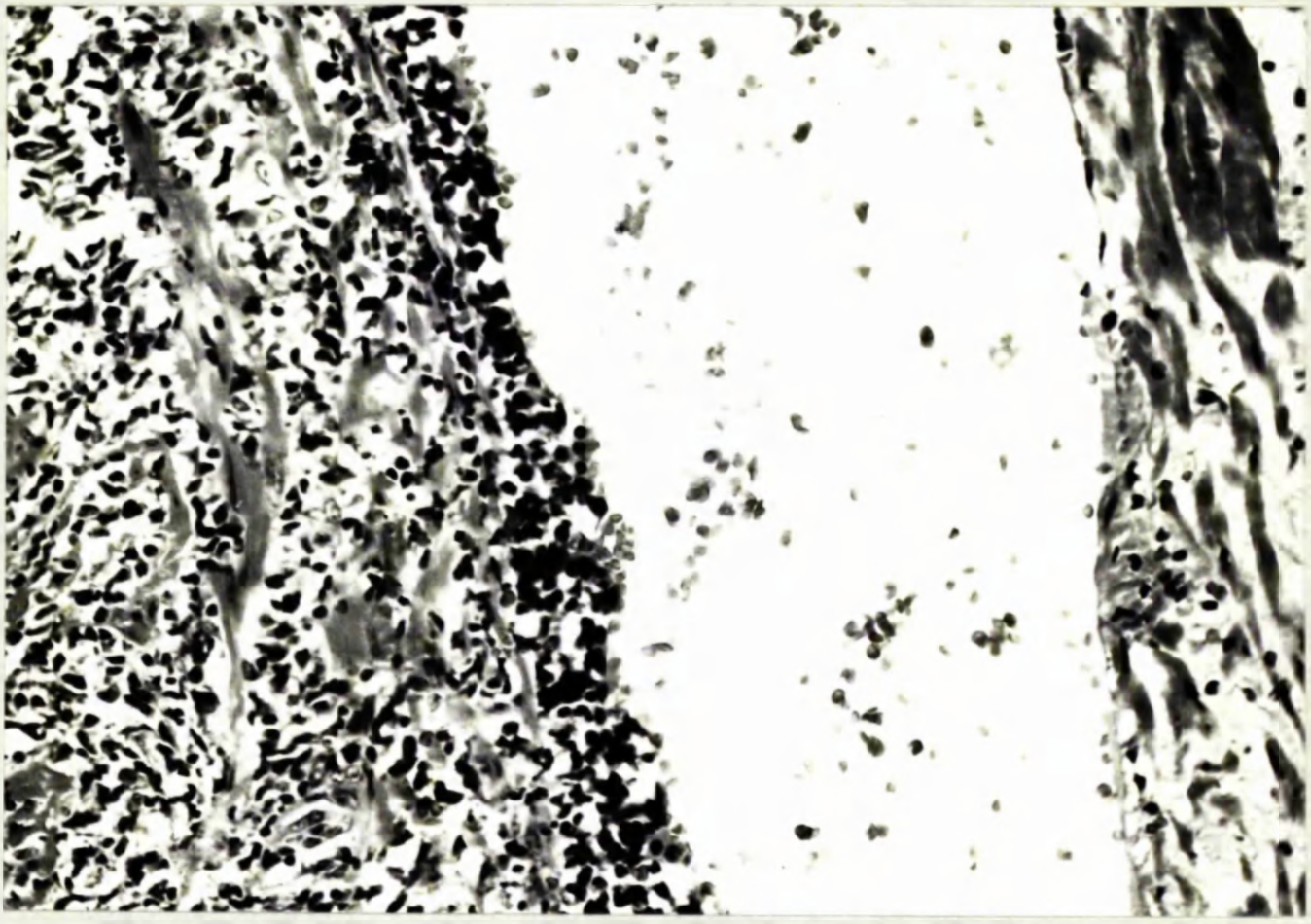


Fig. 48. Infiltration of wall of vein of testicular capsule by reticulum cell sarcoma. The infiltration of the malignant reticulum cells between the smooth muscle fibres of the venous wall is well seen on the left of the picture. H & E X 320.

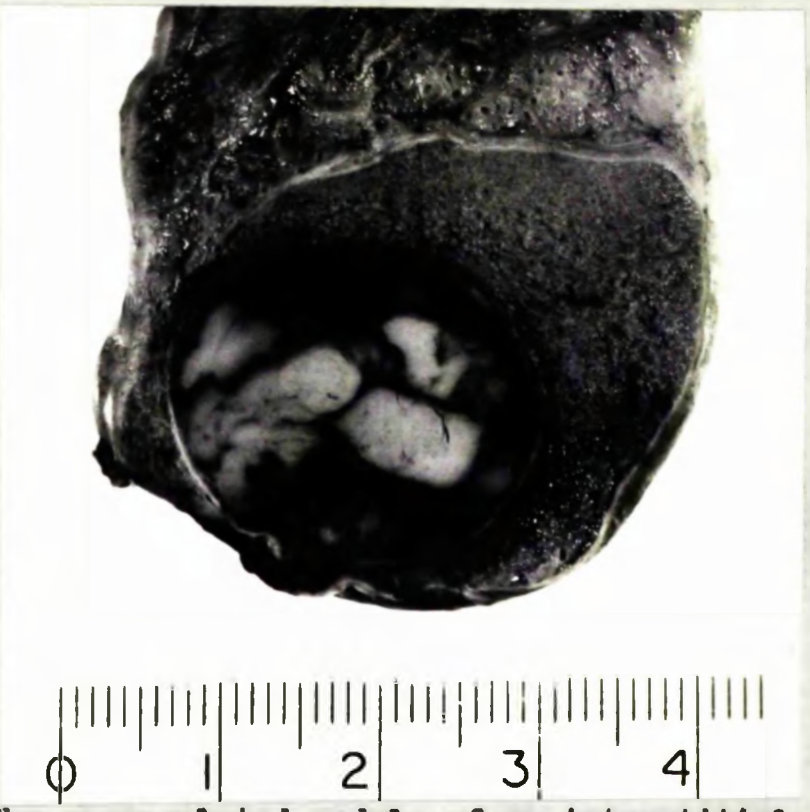


Fig. 49. The encapsulated nodule of an interstitial-cell tumour in the testis of a young man, R.K., aged 24 years. This tumour had a variegated yellow and golden brown appearance.

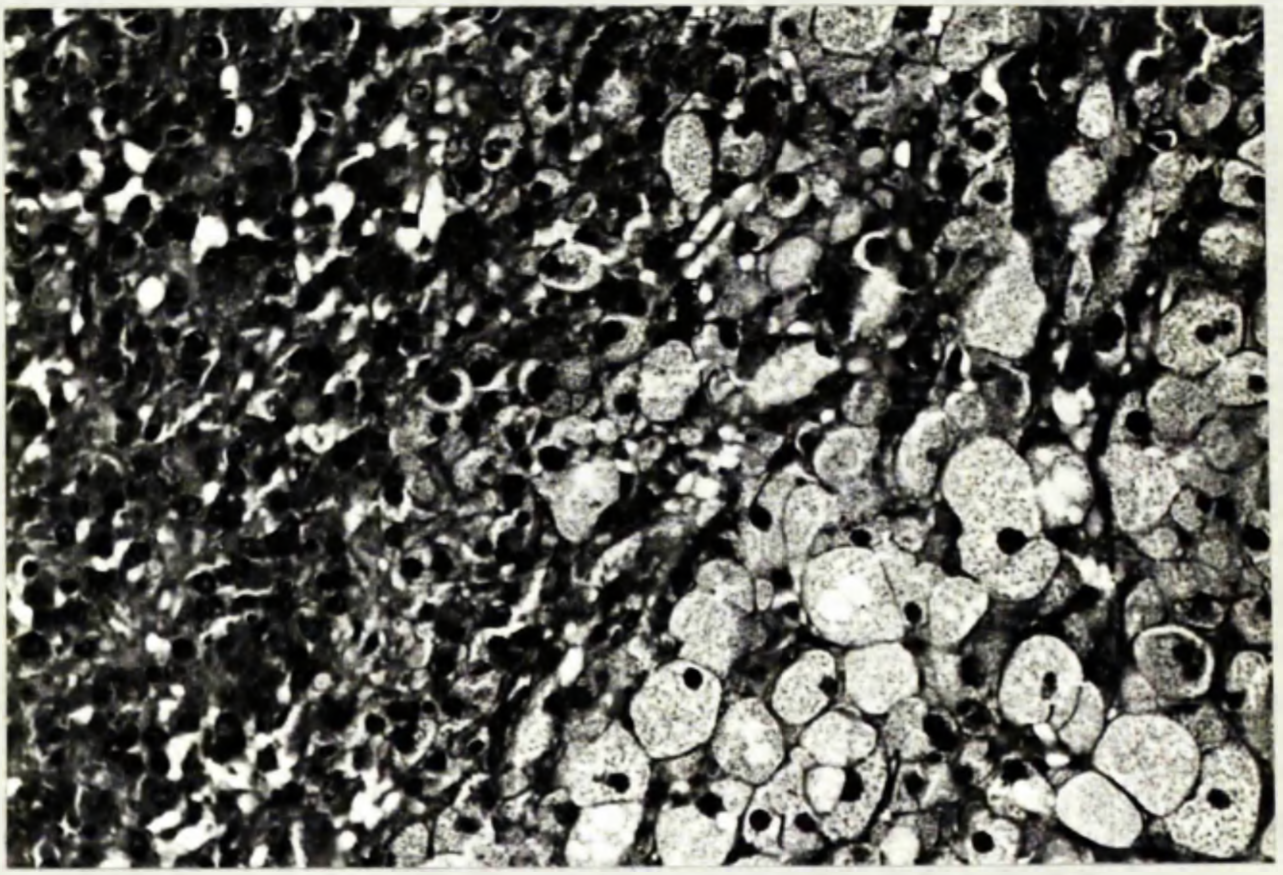


Fig. 50. Human interstitial-cell tumour showing small rather compact granular cells on the left and larger vacuolated cells, mainly with pycnotic nuclei on the right. H & E X 320.

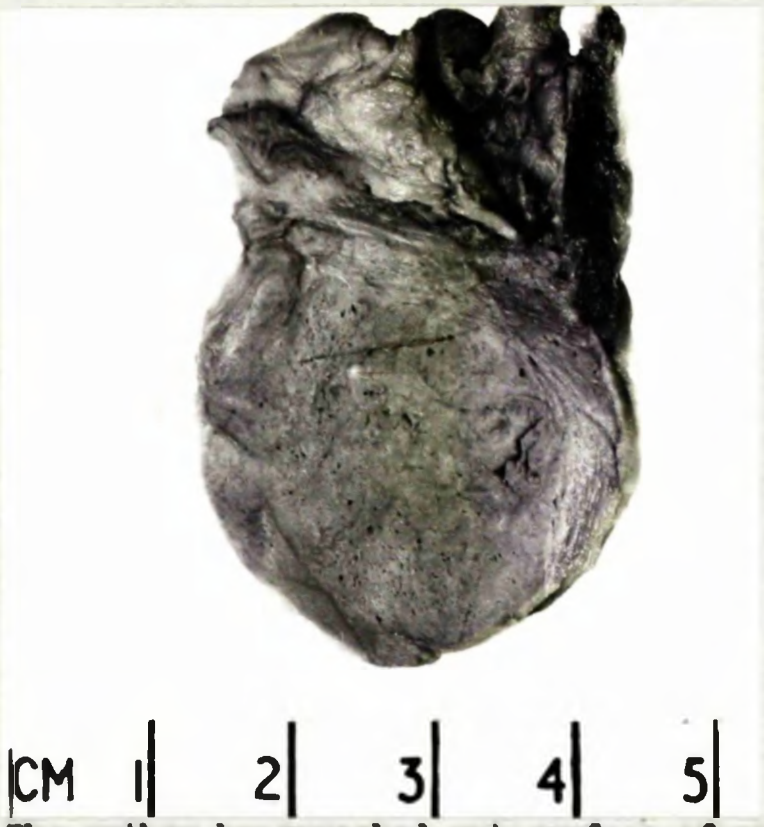


Fig. 51. The rather honeycombed cut surface of an orchioblastoma producing enlargement of the left testis of an eight months old boy.

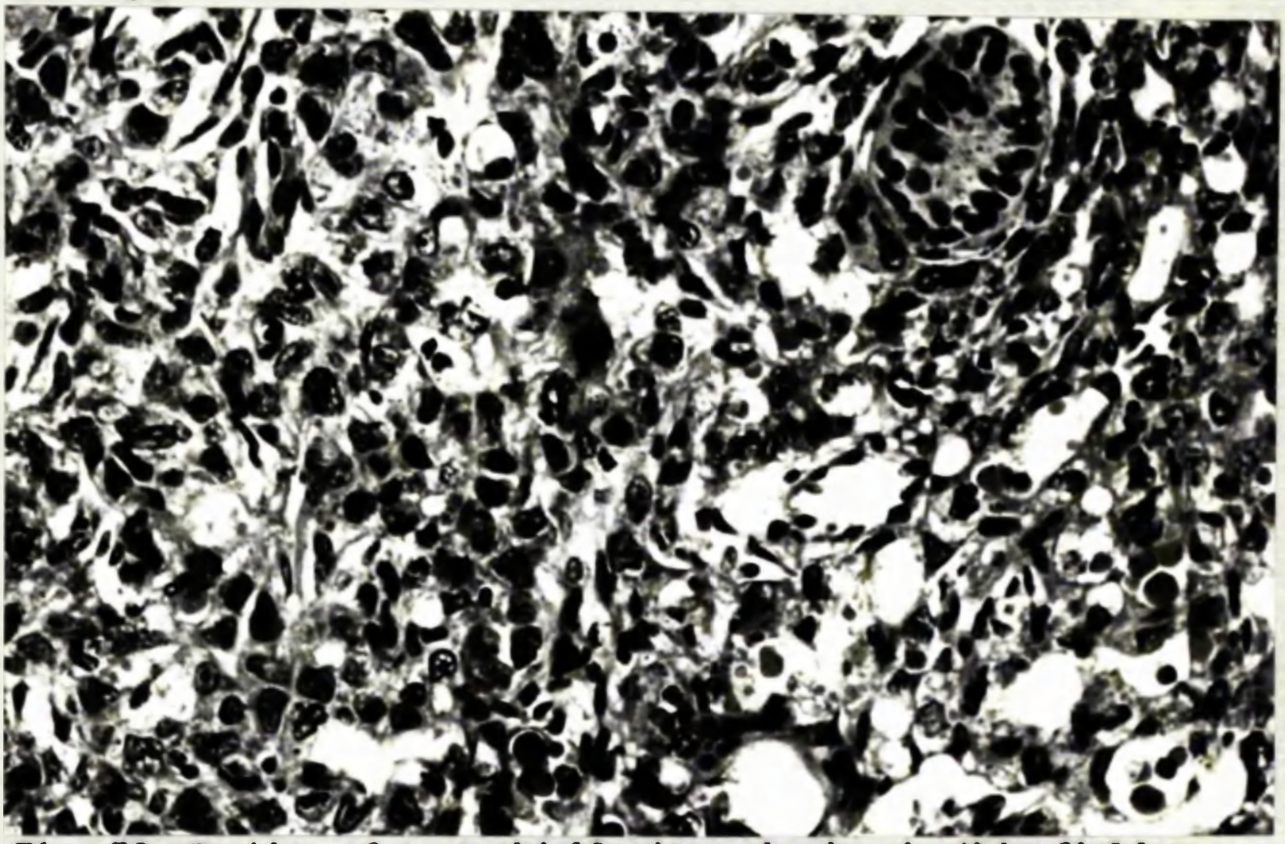


Fig. 52. Section of an orchioblastoma showing in this field a relatively undifferentiated area with cells arranged rather compactly on the left and in a more loose mesh-work on the right, where tubule formation is present. Some of the tumour cells show vacuolation. An infantile seminiferous tubule is seen at the top right. H & E X 320.

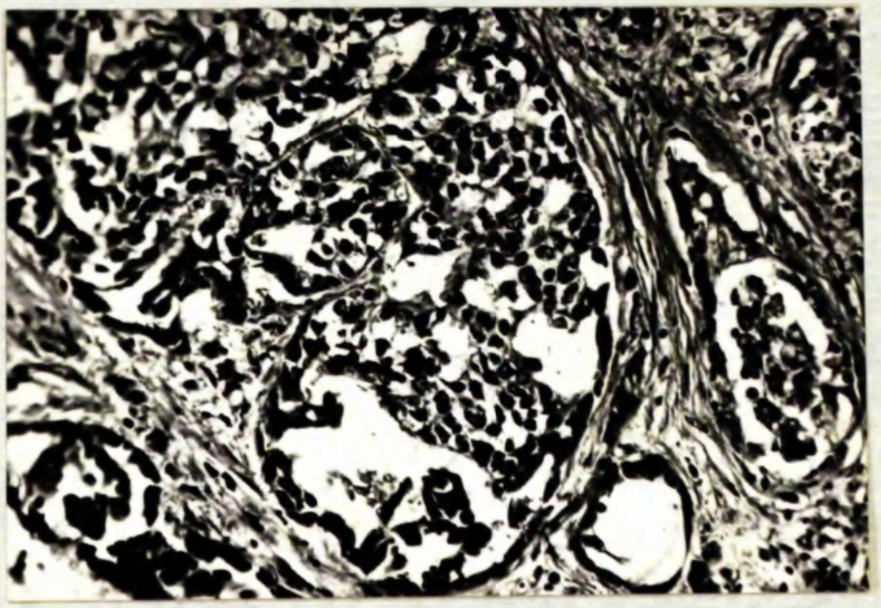


Fig. 53. Papillary adenocarcinoma in tubules of the rete testis. H & E X 180.

Part II

Comparative Oncology of the Testis.

Spontaneous Testicular Tumours of Animals.

In any study of neoplasia, useful information may be obtained by examination and comparison of similar tumours in different species and classes of animals. The variation in incidence among species may in itself suggest genetic and environmental factors of importance in carcinogenesis. Certain tumours are virtually confined to one species, but others have a very wide range although differing slightly in morphology and behaviour from one species to another. In this part of the thesis the observations will be confined to spontaneously occurring testicular tumours; investigations into the experimentally induced tumours are described in the articles appended (Guthrie, 1956, 1962, 1964 a and b and 1966).

Captive animals in zoos, domesticated and laboratory animals form the basis for this comparative oncology. It is from studies of the populations of zoological gardens that most of our information about tumours in wild animals is obtained. In her extensive bibliography of references to disease in wild mammals and birds, Patricia O'Connor Halloran (1955) referred to 12 reports of testicular tumours. Three of these were in mammals and nine in birds. (Table XVI). Recently Maruffo and Malinow (1966) have reported a seminoma in a howler monkey.

The study of testicular tumours in domesticated animals may prove to be of more value as their availability makes possible the examination of more tumours in a particular species and permits

Table XVI

Reported Testicular Tumours in Wild Animals (after Halloran, 1955).

Type	(Class)Order		Family or Genus	Reference
Sarc.	(M)	Carnivora	Dingo	Plimmer, 1915
Carc.	(M)	Artiodactyla	Bison	Tsvetaeva, 1941
Sem.	(M)	Artiodactyla	Caucasian wild goat	Hamerton, 1943
Ter.	(A)	Accipitriformes	Golden eagle	Murray, 1919
C.Emb.	(A)	Passeriformes	Red-beaked weaverbird	Fox, 1928
Carc.	(A)	Piciformes	Banded toucan	Fox, 1941
L.S.	(A)	Psittaciformes	Budgerigar	Hamerton, 1941
Sem.	(A)	Anseriformes	Rosy-billed duck	Ratcliffe, 1942
Sem.	(A)	Psittaciformes	Guiana parrokeet	Hamerton, 1943
Sem	(A)	Anseriformes	Falcated teal	Rewell, 1948a
Sem.	(A)	Columbiformes	Collared turtle dove	Rewell, 1948b
Carc.	(A)	Ciconiiformes	Yellow crowned night heron	Ratcliffe, 1949

Abbreviations: Sarc. - Sarcoma; Carc. - Carcinoma; Sem. - Seminoma; C. Emb. - Carcinomatoid Embryoma; L.S. - Lymphosarcoma; Ter. - Teratoma; (M) - Mammalia; (A) - Aves.

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a study of their natural history. Also they share to some extent man's environment and are subjected to the increasing complexity of man's drugs and processed foods. Moreover they would seem to be suitable subjects for experimental therapeutics, where as in the dog, there is a high incidence of testicular tumours (Knight and Douglas, 1943; Dow, 1962). The absence of testicular tumours in particular species has been commented on by Cotchin (1957) with respect to the cat and by Monlux, Anderson and David (1956) after the examination of 908 bovine, 66 ovine and 28 porcine tumours found at routine abattoir examinations. Farm animals however have a relatively short life span before slaughter and this may explain the low incidence of neoplasms in those animals reared for human consumption. In these circumstances neoplasia is seldom of economic importance and only arouses academic interest at present. Recently Jensen and Flint (1963) described intratubular seminoma in five adult rams, in two bilaterally. This is a species in which gross testicular tumours have not yet been described. Sertoli-cell adenomas have been described in new born bulls (Cotchin, 1960 a) and in the adult bull, Montpellier and Poisin (1929) described a seminoma. Fibrosarcomas arising in the region of the testis in the bull after castration by torsion have been described by Bariac (1924) and Fouque (1927).

The earliest records of testicular tumours in domesticated animals refer to the horse and the dog, animals which often survive to old age due to their protected existence.

Teratomas in the testes of horses attracted attention more than a century after their discovery in man (see Part I, Chapter I). Meckel (1818) found pieces of bone, in the capsule of the testis of a horse, and inside a greasy mass with hairs, and later Patu (1833) found inside an equine testis a complex tumour the size of an infant's head and containing bone, cartilage and hair. Walley (1894) described a round cell sarcoma of the testicle of a horse with a large intra-abdominal metastasis. This was probably a seminoma. Sticker (1902) reported 13 cases of testicular tumours in horses and 18 cases in dogs. An enormous seminoma in a horse was described by Ball, Douville and Lombard (1924), but in general the equine tumours have been classified as dermoids or teratomas.

In a study of undescended testes in horses Crew (1922) found four testicular dermoids, which he believed to have arisen during foetal life, and so prevented normal testicular descent. The presence of cartilage, teeth and hair in a dermoid cyst of the undescended testis of a two year-old colt was reported by Wisnicky and Beach (1927/28). A full description of the equine testicular teratomas was given by Willis (1938), and Willis and Ruddock (1943). The latter paper described three teratomas found in scrotal testis at gelding of young horses and referred to 24 previously reported examples all between 13 months and three years of age. Several of those examples were in undescended testes. Willis and Ruddock illustrated the multiplicity and bilaterality of the growths in one of their three cases. A somewhat different type of equine testicular

tumour was described by Edington and Cappell (1930-31). This was an adenocarcinoma of an undescended testis with multiple pulmonary growths which could not be identified with certainty with the testicular tumour.

Apart from the horse, testicular teratomas in farm animals have been confined to the domestic fowl and the pig. The reports of spontaneous teratomas in the former have been reviewed by Mashar (1932) who found 13 examples, the majority of which were definitely testicular in origin; the others arising from the posterior wall and possibly testicular in origin. Campbell (1951) adds a further case. This is a low spontaneous incidence and is of interest in view of the successful experimental production of testicular teratomas in fowl originally reported by Michalowsky (1929) and further described in the articles appended (Guthrie, 1962 and 1964, a and b and 1966). A few teratomas have been found in the cryptorchid testes of swine (Steiner and Bengston 1951)

Several large series of canine testicular tumours have appeared within the last 30 years. Zuckerman and McKeown (1938) in their series of 35 tumours found three interstitial-cell tumours, 17 seminomas and 15 adenocarcinomas. The exact nature of their "adenocarcinomas" is uncertain; most of them were probably Sertoli-cell tumours as there were associated prostatic changes presumably of hormonal origin.

Of fifty-two testicular tumours described by Innes (1942) 49 were canine, two were equine, one seminoma and one teratoma

and one was bovine, an interstitial-cell tumour. The canine tumours consisted of 32 seminomas, 15 Sertoli-cell tumours and two malignant interstitial-cell tumours. Innes drew attention to generalised alopecia in three of the 15 dogs with Sertoli-cell tumours with subsequent prolific hair growth after orchidectomy. Two of these dogs had also become sexually attractive to other male dogs. Huggins and Moulder (1945) extracted two canine Sertoli-cell tumours for oestrogen and found in one values in excess of that obtained from the ovaries from bitches at oestrus. Examination of the fat content of normal canine testes and the various types of tumours was carried out by Huggins and Pazos (1945), who analysed 64 testicular tumours from 41 dogs. Only the seminomas had a fat content below that of the normal testis. The Sertoli-cell tumours had raised values, but the interstitial-cell tumours had the highest range, 4 to 14.9g per 100g, wet weight. Mulligan (1949) in his excellent monograph "Neoplasms of the Dog" referred to the feminization associated with Sertoli-cell tumours; an alopecia mainly ventral, loss of libido, sexual attraction for other males, mammary hypertrophy and atrophy of the penis and the other testis. In the United States of America Scully and Coffin (1952) studied 177 canine testicular tumours and more recently in London, Cotchin (1960 b) encountered 136 testicular tumours constituting 5.8 per cent of a series of 2,361 canine tumours mainly removed at operation. In Glasgow, Dow's post-mortem survey of 580 unselected dogs revealed 94 testicular tumours,

an incidence of 16 per cent.(Dow, 1962). Laboratory animals cannot be said to lead natural lives, but their spontaneous neoplasms merit careful study. Although these tumours are not induced by definite intent, factors in their breeding or environment may control their incidence. An increasing number of animal species are now used in laboratory experiments, but the vast majority are still rodents.

Of interest in recent years has been a spontaneous testicular tumour of mice. This is the congenital type occurring in the in-bred strain 129 mice reared at the Jackson Laboratory, Bar Harbor, Maine. Its morphology, biology and its karyotype have been studied by Stevens and co-workers in a number of reports (Stevens and Little, 1954; Stevens and Hummell, 1957; Stevens and Mackensen, 1961; Stevens, 1962 a and b, Stevens and Bunker, 1964). This essentially benign teratoma has an incidence of approximately one per cent in strain 129 mice and Stevens (1959) found a similar incidence in foetal as in older animals and concluded from his various observations that they originated during a sharply defined prenatal period.

In laboratory rats spontaneous testicular tumours are rare. In a large colony Curtis, Bulloch and Dunning (1931) found one seminoma. Gilbert and Gillman (1958), however found 65 testicular tumours among 641 male albino rats. In a review of the literature Berdjis (1964) found 110 examples including those mentioned above. In a study of testicular tumours in normal and

X-irradiated rats, Berdjis found seven among the 69 normal Sprague-Dawley rats and 39 in the X-irradiated group of 156. All seven tumours in the normal rats and 29 of the 39 tumours in the irradiated rats were interstitial-cell tumours. In the irradiated rats, two seminomas, two fibrosarcomas, two adenocarcinomas and two nodules resembling Sertoli-cell adenomas were also found. Attempts by the author to induce testicular tumours in albino rats resulted in interstitial-cell tumours and fibrosarcomas (Guthrie, 1956- article appended).

In cross strains of white mice Gardner (1943) found interstitial-cell tumours.

Present Material.

This is based on 56 spontaneous animal testicular tumours from 49 animals. The majority of these are canine and were obtained by the co-operation of veterinary surgeons and the Pathology Department of the Royal Veterinary College, London.

Zoological specimens from eight animals were obtained from the Zoological Society of London and with one exception they are avian in origin.

The various types of testicular tumour examined will be discussed under the following headings:-

1. Mammalian Testicular Tumours.

   A. Dog.

   B. Horse.

   C. Other mammals.

2. Avian Testicular Tumours.

A. Domestic fowl.

B. Other birds.

1. Mammalian Testicular Tumours.

A. Dog.

Forty-four canine testicular tumours from 40 dogs were available for study. Four testicular tumours were found in three dogs killed because of age and debility. In eight dogs subjected to orchidectomy for an enlarged testis, the entire tumour-bearing testis with attached epididymis and short length of cord was received fixed in formalin. In the other cases only part of the orchidectomy specimen was received from the Royal Veterinary College, London. Several blocks of tissue were selected from each tumour and where possible these blocks included the junction between tumour and surrounding testis, parts of the testis away from the tumour, the epididymis and spermatic cord. The fixed blocks were dehydrated in alcohols, cleared in chloroform and embedded in paraffin wax with melting point of 58°C. Sections five microns thick were stained with Ehrlich's haematoxylin and aqueous eosin. In selected cases, Gordon and Sweet's reticulin stain and the periodic acid-Schiff (P.A.S.) method before and after diastase were used. Lipids in frozen sections were demonstrated by Sudan III and IV and Oil Red O and in some cases unstained frozen sections were examined in polarised light.

Table XVII

Incidence of Different Types of Canine Testicular Tumours.

Type	No. of Dogs	
Seminoma	17	
Sertoli-cell Tumour	15	
Interstitial-cell Tumour	5	(incl. one bilateral)
Seminoma and Sertoli-cell Tumour	1	
Seminoma and Interstitial-cell Tumour	2	
Total	40	

Abbreviation: incl. - including.

Table XVIII

Breed Incidence of Canine Testicular Tumours.

Breed	No. of Dogs					Total
	SCT	SEM	ICT	SEM+ICT	SEM+SCT	
Collie	-	1	-	-	-	1
Greyhound	-	-	-	1	-	1
Boxer	-	-	1	-	-	1
Poodle	-	1	-	-	-	1
Sealyham	-	1	-	-	-	1
Pekingese	3	-	-	-	-	3
S.H.F. Terr.	1	-	-	-	-	1
W.H.F. Terr.	-	2	1	-	-	3
Terr. unspec.	1	1	1	-	-	3
Scot. Terr.	1	1	-	-	-	2
Labrador	1	-	-	-	-	1
Spaniel	1	-	-	-	-	1
Golden Ret.	1	-	-	-	-	1
Mongrels	-	3	1	1	1	6
Others	6	7	1	-	-	14
Totals	15	17	5	2	1	40

Abbreviations: S.H.F. Terr. - Smooth-haired fox terrier. W.H.F. Terr. - Wire-haired fox terrier. Scot. Terr. - Scottish Terrier. Terr. unspec. - Terrier unspecified. Golden Ret. - Golden Retriever. SCT - Sertoli-cell tumour. SEM - Seminoma. ICT - Interstitial-cell tumour.

Incidence of Different Types of Tumour.

Seminoma occurring alone accounted for 17 of the 44 tumours in this series (39 per cent), while Sertoli-cell tumours occurring alone accounted for 15 (34 per cent); interstitial-cell tumours occurring alone numbered six (13 per cent) occurring in 5 dogs, one being bilateral (Table XVII). Information about the breed was available in 25 dogs. These data are tabulated in Table XVIII.

No information is available about the proportion of different breeds in the population to which these dogs belong and so the relative incidence in different breeds can only be surmised. This unfortunately has also been true of all the larger series such as Cotchin's (1960).

Clinical Data.

Age Incidence.

The average ages of the different types of tumour are compared with those of previous series in Table XIX.

Table XIX.

Age Incidence of Dogs with Testicular Tumours.

Author	Average age of dogs with testicular tumours (years).			
	SEM	SCT	ICT	SEM +ICT
Jones and Friedman (1950)	11.1	7.6	12.1	-
Scully and Coffin (1952)	11	10	10	-
Cotchin (1960)	10	8.5	11.5	-
Present Series.	11.3	8.3	11.2	13

Sem. Seminoma. SCT. Sertoli-cell tumour. ICT. Interstitial-cell tumour.

In the present series the range for 17 seminomas was from 9 to 15 years; for 15 Sertoli-cell tumours 4.5 to 13 years; for five interstitial-cell tumours 8 to 15 years. The two combined seminomas and interstitial-cell tumours occurred at 12 and 14 years of age and the combined seminoma and Sertoli-cell tumour at ten years of age. It would appear that Sertoli-cell tumours tend to occur in middle-aged dogs, while seminomas and interstitial-cell tumours occur in the older dogs. Dow's post-mortem studies (1962) showed an increase in numbers with advancing years of all types of tumour in relation to number examined.

Side Affected.

The laterality of the tumour and the site of the testis are shown in Table XX with respect to the main tumour groups.

Table XX

Laterality and Site of Testis in Canine Testicular Tumours.

	Right		Left		Side Unknown		Ratio D/U.
	D	U	D	U	D	U	
Sem.	6	0	9	0	2	0	17.0/0
SCT	2	3	0	2	7	1	1.5/1
ICT	1	0	*2	0	3	0	6.0/0
Sem+ICT	2	0	0	0	2	0	4.0/0
Sem+SCT	0	2	0	0	0	0	0/2.0
All Types	11+5		11+2		14+1		9.0/2
Totals	16		13		15		

Abbreviations: D- Descended Testis. U.-Undescended Testis.

Sem.- Seminoma. SCT- Sertoli-cell Tumour. ICT- Interstitial-cell Tumour.

*Includes one bilateral tumour.

As can be seen from Table XX, there was no significant involvement of one side rather than the other. In this small series apart from a combined seminoma and Sertoli-cell tumour the only tumours developing in undescended testes were Sertoli-cell tumours. All the undescended testes were in the groin.

Familial History.

No history of familial involvement was obtained, nor is there any record of this in the large published series.

Trauma or Other Preceding Testicular Pathology.

The history of preceding trauma or other testicular abnormality is dependent on the observation of the dog's owner or veterinary practitioner. One dog was noticed previously to have had a right testis smaller than the left. Both testes were removed. The left testis was found on examination to contain several minute nodules of intratubular seminoma, but the right contained a seminoma at one pole (Fig. 59).

Clinical Presentation.

The chief clinical feature was a gradual enlargement of the testis noticed by the dog's owner. Until the scrotum was considerably distended, this apparently caused the dog little discomfort. Three dogs were noticed to be losing hair on the body. In one this alopecia was marked around the root of the tail, on the ventral aspect of the abdomen and inner aspect of the thighs. Another showed nipple enlargement. All three had testicular tumours obvious on clinical examination and subsequent examination

showed that they were Sertoli cell in type. Neither the seminomas nor the interstitial-cell tumours presented with hormonal dysfunction. Understandably, unless hormonal effects like alopecia or feminization are evident, a small testicular tumour is unlikely to be detected in the dog as it might be in a human being. Consequently, unless the tumour is found incidentally at post-mortem examination, the neoplastic testis is likely to be generally and moderately enlarged at the time of its discovery.

Description and Behaviour of Tumour Types.

Seminoma.

In the present series 17 seminomas all unilateral occurred in scrotal testes. As mentioned above seminoma occurring alone accounted for 39 per cent of the 44 tumours in this series. In 16 cases the specimens were obtained by orchidectomy; in one the dog was killed because of age and debility.

Naked Eye Appearances.

The canine seminoma occurs as a fairly well defined rounded or nodular mass which causes a localised bulging of the testicular tunica (Fig. 54) or as multiple separate nodules of varying size throughout the testis (Fig. 55). In the more advanced tumour the whole testis shows a fairly firm uniform enlargement with distended veins across the expanded tunica albuginea (Fig. 56 a and b). On the section seminoma is usually of a homogeneous white, grey or pinkish white appearance with a tendency to bulge outwards from the surrounding yellowish brownish testicular parenchyma due largely to the retraction of the latter.

Several show lobulation due to fine fibrous septae and this can be reflected in a coarse nodularity of the affected part of the testicular tunica. The consistency of the tumour tends to be firm, although there is considerable variation and several are rather soft and encephaloid (Fig. 57). Areas of necrosis and haemorrhage are sometimes present especially in the larger tumours (Fig. 58). In the present collection of 17 seminomas five show multiple nodules either of multicentric growth or of a satellite nature and the others a more or less single coherent growth. In the latter type, the overall length of the testis may be within normal limits or even reduced (Fig. 59).

In the larger tumours, the surrounding testicular parenchyma is compressed and brownish, while in the smaller tumours the surrounding parenchyma is of the normal yellowish brown granular appearance.

The overall size of the seminomas in the present collection varied from 2.0 cms. in diameter up to 12.0 cms. in longest diameter. Although the body sizes of breeds involved vary considerably, the largest tumour in the series (Fig. 58) came from a wire-haired fox terrier.

Histology.

The histological pattern of the canine seminoma is either an intratubular proliferation of large spheroidal cells with or without interstitial infiltration or a more diffuse growth of the cells with obliteration of the seminiferous tubules.

Intratubular Type with or without Interstitial Infiltration.

The smallest nodules seen, from 2 to 4 mms. in diameter occurred in the left testis of a nine year old dog. The right testis contained a clinically detectable seminoma (Fig. 59). Histologically these small nodules consist exclusively of intratubular seminoma (Fig. 60). This type of growth, seminoma-in-situ is also present in three of the 17 seminomas (18 per cent) and there is close similarity between the intratubular and extratubular forms of the tumour (Fig. 61). The tumour cells are large with round or oval nuclei containing granular chromatin with a prominent single but occasionally double nucleolus. The cytoplasm is scanty, usually faintly eosinophilic and occasionally finely granular although there is some variation in its staining with acidic dyes. Occasionally small intra-cytoplasmic vacuoles are present. Cytoplasmic vacuoles which stain positively by the P.A.S. method stain negatively after treatment of the section by amylase. This indicates some glycogen content, but the amount is less than that present in the Sertoli cells. Frozen sections show no lipid in healthy parts of the tumour. Multinucleated giant cells are usually present in both intratubular and extratubular forms, and sometimes giant cells with mainly peripheral nuclei are present in large numbers in the intratubular foci. As seen in five micron sections these cells have from two to 12 nuclei surrounding a granular cytoplasm. The nuclei resemble the other tumour nuclei and occasionally show mitoses. Lymphocytes frequently surround

these intratubular seminomas (Fig. 62).

When there is direct extension of the intratubular seminoma into the interstitium of the testis the extratubular growth is almost identical morphologically to the intratubular form described above, although mitotic rate is nearly always higher and multinucleated giant cells are less common.(Fig. 63a). Lymphoid foci are common and are present in three of the six dogs showing this type of growth(Fig 63b).

Diffuse Type.

The cellular basis of this type is the same as the intratubular type except that there is more variation in cell size and form, which may approach the spindle type. Multinucleated giant cells are less frequent and the solid tubular arrangement of the other type is not seen, although search around the periphery may show tubules containing seminoma. Eleven dogs showed this type of growth, the features of which are illustrated in Figs. 64 and 65. The former shows the variation in cell form with some tendency to a spindle form. The latter shows a narrow tubular patterning with a flag-like arrangement of the cells along the fine stromal fibres. With further anaplasia, it may be difficult to identify with certainty the tumour as a seminoma.

Changes in other Parts of the Testis, and in Opposite Testis.

The seminiferous tubules tend to be compressed immediately around the seminoma except in early extratubular spread in small tumours. Beyond this the tubules show atrophy and a lining

exclusively of Sertoli cells in 15 of the 17 dogs with seminomas occurring alone. In the other two dogs spermatogenesis is depressed, but spermatozoa are present in occasional tubules. Both these dogs were six and seven years old at the time of orchidectomy. The interstitial cells of Leydig show hyperplasia (Fig. 66) in five dogs with tubular atrophy.

The opposite testis available in two dogs shows spermatogenesis in both with areas of tubular atrophy and intratubular seminoma in one (Fig. 60). Interstitial cells were within normal limits in both cases.

Metastases.

All the seminomas studied were obtained by orchidectomy except one where the tumour was large and the dog old and debilitated. The animal was killed and at post-mortem examination was found to have metastases in the iliac lymph glands on the side of the tumour. The seminoma was of the diffuse variety. Four out of the 45 dogs in Dow's post-mortem series (1962) showed metastases.

Prognosis.

Owing to the difficulty in tracing dogs post-operatively little useful information was obtained. Three dogs were traced for five to six years after orchidectomy and were reported to be alive. Cotchin (1960) comments on the unrewarding attempts to obtain follow-up histories in the conditions of veterinary practice. Although the canine seminoma occurring as it does predominantly in elderly dogs, is not generally considered to be

of great malignancy (Willis, 1960), adequate survival studies following surgical removal of seminomas have not been reported.

Sertoli-Cell Tumours.

Sertoli-cell tumours occurring alone numbered 15 and accounted for 34 per cent of the total in the series. One was found at post-mortem examination of a dog killed because of debility. The others were removed surgically.

Naked Eye Appearances.

The affected testis in all 15 cases shows generalized enlargement and a distinct nodularity or bossing of the capsular surface. The largest testis containing a Sertoli-cell tumour came from a Labrador dog and measured 8.0 x 6.0 x 5.5 cms. The smallest from an unknown mongrel, measured 5.0 x 3.0 x 3.0 cms. The sectioned surface of the majority of the tumours has a fairly homogeneous granular appearance with fibrous tissue forming a spongy network containing whitish, creamy or definitely yellowish tumour (Fig. 67). There is an occasional resemblance to the seminoma due to a smooth sectioned surface, but the Sertoli-cell tumour has frequently a distinctly yellowish appearance due to a high lipid content (Fig.68). Cystic spaces are not uncommon, but areas of necrosis and haemorrhage are rare and tend to follow direct injury or torsion (Fig. 69).

Histology.

The essential structure of the Sertoli-cell tumour is revealed by its alternative name of tubular adenoma. The tubules are lined or filled by neoplastic Sertoli cells varying from the

well differentiated rather elongated cells with copious fibrillar cytoplasm to anaplastic spindle cells recognisable with difficulty as being derived from Sertoli cells. The tubules themselves vary in size from about 15 microns to just over 1 mm. in diameter and although a whole tumour or parts of a tumour usually show a consistent size of tubular framework, transition from small to large calibre does occur. Malignancy is hard to define in the absence of extra-testicular spread. The well differentiated tubular structure with single or double layer of Sertoli cells and minimal streaming across the lumen has been labelled adenoma and is clearly benign (Fig. 70). There is a breakdown of tubular pattern in six tumours and in these small nests and columns of cells without support of basement membrane are seen in the surrounding fibrous tissue. This and cellular atypism suggests early malignancy (Fig. 71). Marked increase in tubular calibre and filling of the lumen with Sertoli cells many of which show palisading occurs in some cases (Fig 72a). These large tubules may be subdivided by septae growing out as fibrous cores into the lumina. Central plugs of necrotic cells, the ghosts of which are visible (Fig. 72b), are also seen in this type. The thickness of the tubular basement membranes is variable, and in two cases marked intertubular growth of fibrous tissue separates narrow tubules filled with Sertoli cells (Fig. 73). This is referred to as the sclerosing type by Dow (1962). The normal Sertoli cell, as the homologue of the granulosa cell of the ovarian follicle,

is a nurse cell and contains a variable amount of lipid. This lipid content may be marked in some tumours and macroscopically gives them a rich yellowish or golden yellow colour, like the one previously illustrated (Fig. 68). This lipid-rich tumour has vacuolated Sertoli cells, sometimes signet-ring in form due to displacement of the nuclei by the lipid (Fig. 74 a and b). The lipid vacuoles in frozen sections stain with Sudan III and IV and with Oil Red O, but the Schultz reaction is negative. Fine brown granules of lipochrome nature are also frequently seen in the foamy cells. Small granules of glycogen are almost invariably present. None of the cysts in the specimen illustrated in Fig. 69 have a well defined lining of cells. Papillary ingrowths into the cyst are fairly common.

Changes in the Remainder of the Testis.

Spermatogenesis is present where the tumour is relatively small and a portion of testis remains. It is present in two testes only and in both of these, atrophic testis surrounds the tumour. In all the others the seminiferous tubules show atrophy of the spermatogenic cells and have a lining of Sertoli cells only. Occasionally in serial section tubules apparently outwith the tumour can be traced into obviously neoplastic tubules. Interstitial cells are not seen in the stroma of any of the 15 tumours, but they are present in apparently normal numbers outside the tumours. In the dog killed because of age and debility tubular atrophy surrounds the tumour, but the contra-lateral testis

shows normal spermatogenesis.

Metastases.

No metastases were known to be present at time of orchidectomy and none of the 15 cases showed spread into the epididymis. Metastases were found in five out of 36 dogs with Sertoli-cell tumours in Dow's post-mortem survey (1962).

Prognosis.

No follow-up study has been possible except in two dogs which are still alive and well five years after orchidectomy. Neither of these had shown feminization.

Interstitial-cell Tumour.

Six interstitial-cell tumours occurring alone are included. The breeds involved are indicated in Table XVIII. Three were removed surgically. Bilateral tumours were found at post-mortem examination of a Boxer dog aged 10½ years and another was found at post-mortem of an aged mongrel dog. The youngest dog was aged 8 years and the oldest 15 years. The average age of 11.2 years is compared with the average age for other tumours in Table XIX.

Naked Eye Appearances.

All six are among the smallest testicular tumours in this collection. The largest is 4 cms. and the smallest 2 cms in diameter. All had caused local enlargement of the testis, and the smallest a bulging of the upper pole noticed only at post-mortem examination in an aged mongrel.

On section the cut surface shows a well demarcated tumour

rounded or oval in shape and yellowish golden or brownish in colour with a rather haemorrhagic and friable surface. The small tumour found incidentally at post-mortem examination is illustrated (Fig. 75).

Histology.

The cells of the interstitial-cell tumours resemble the normal interstitial cells of Leydig. They are epithelial-like and arranged in mosaic, acinar or trabecular form rather reminiscent of the adrenal cortex in its various layers. Alternatively the cells are arranged in solid masses. The stroma consists of fine rather vascular connective tissue. Around groups of tumour cells only a fine reticulin can be seen. In places the vascular channels consist of large sinusoids and haemosiderin deposits indicate previous haemorrhage. The tumour cells which are larger than the normal interstitial cells are polygonal although they may be columnar when arranged radially around blood vessels. The nuclei are usually small and dense, but sometimes the chromatin is light or marginally distributed along the prominent nuclear membrane. A single nucleolus is present. The cytoplasm is granular and eosinophilic, but vacuoles are almost invariably present and may be numerous and small (Fig. 76), or larger tending to signet-ring forms (Fig. 77). Some fine lipochrome granules are present in two specimens. Frozen sections stained with Sudan III or IV or Oil Red O confirm the presence of lipid which is usually bi-refringent and gives a positive Schultz

reaction for cholesterol. Although Collins and Pugh (1964) state that Reinke crystalloids are not seen in species other than man these crystalloids were seen in four of Dow's (1962) cases, and are seen in one of the present collection of six tumours. No glycogen can be detected.

Occasional cells are binucleated, but mitoses are rare. One mitotic figure is seen in one section from the largest tumour. There is no evidence of invasion.

Changes in the Other Parts of the Testis.

Spermatogenesis is present in one testis, containing an interstitial-cell tumour, measuring 3 x 2 x 2 cms., but in the others including the dog with the bilateral tumours the seminiferous tubules are atrophic with a lining of Sertoli cells and in one the basement membranes are markedly thickened.

Changes in Other Organs.

In the case of the dog with bilateral interstitial-cell tumours found at post-mortem examination, the prostatic gland was hyperplastic and cystic. No metastases were detectable.

Prognosis.

No information on prognosis can be given from this study, but malignant interstitial cell tumours have been described by Innes (1942), Mulligan (1949) and Dow (1962).

Combined Tumours.

Three dogs each bearing a double tumour in the same testis, are not included in the above account. These six tumours are described

below.

Seminoma and Interstitial-cell Tumour.

Two rather small interstitial-cell tumours, measuring 1.0 and 1.5 cms. in diameter occurred in association with larger seminomas 3 and 4 cms., in diameter respectively. The larger set of tumours were removed from a greyhound aged 12 years and had originated in a right scrotal testis. The smaller set of tumours came from a crossbred dog aged 14 years. The affected testis was descended, but laterality was not known. Both had presented with testicular enlargement only.

Histology.

The seminomas in both cases are of the intratubular type with interstitial infiltration and are separated by a zone of atrophic seminiferous tubules and fibrous tissue with scanty lymphocytic exudate. Close to the seminoma, in both cases intratubular seminoma can be seen (Fig. 78). The interstitial-cell tumours are typically benign in morphology in both cases and there is no infiltration of one tumour by the other. In the greyhound with the 4 cm. diameter seminoma, infiltration by seminoma of lymphatic channels can be seen under the capsule and in the spermatic cord.

Changes in Other parts of the Testis.

Apart from intratubular seminoma, the seminiferous tubules show atrophy. In one the interstitial cells of Leydig are increased in numbers, forming small focal collections, but in the other they

are definitely scarce.

Metastases.

Neither dog was known to have evidence of metastases at time of orchidectomy. Neither was traced subsequently.

Combined Seminoma and Sertoli-cell Tumours.

Only one of these is included in the present collection. It was removed from the right groin of a mongrel of unknown age.

Naked Eye Appearances.

The testis contains a large granular yellowish white tumour, 5 cms. in diameter, in its upper half and a smaller soft whitish nodule 1.5 cms. in diameter immediately below this.

Histology.

The boundary zone here is rather thin, but no intermingling of the two growths is evident. The seminoma is of the diffuse type, while the Sertoli-cell tumour is moderately differentiated and an adenoma (Fig. 79). No intratubular seminoma is seen in the atrophic seminiferous tubules. Spermatogenesis is absent. No invasion of lymphocytes can be seen and there is no record of metastases or spread being detected at operation. The testis was descended, but the laterality was unknown.

B.Horse.

Fifteen pairs of testes from colts aged 11 months to 4 years were obtained at time of gelding. The specimens were bisected and small pieces of tubules were obtained for study of the normal chromosomes of the horse by squash preparations. This was

preparatory to a study of equine testicular teratomas if such were found. The bisected testes were fixed in 10 per cent formalin and later cut into slices approximately 3mms. thick. Both sides of each slice were examined under the dissecting microscope and two or three blocks were selected for processing to paraffin sections and staining by Ehrlich's haematoxylin and aqueous eosin. No neoplasms nor indeed any abnormality were seen on microscopy. Despite the assertion of Willis and Ruddock (1943) that these teratomas are common in the horse, scrutiny of the published work gives little idea of their incidence in the equine population. None of the four veterinary surgeons who provided testes from colts at gelding had encountered any in the last twenty years. All four had large racing and other stables within their practices in Berkshire and North Hampshire, and only one who had been in practice for almost 30 years could recall a teratoma in the undescended testes of a colt which was destroyed after an accident.

The Royal Veterinary College in London had one specimen of an equine testicular teratoma R.V.C. 9167 and provided sections of this. This specimen shows numerous cystic spaces lined by stratified squamous, respiratory and intestinal types of epithelium. There are isolated nodules of cartilage and adipose tissue. Groups of well differentiated mucous glands and related ducts are present close to the cavities lined by the respiratory and intestinal mucosa. There are also ductal structures lined by melanin pigmented cubical and columnar epithelium (Fig. 80). Mature ganglion cells

are also present. Histologically this is a fully differentiated teratoma and shows no histological evidence of malignancy.

C. Other Mammals.

(1) Nyala (Tragelaphus angasii).

This specimen of antelope comes from a fairly localised area of South-East Africa and both testes were removed from one dying from broncho-pneumonia in the Zoological Gardens at Regents Park, London. The testes were obtained shortly after death from the Pathologist, Zoological Society of London. The animal had only been ill for a day or two and no unusual behavioural features had been noted (Ref. D.B. 713/58).

Naked Eye Appearances.

The right testis measuring 9.0 x 7.0 x 6.0 cms., is enlarged with a smooth but thickened tunica and is almost completely replaced by a somewhat variegated tumour, lobulated with brown, golden yellow and whitish areas and showing an extensive area of coagulative necrosis in its central part (Fig. 81). Darker areas of haemorrhage are also present. The sectioning also reveals numerous small gritty areas of liquefaction. A few small cysts are present. The left testis, much smaller, measures 3.5 x 3.0 x 2.5 cms. and is replaced by a similar yellowish brown and whitish tumour (Fig. 82). The right spermatic cord is thickened, but sections show only vascular dilatation and thickening of veins.

Histology.

The microscopic structure consists of diffuse sheets and

anastomosing columns of epithelial-like cells with granular eosinophilic (Fig. 83a) and in places distinctly foamy cytoplasm (Fig. 83b). Mitotic figures are not infrequent in both the sheets of foamy cells and in the darker cords. In a few areas the cells closely resemble the normal interstitial cells of the Nyala, but in large parts of the tumour variation in cell size and shape is conspicuous. The more compact and less foamy cells where arranged in narrow trabeculae show a fine fibrous and vascular stroma. Foci of amorphous calcification are seen in the fibrous stroma (Fig. 83a). Extensive necrosis is seen in the central area and small cysts are surrounded by neoplastic cells without any particular orientation.

Around the periphery at one point atrophic and hyalinised seminiferous tubules are present. Although no invasion or metastases are seen, this is cytologically a malignant interstitial-cell tumour of the testis. The left testis shows a similar appearance. As no metastases were present outside the testis it appeared unlikely that the left-sided growth was a metastasis.

(2) Caucasian Wild Goat.

Through the courtesy of the Zoological Society of London, a section was obtained of the seminoma in a wild goat (ref. 18/40), which died in the Zoological Gardens. This was reported by Hamerton (1943). Both testes show a unicellular interstitial cell growth of small clear cells of uniform size. Only the peripheral part of the specimen is well fixed and here the cells have an alveolar arrangement. In both testes the seminiferous tubules are atrophic,

but a more marked fibrous stroma is present in the left side.

(3) Sheep.

Sections of the intratubular seminomas in the testes of sheep described by Jensen and Flint (1963) were sent from Colorado to the author. This finding in seven testes from 78 adult rams is quite remarkable as seminoma occurring as a tumour has not so far been described in the ram. The appearances are illustrated in Figs. 84 to 86. The affected tubules along varying segments of their length are filled with polygonal cells with spherical nuclei and moderate amounts of finely granular cytoplasm. The nuclei with well defined nuclear membranes, small chromatin granules and usually single nucleoli resemble the normal spermatogonia. Jensen and Flint (1963) confirmed that the cells contained no lipid. In Fig. 85 the occasional Sertoli cell is seen close to the basement membrane in the neoplastic tubules. The intratubular neoplastic process seems to be multifocal, and the seminiferous tubules show changes ranging from depressed spermatogenesis to atrophy of the spermatogenic elements. In the former case, spermatogonia, spermatocytes and spermatids are present without formed spermatozoa (Fig. 85), whereas in the latter the tubules are lined largely by Sertoli cells (Fig. 86). Interstitial cells of Leydig do not appear to be increased in number, although they are quite prominent in all parts of the affected testis.

2. Avian Testicular Tumours.

A. Domestic Fowl.

A bilateral testicular teratoma arose spontaneously in a Light Sussex/Rhode Island Red hybrid. This cockerel was reared in company with a commercial flock of pullets at the Hampshire hospital farm where the author has kept an experimental flock of Brown Leghorns. The history was remarkable.

Clinical Features.

This bird had been bought as a day-old pullet, but was later noticed to grow the brilliant feathers of the cock of this hybrid strain with male comb, wattles and spurs. He was intensively reared indoors and at 7 months of age his health began to deteriorate. Comb became atrophic, breathing became laboured and he lost weight. "Gapes" was suspected and while the author was carrying out a physical examination there was a sudden regurgitation from the crop and the bird asphyxiated. As a large abdominal mass was palpable, resuscitation was abandoned.

Post-mortem Examination.

At post-mortem examination an enormous bosselated and cystic tumour was found occupying the right side of the peritoneal cavity behind and below the liver with forward displacement of the intestines. The left testis appeared rather small in size. The liver was pale and fatty but otherwise no definite abnormality affected the abdominal organs. Grain blocked the larynx with fluid contents of trachea and bronchi. No metastases were found either

grossly or histologically. The atrophic comb is illustrated in Fig. 87.

Naked Eye Appearances.

Right Testis.

The coarse neoplastic nodular testis measured 15 x 9 x 8 cms. and weighed 670 gms. It sectioned with difficulty due to numerous calcified and ossified areas. The other feature of the cut surface was the presence of numerous cystic spaces and channels, some containing mucous and others horny material. Gelatinous nodules of cartilage, 1-2 mms. in diameter were visible in several areas (Fig. 88).

Histology.

The structure is that of a teratoma consisting of a variety of mature and a few relatively immature adult tissues.

The teratoma and the adjacent stretched seminiferous tubules are illustrated in Fig. 89. Here the nodules of cartilage and keratinized structures are seen. Other parts contain adipose tissue, endochondral ossification and neural tissue. Respiratory and intestinal types of epithelium line cavities or parts of cavity and bands of smooth muscle tissue are scattered throughout. No embryonal carcinoma or indeed any solid unicellular growth can be detected.

Left Testis.

This was smaller than the normal size of the testis for June the month of death. Section revealed a small variegated

nodule with horny cysts, producing a localised bulging of the tunica albuginea as its outer limit was only 2 mms. below the surface (Fig. 90). The nodule measured 0.4 x 0.3 x 0.3 cms., but a collection of minute epidermoid cysts filled with keratin lies 0.4 cms. from the nodule. A spherical whitish nodule 0.4 cms. in diameter lies 0.8 cms. from the cystic nodule and nearer the lower pole.

Histology.

The left testis shows foci of teratomatous growth. These foci contain a variety of tissues nearly all of which are well differentiated. No embryonic carcinoma or traces of a unicellular precursor are seen in serial sections of the entire testis.

In Fig. 91 the main cystic mass of the tumour is seen separated by seminiferous tubules from a collection of horn cysts and mucin-secreting columnar cell tubules. In the main nodule keratinizing epidermoid structures and mature neural tissue predominate. The other more solid nodule consists of neural tissue only. Neurones, in a glial network which can be stained by Holzer's method are illustrated in Fig. 92. Small ependymal lined cavities are also seen. Spermatogenesis is absent in the right testis, but somewhat depressed in the left. As no extra-testicular tumour growth has been detected either on naked eye examination or on microscopy at post-mortem examination it seems reasonable to regard each testicular growth as separate primary tumours and to regard the left testicular growth at any rate as multifocal

in origin.

Changes in Other Parts of the Testis.

Spermatogenesis is absent in the right testis. The left testis is inactive: spermatogenesis is depressed.

Pituitary Gland.

This shows normal numbers and distribution of acidophils, but marked increase in chromophobes, many of which are enlarged. Although a few P.A.S. positive colloid filled acini are seen, no cells show P.A.S. positive granules. This is in contrast to the normal or increased numbers of granular cells staining P.A.S. positive but Gomori aldehyde fuchsin negative cells in experimentally induced testicular teratomas. (Guthrie, 1964 a and b). The nature of the large chromophobes is uncertain.

B. Other Birds.

These examples were obtained by courtesy of the Zoological Society of London.

(i) Budgerigar.

Two budgerigars of unknown age had interstitial-cell tumours of the testes. Both had normal cock feathering and colouring.

V10. This adult bird had bilateral nodular yellowish growths, each measuring 2.5 x 2.0 x 1.5 cms. and weighing 4 and 5 gms. (Fig.93).

V.57. Zoological Society of London. (Z.S.L. 4/58.) This was a 5½ year old cock found dead on the 23rd June 1948 and showing at post-mortem examination an enlarged testis measuring 2.0 x 1.0 x 1.0cms. The left testis was not seen.

Histology.

The tumours consist of various arrangements of large eosinophilic granular cells with varying lipid vacuolation of their copious cytoplasm. The nuclei are vesicular with prominent nuclear membrane and single nucleolus, or pycnotic (Fig. 94). The granules give a moderate positive reaction with the P.A.S., stain not abolished by previous treatment with amylase. Frozen sections stained by Oil Red O show a peppering with lipid in most areas of the tumour, but in some parts of V57 the foamy cells are large with large vacuoles of lipid. All three tumours show a fine reticulin framework and a rich vascular stroma. Although anastomosing columns of cells are present in parts of these tumours, solid alveolar arrangement is also constant. There is a lymphocytic exudate. Atrophic seminiferous tubules are visible at the periphery only. There are no features suggestive of malignancy.

(ii)Chestnut Sparrow. V.58. Z.S.L. 370/57.

One testis, side unknown, is uniformly enlarged to 1.8 x 1.5 x 1.0 cms. and shows on sectioned surface a whitish granular appearance.

Histology.

The whole testis appears to consist of large tubules lined by a single and occasionally a double layer of Sertoli-like cells. The tubules vary slightly in size and are separated by fibrous tissue. No normal seminiferous tubules can be recognised. This would appear to be a Sertoli-cell adenoma.

(iii) Red-breasted Teal. V. 55. Z.S.L. 258/33.

One section of a tumour from the site of the right testis was provided by the Zoological Society of London. This shows a proliferation of tubular structures containing large cells with coarse granular eosinophilic cytoplasm in one or occasionally two layers on a basement membrane. Numerous binucleated and multi-nucleated tumour cells are present, but in the cells with one nucleus this is vesicular with an eccentric position in a fairly abundant granular cytoplasm. In places a solid intertubular growth of these cells is present. No normal seminiferous tubules are seen. This would appear to be an interstitial-cell tumour.

(iv) Persian Chukor. V. 59. Z.S.L. 384/59.

Both testes were obtained. One was enlarged to 2.6 X 1.8 X 1.8 cms., was firm in consistency and had a bright yellow cut surface. The other measured 1.5 X 1.0 X 0.8 cms. The larger testis contained a tumour nodule consisting of granular or distinctly foamy cells due to lipid. Parts are necrotic. This is an interstitial-cell tumour, not unlike the same type in the other birds described above.

A Comparative View.

(1) Teratoma.

Spontaneous testicular teratomas occur in man, the horse, domestic fowl and the strain 129 mouse. Their frequency in these species has already been discussed. That they do occur in other species of bird is indicated by Murray's (1919) report of a

testicular teratoma in a golden eagle, but they are either rare or relatively unobtainable.

The outstanding difference between the human testicular teratoma and the others is the malignant propensity of the vast majority of the human tumours. Nearly all the equine testicular teratomas have been incidental findings at gelding of young colts or discovered on removal of an imperfectly descended testis. In many respects these equine tumours resemble the teratomas of childhood and human ovarian teratomas.

Although malignant change does occasionally arise in the human ovarian teratoma, no unequivocal reports of a malignant equine teratoma have yet appeared (Cotchin, 1962). Perhaps the parallel of the equine testicular teratoma is the fully differentiated testicular teratoma of man. It will be recalled that this particular variety of teratoma has a spread over the early decades of life and that seven of the Testicular Tumour Panel's 13 cases occurred in children of less than 14 years of age (Pugh and Smith, 1964). Its equine counterpart occurrs largely in the first three years of life which with the average equine life span of 30 years is roughly equivalent to the years of childhood. Again the non-metastasising testicular teratomas of strain 129 mice appear to originate in an embryonal type of growth localised within the tubules in the 15-16 day foetus (Stevens, 1962 a). In later foetal life the growth ruptures the seminiferous tubules and at 19 days, primitive

epithelial structures are present. After birth development of teratomatous structure increases. There is no evidence so far to show that the fully differentiated human and equine teratomas have passed through this process of development. If all teratomas pass through this undifferentiated embryonal phase, it may be that the process of advanced differentiation with non-persistence of the embryonal elements can only occur in early life. Growth hormone or inducing factors responsible for development are of course particularly active at this period. The effect of growth hormone on the relatively undifferentiated teratoma might be of interest.

The testicular teratomas in domestic fowl, both spontaneous and experimental, show the wide range of somatic structures at differing stages of development usually found in the teratoma of the human adult male. Chorionepithelioma is absent as would be expected from the lack of chorionic development in the bird.

Little is yet known about the hormone dependance of the testicular teratoma. Initial observations by the author in the appended article (Guthrie, 1966) indicate that synthetic anti-gonadotrophins suppress the growth of teratomas induced by zinc in the fowl.

Seminoma.

Because of the high incidence of seminoma in the dog (Dow, 1962), the canine seminoma can be usefully compared in morphology, biological behaviour and incidence with its human counterpart. In particular the dog has afforded the opportunity

for the study of exclusively intratubular seminoma, seldom discovered in man except in association with an established extratubular seminoma or teratoma. Intratubular seminoma in the dog has been found in post-mortem studies and in study of the contra-lateral testis in unilateral tumour. This confinement of the seminoma to the seminiferous tubules provides the evidence for the intratubular origin of the seminoma.

Scully (1961) considered that the canine seminoma was more like the spermatocytic than the classical variety of the human seminoma. This if true might be significant if the human spermatocytic seminoma had a different behavioural pattern from the other seminomas. The 15 tumours allocated to the spermatocytic group by the British Testicular Tumour Panel had not proved fatal at the time of publication (Thackray, 1964), but this number is too small for adequate assessment.

Although Willis (1960) records a canine seminoma with metastases, he refers to the canine seminomas as being much less malignant than their human counterparts, growing slowly and rarely metastasising. In fact we do not appear to have any definite information about the rate of growth of either human or canine seminomas within the testis, and only a few observations on the growth rate of metastatic human seminoma in the lungs (Spratt and Spratt, 1964). Also 10 per cent of canine seminomas in Dow's post-mortem series had metastases. The belief that the canine seminoma is less malignant than the human seems therefore

to have no firm basis.

Many authors have commented on the tendency for seminoma to occur in older dogs and as can be seen from Table XIX the average age in most series is about 11 years. It is difficult to equate accurately the total life span or even the reproductive life span of one species with another. If one takes a life span of 15 years in the dog, then on an arbitrary basis 70 years in man is roughly equivalent. The peak incidence is usually raised by the inclusion of post-mortem cases as many dogs are killed not because of their tumour, but because of their advanced age. But Cotchin's (1960) series is almost entirely surgical and his peak incidence at 10 years would be roughly equivalent to 46 years in the human, which is only slightly later than the peak in human seminomas (Chapter I). The human spermatocytic seminoma with which Scully (1961) has compared the canine seminoma also occurs at a later period than the classical seminoma (Thackray, 1964).

As with the human, seminoma has been reported to follow atrophy of the canine testis and in many of the minute nodules of intratubular seminoma, the malignant in-situ change is seen to be continuous with atrophic seminiferous tubules (Dow, 1962).

The association of seminoma with tubular atrophy is common to man, dog and ram. It will be recalled that only two of the 17 canine seminomas in the present small series showed spermatogenesis even in tubules at some distance from the tumour.

The initiation of the neoplastic process in these tubules largely lined by Sertoli cells and occasional spermatogonia is only seen clearly in the dog and in the ram. Failure of tubular development as in the undescended testis is associated with an increased incidence of testicular tumour both seminoma and teratoma in man. Although none of the 17 canine seminomas in the present series arose in undescended testes 26 per cent of 69 dogs in Cotchin's (1960) series had seminomas arising in ectopic testes. Six per cent of human seminomas in the author's series (Chapter II) and eight per cent in the British Testicular Tumour Panel's series of 400 seminomas arose in undesconded testes (Thackray, 1964).

A similar lymphocytic reaction is frequently present in both human and canine seminomas. It appears to be an early feature and its presence around tubules showing intratubular seminoma in the dog has already been described.

Information about true incidence of animal neoplasms is hard to obtain as tumours are not centrally or regionally registered. Another way to compare the incidence, in this case of seminomas, is to consider it in relationship to other forms of malignant disease. In a mainly surgical series Cotchin, (1960) found that 5.8 per cent of 2361 canine tumours (presumably from both sexes) were testicular and one third of these were seminomas (1.9 per cent). Statistical reports of St. Bartholomews Hospital, London from 1948-57 showed 58 cases of testicular tumour out of a total of 5470 males with malignant disease, an incidence of about

1 per cent. A somewhat higher figure of 1.5 to 2 per cent is quoted by Gilbert and Hamilton (1940). Seminomas would account for about half of these (Chapter I). These figures are difficult to compare as Cotchin's canine tumours included both benign and malignant types. Nevertheless Dow's (1962) examination of 580 unselected dogs submitted for routine necropsy showed that 8 per cent had seminomas, a remarkably high incidence. At St. Mary's Hospital, London from 1952-61, 0.1 per cent of male deaths were attributed to seminoma. Unlike Dow's canine series, none were incidental findings.

No comparable figures of any kind exist for species other than man or dog, except perhaps for Jensen and Flint's (1963) finding of intratubular seminoma in 10 per cent of 78 "undesirable" rams collected from Colorado. The early castration which is practised in domestic animals not required for breeding vitiates the collection of adequate statistics.

Sertoli-cell Tumour.

Sertoli-cell tumours are almost as common as seminomas in the dog, but their extreme rarity in man and other species has prevented comparative studies. Only six of the Testicular Tumour Panel's 995 cases were classified as Sertoli-cell tumours (Collins and Symington, 1964). Focal Sertoli-cell hyperplasia leading to small nodules visible to the naked eye is not uncommon in undescended testes and in human male pseudo-hermaphrodites. In this type of intersex Neubecker and Theiss (1962) reported several Sertoli-cell adenomas. The discovery of congenital Sertoli-cell

tumours in bulls (Cotchin, 1960 a) calls for further investigation in that species, as both the foetal condition and subsequent development are unknown.

Following the injection of cadmium chloride solution into the testes of domestic fowl the author has noted the presence of Sertoli-cell nodules up to 4 mms. in diameter surrounding the cadmium scars (Guthrie, 1964 b). The two fowl with this condition showed in their pituitary glands marked increase in numbers and granularity of the P.A.S. positive gonadotrophs. No information appears to be available on pituitary cytology in man or dog with Sertoli-cell tumour.

Interstitial-cell Tumours.

These tumours have rather similar appearances in all species. Like Sertoli-cell tumours they have a hyperplastic counterpart which is commoner and is found in both dog and man in undescended testis and in testicular atrophy from varying causes. As in so many areas the borderline between hyperplasia of a functional nature and true neoplasia can be hard to define.

Experimental interstitial-cell tumours have been produced by a variety of methods. Bonser and Robson (1940) induced them in mice by injecting the synthetic oestrogen, triphenylethylene. The tumours arose in association with tubular atrophy. This followed Burrow's discovery (1935) that hyperplasia of the interstitial cells of the murine testis resulted from the administration of oestrogens. Another mechanism of induction was by intrasplenic

testicular grafts after bilateral orchidectomy in rats (Twombly, Meisel and Stout, 1949). In the author's early experiments (Guthrie, 1956-appended) interstitial-cell tumours appeared only in the left testis after methyl-cholanthrene implantation into the right testis. On the other hand two interstitial-cell tumours in the inoculated testis arose after implantation of 2-acetyl-amino-fluorene. One of these was associated with fibrosarcomatous deposits in peritoneum, liver and kidneys and some points of similarity between these and the testicular tumour raised the possibility of this being a malignant interstitial-cell tumour. The difficulty in diagnosing malignancy in interstitial-cell tumours seems common to all species and to both spontaneous and experimental tumours. The interstitial cell of Leydig is generally considered to be a modified fibroblast, arising from fibroblasts of the interstitium or the fusiform cells of the lamina propria (Fawcett and Burgos, 1960). In its malignant form an interstitial cell tumour might therefore be fibre forming and composed of fusiform cells. This is essentially a fibrosarcoma and only the detection of its specialised morphology in parts of the tumour would reveal its histogenesis. In man, proven malignant interstitial-cell tumours are extremely rare (Short and Coe, 1963). In any tumour the presence of metastases constitutes the only absolute proof of malignancy. In an assessment of eight recorded cases of malignant interstitial-cell tumours with metastases in man, Blundon, Russi and Bunts (1953) noted that the testicular growths had the same histological

features as benign tumours and that three of them could not be clearly differentiated from hyperplasias. On the other hand an anaplastic sarcomatous tumour arising in the testis may be of interstitial-cell origin, but in the absence of abnormal hormone production its histogenesis may remain obscure.

Other Types of Testicular Tumour.

One might speculate on the non-occurrence of certain types of tumour in particular species. Two relatively rare human testicular tumours, the orchioblastoma of the infant testis and the adenomatoid tumour of the epididymis are not recorded in other species. The orchioblastoma (see Chapter VII) is confined to a very limited segment of man's long life span. The equivalent period in most of the animals discussed above would be less than a year. The lymphomas presenting in the testis appear to be virtually unknown, except in man. As seen in Table XVI lymphosarcoma of the testis has been recorded in a bird. In man lymphoma of the testis (Chapter V) shows its peak incidence between 60 and 80 years (Gowing, 1964). The curtailed life span of many of the domestic species, would diminish the incidence of tumours tending to occur in old age. Lymphosarcoma in other sites is of importance in cattle, dogs, cats and pigs and sheep and occurs at all ages (Cotchin, 1962). Its involvement of the testis may not always be noticed during life or even at necropsy.

Fig. 54. Canine seminoma showing single nodular growth and localised bulging of testicular capsule. X 1.1

Fig. 55. Multiple nodules of seminoma in canine testis. This resembles the human spermatocytic seminoma.

Fig. 56a. Uniformly enlarged canine testis due to seminoma with distended veins in testicular capsule.

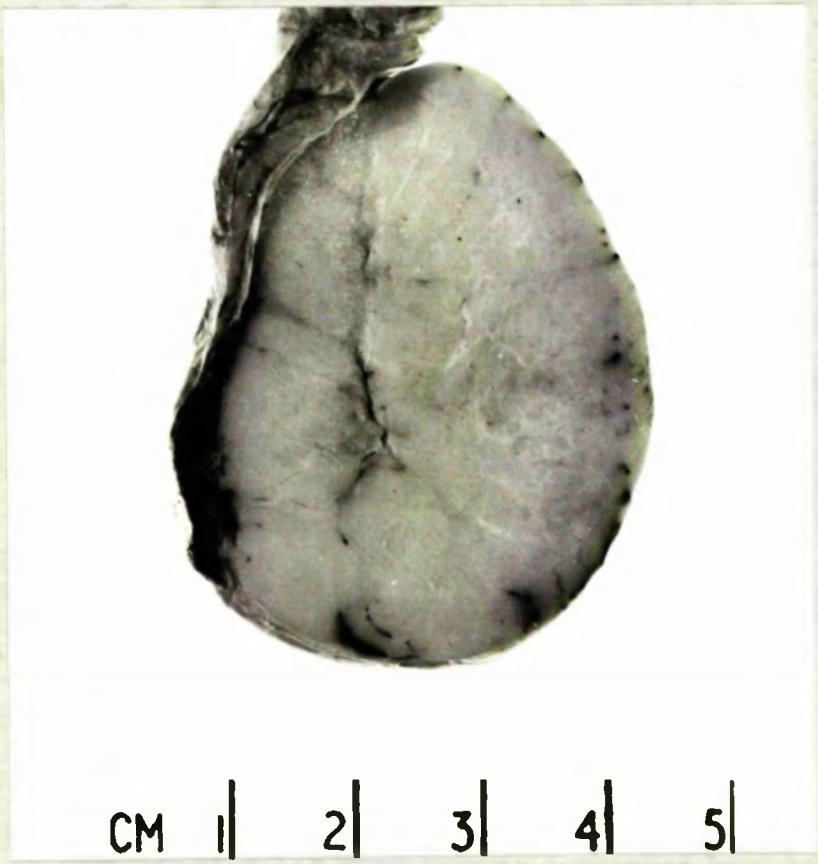


Fig. 56b. Section of seminoma illustrated above showing solid white lobulated tumour.

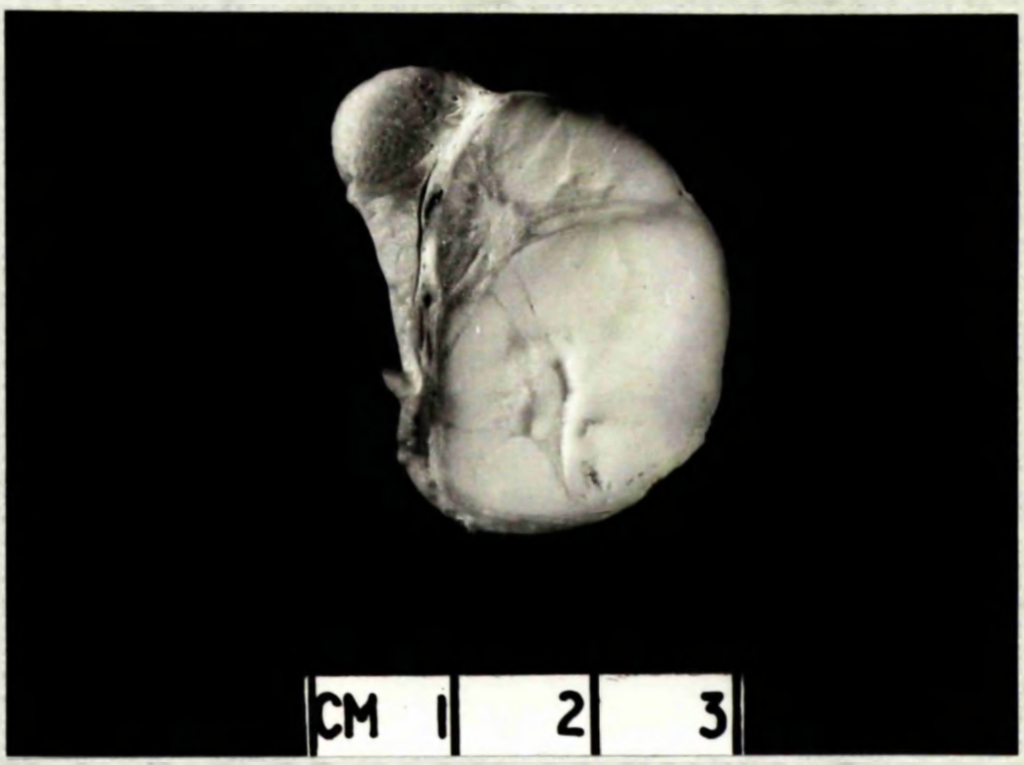


Fig. 57. Poodle aged 7 years. Encephaloid type of seminoma replacing greater part of testis.

Fig. 58. Wire-haired fox terrier aged 15 years. Enormous seminoma showing areas of necrosis and haemorrhage on the cut surface on the right. The left of the picture shows the external aspect. The lobulation of the tumour is apparent in both views.

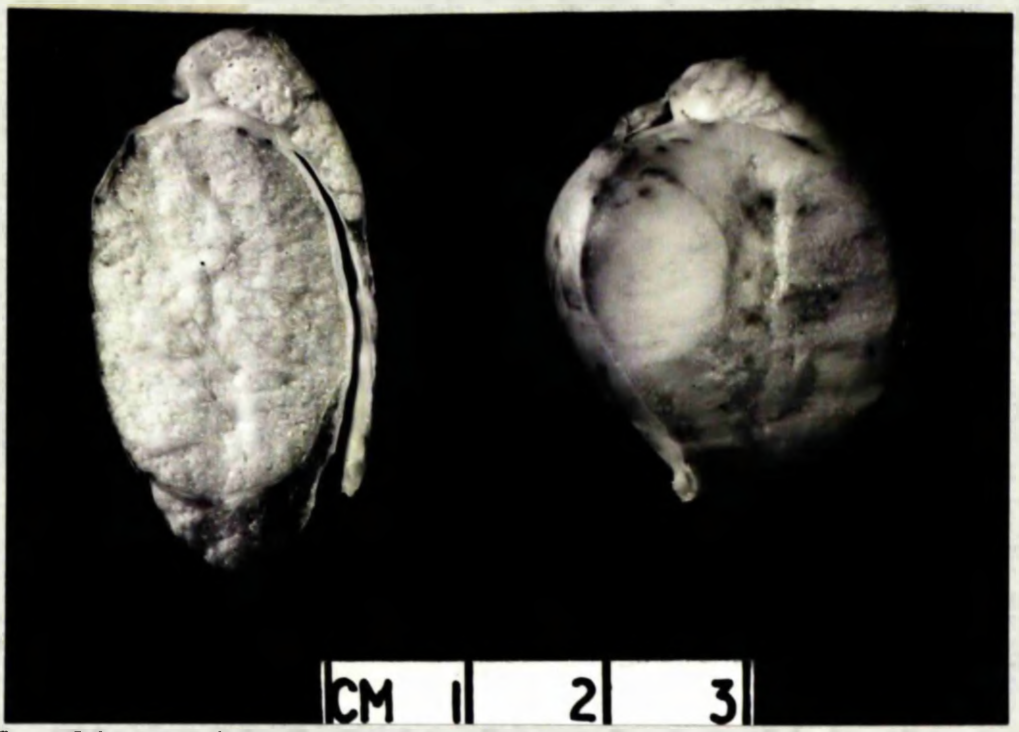


Fig. 59. Slices of both testes from a 9 year old dog treated by bilateral castration. The left testis shows several minute white nodules, the right a single large nodule of seminoma.

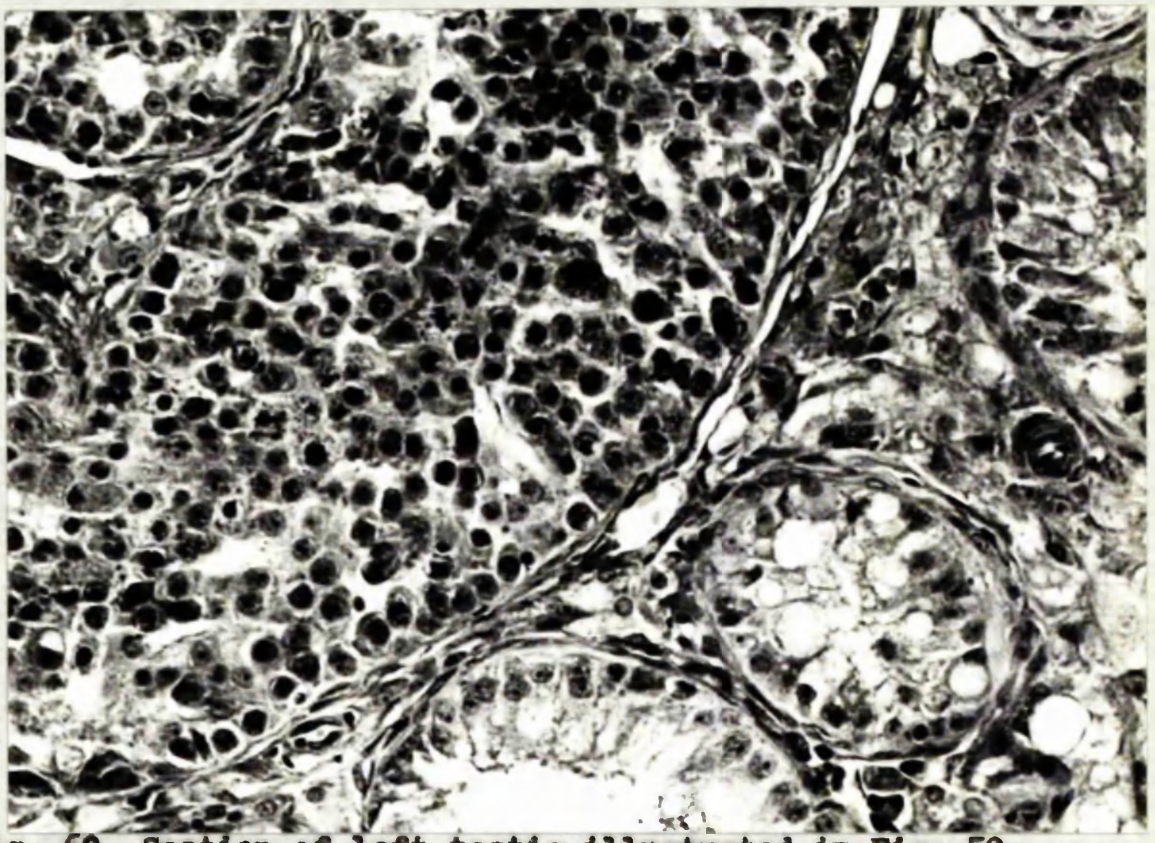


Fig. 60. Section of left testis illustrated in Fig. 59. Intratubular seminoma in distended seminiferous tubule extending across left side of picture. The tubules to the right and at the bottom are lined largely by Sertoli cells. H & E X 300.

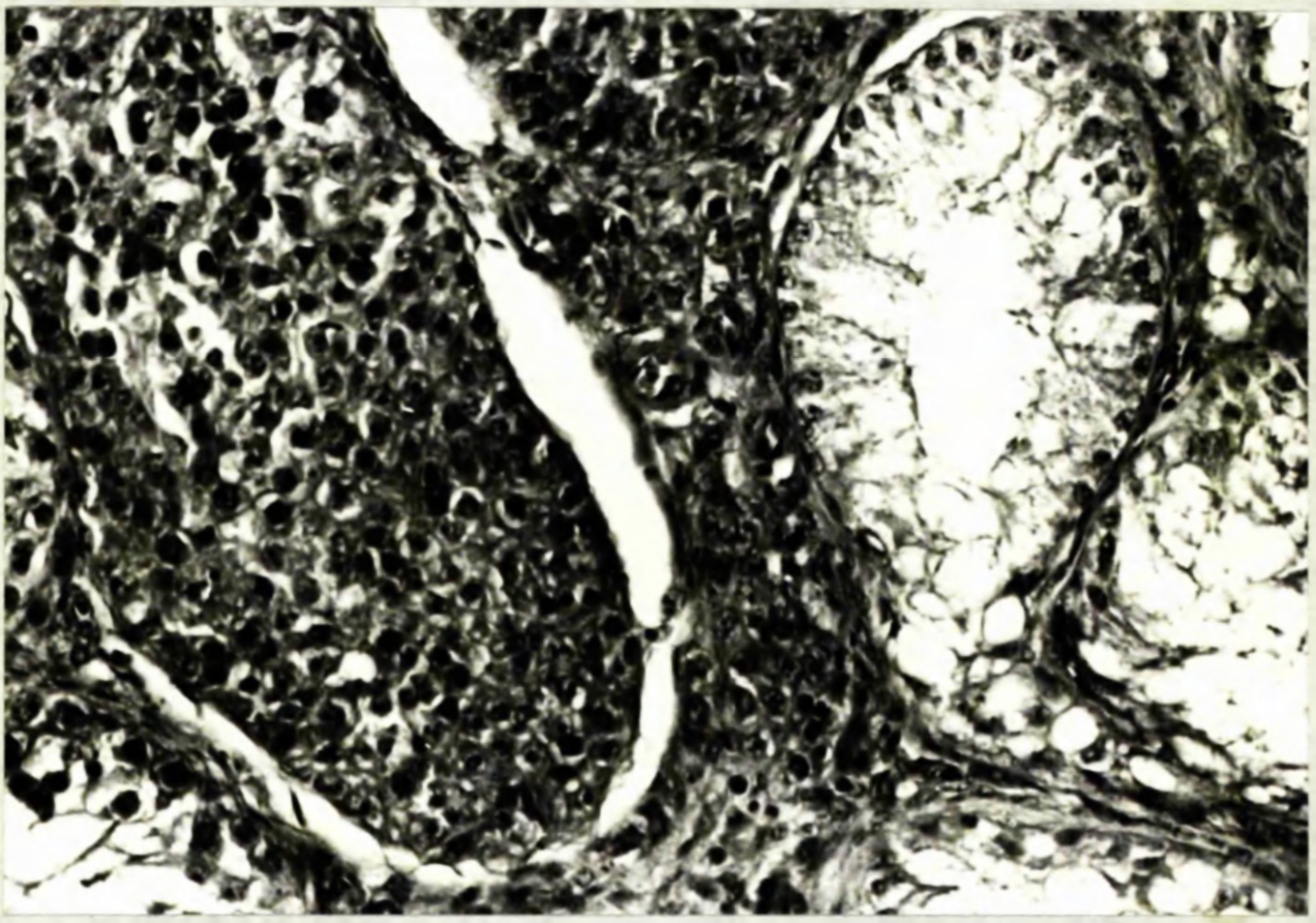


Fig. 61. Intratubular seminoma in the seminiferous tubule on the left, atrophic tubules on the right and invasive intertubular seminoma in the centre. H & E X 320.

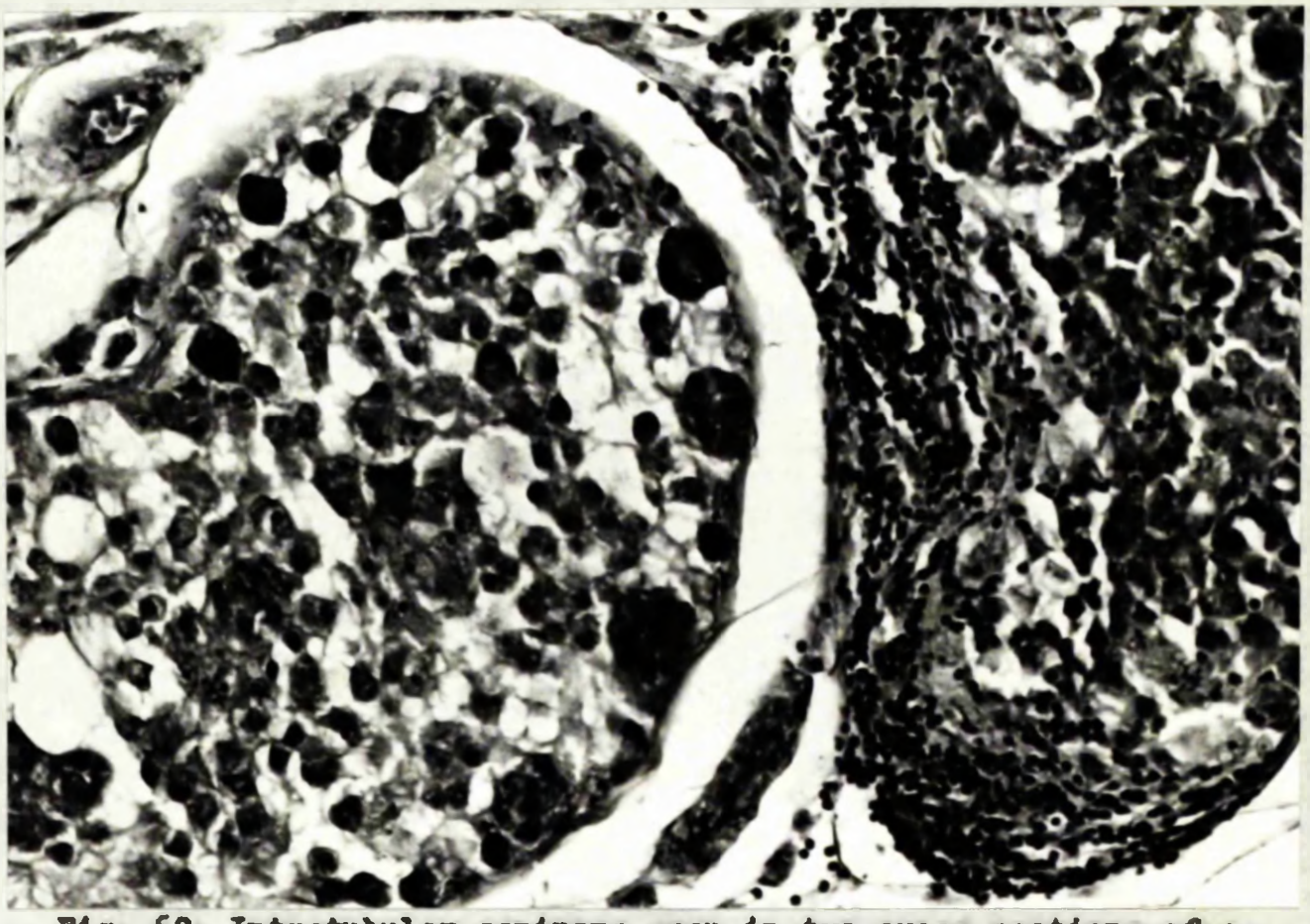


Fig. 62. Intratubular seminoma seen in two cross sections of a seminiferous tubule and showing numerous multinucleated giant tumour cells. Lymphocytes surround the tubule on the right. H & E X 320.

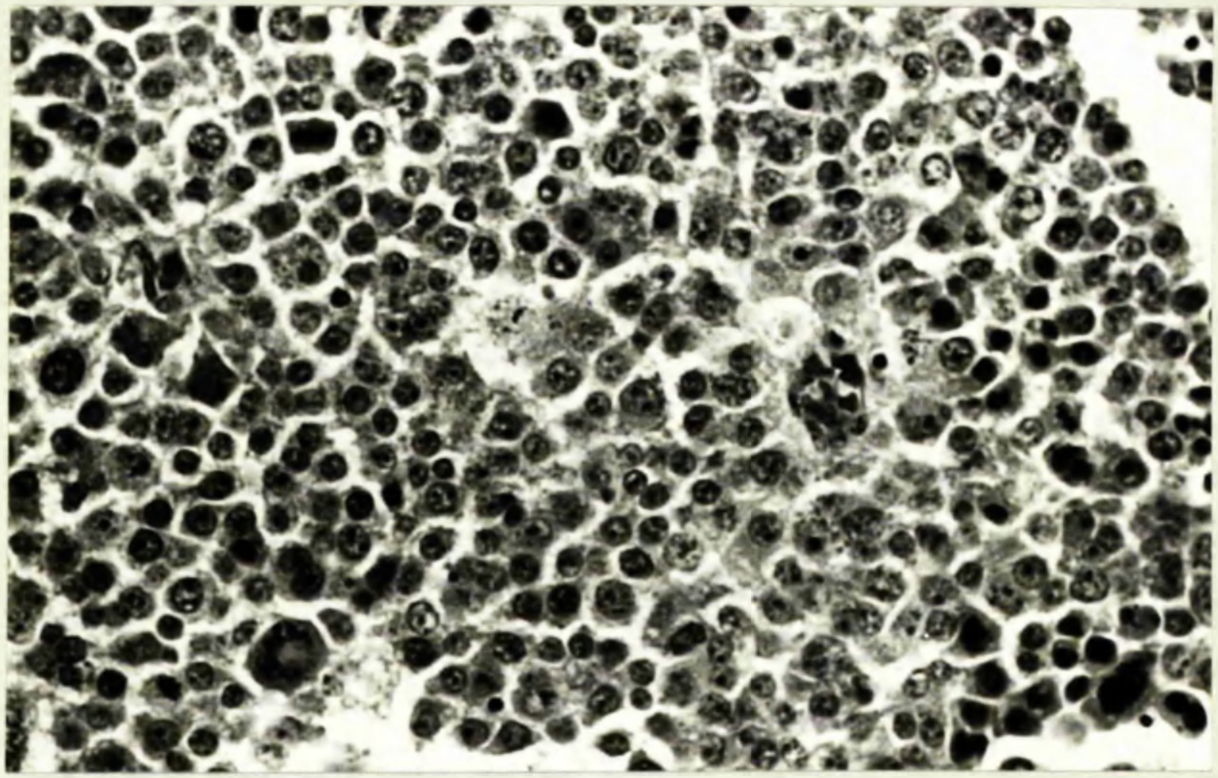


Fig. 63a. Numerous mitotic figures, but few multinucleated giant cells seen in interstitial extension of intratubular seminoma. H & E X 410.

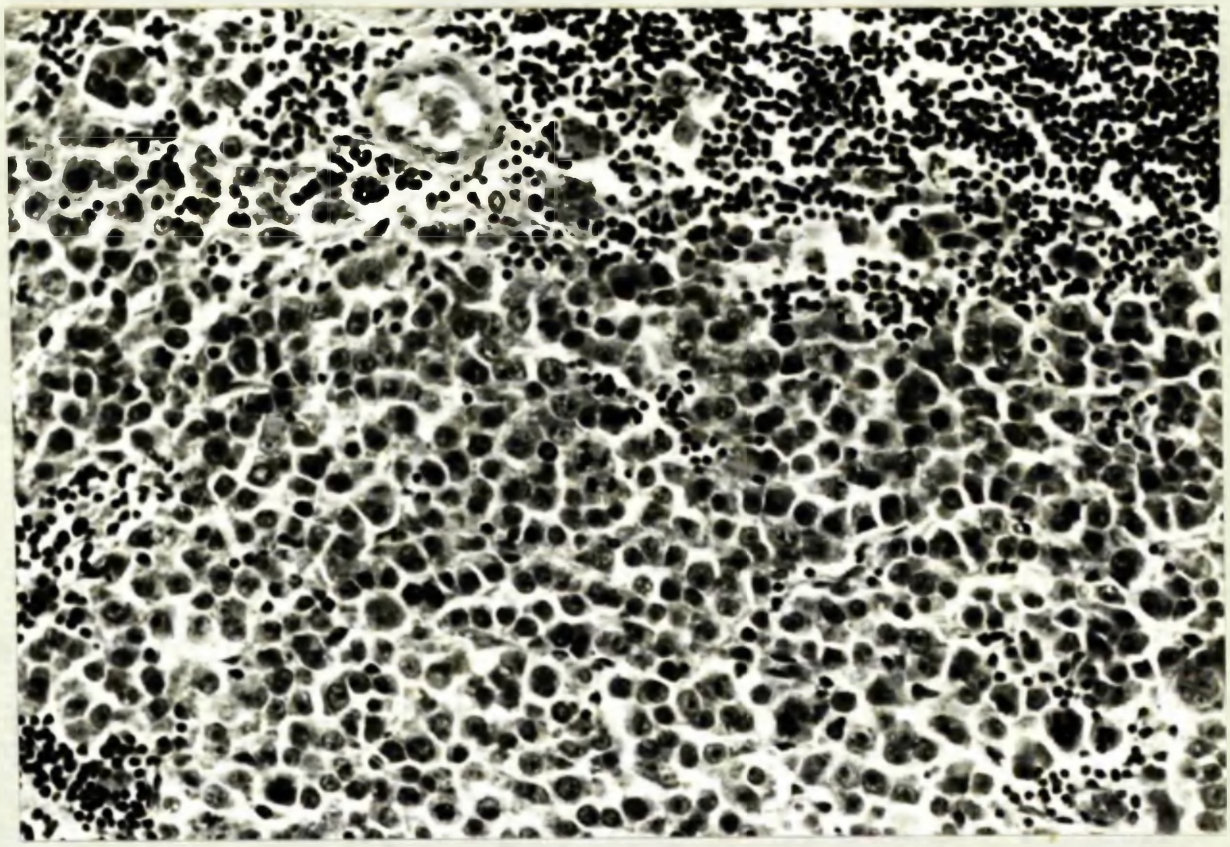


Fig. 63b. Lymphoid foci in interstitial extension of intratubular seminoma. H & E X 320.

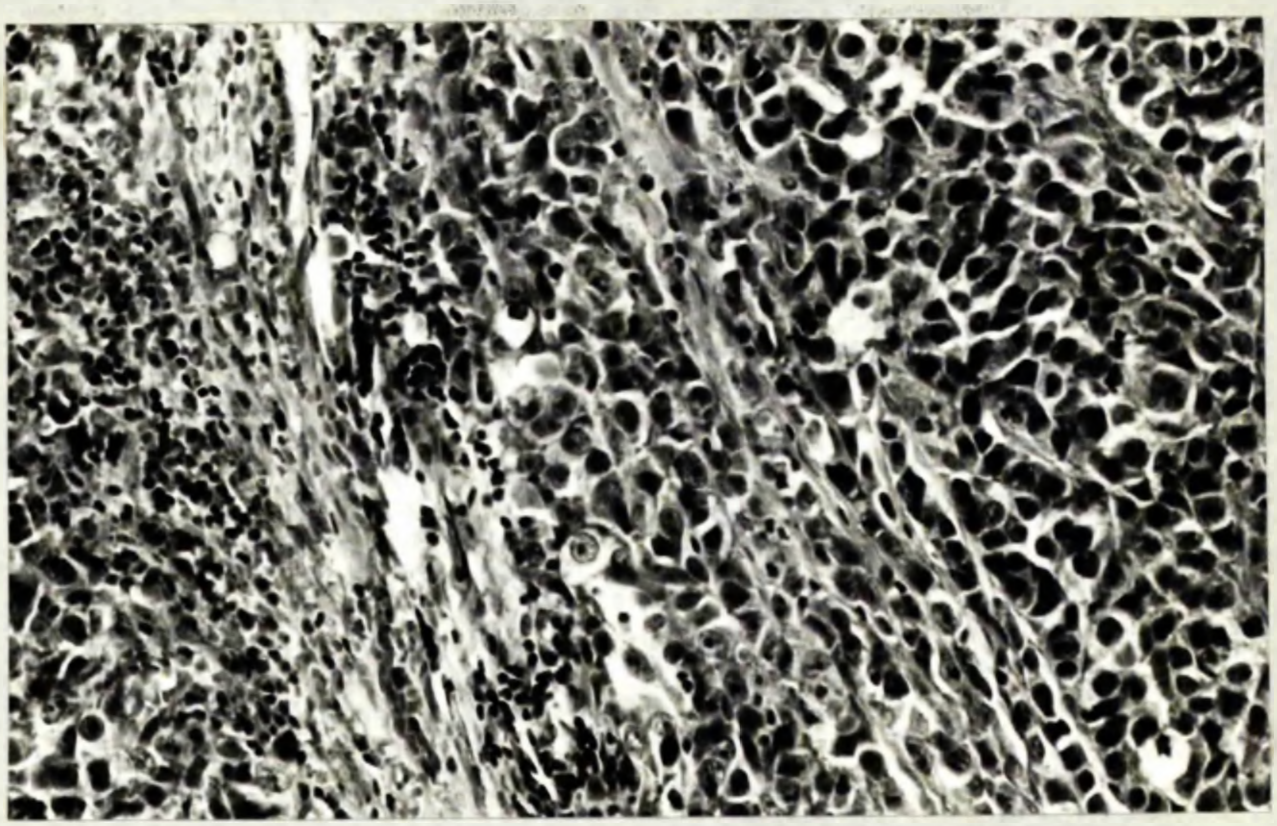


Fig. 64. Diffuse type of canine seminoma, showing some lymphocytic infiltration on the left. H & E X 320.

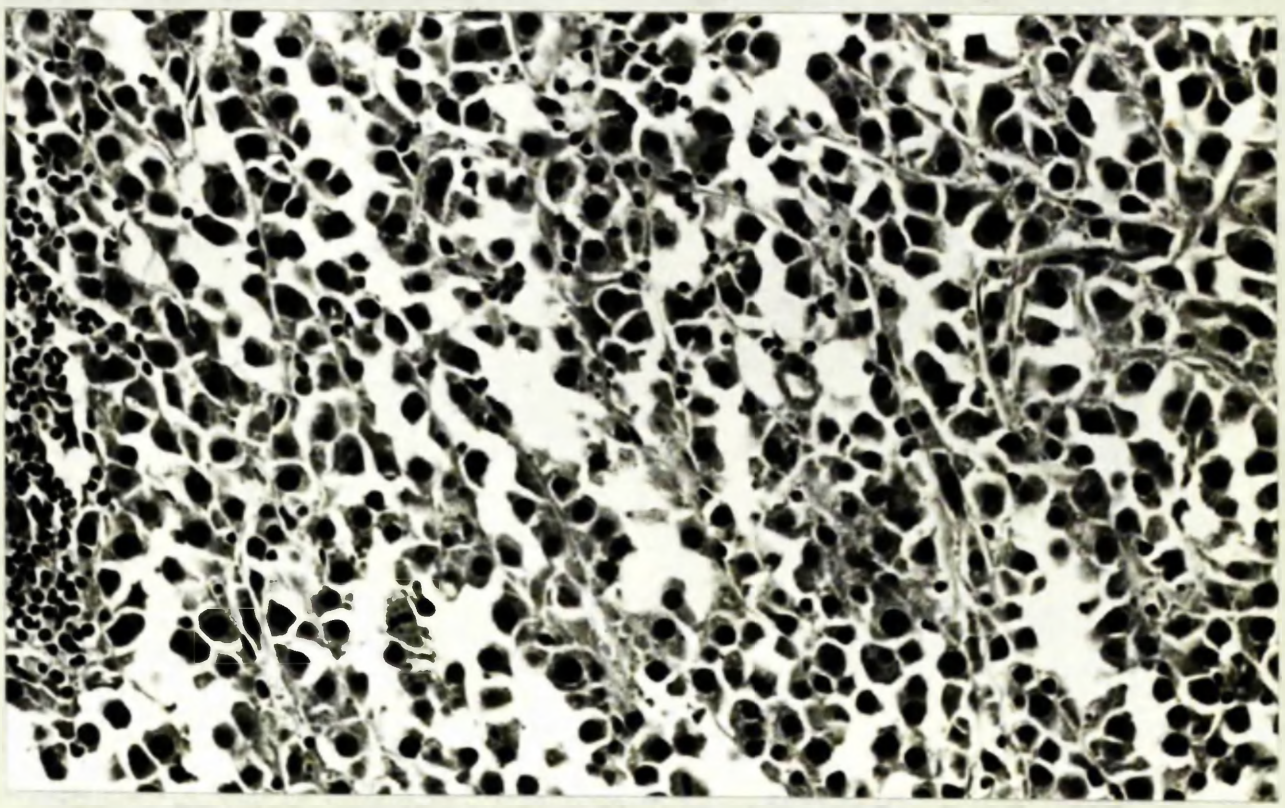


Fig. 65. Diffuse type of canine seminoma showing in this area flag-like cells arranged along fine fibrous trabeculae. There is also lymphocytic infiltration on the left of the picture. H & E X 500.

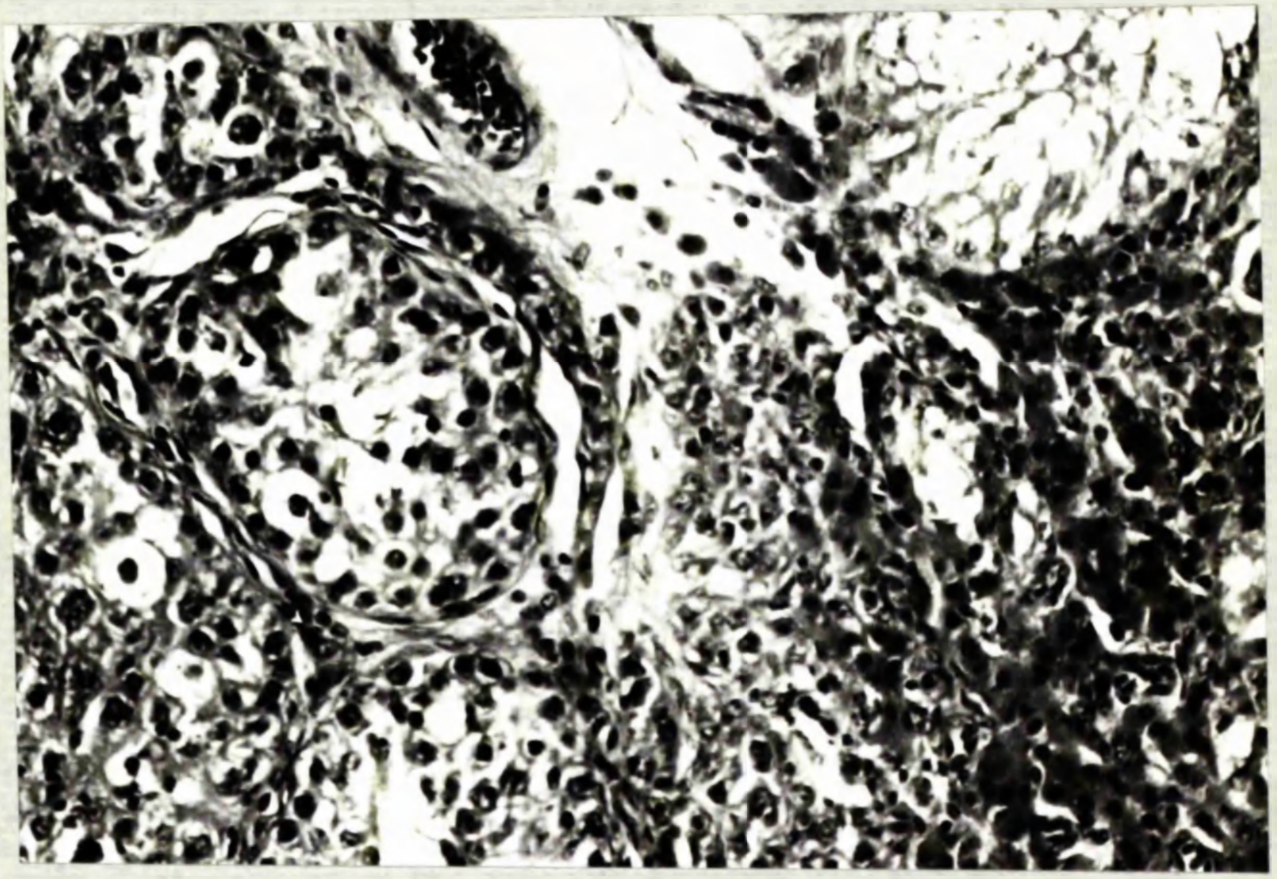


Fig. 66. Interstitial-cell hyperplasia (on right of picture) in a testis with intratubular and invasive seminoma. Intratubular seminoma is seen on the left; invasive seminoma is not included in the picture. An atrophic seminiferous tubule lined only by Sertoli cells is seen at top right. H & E X 320.

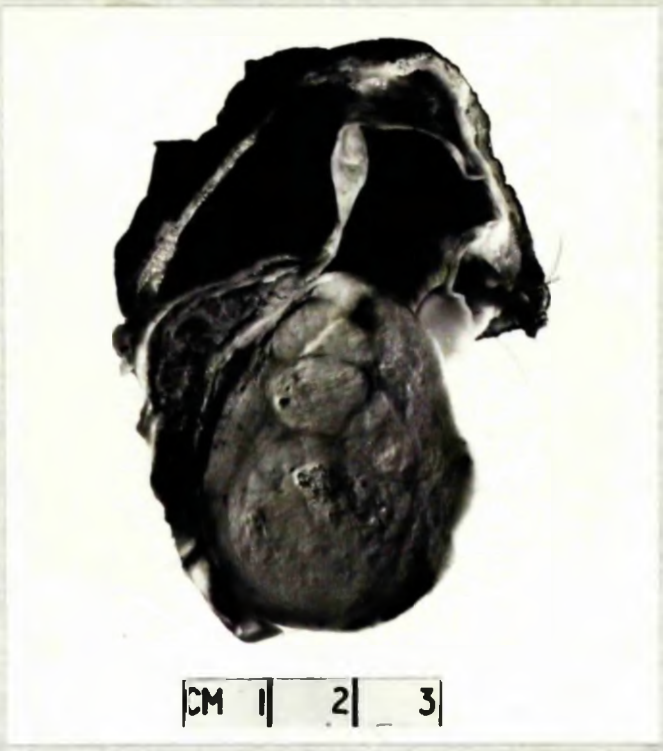


Fig. 67. Canine testis enlarged and largely replaced by Sertoli-cell tumour. The tumour of granular appearance due to its tubular structure is divided by fibrous septae.

Fig. 68. Canine Sertoli-cell tumour with the smooth cut surface resembling the seminoma. X 1.1

Fig. 69. Cystic spaces and areas of haemorrhage in a Sertoli-cell tumour in the ectopic right testis of a Pekingese.

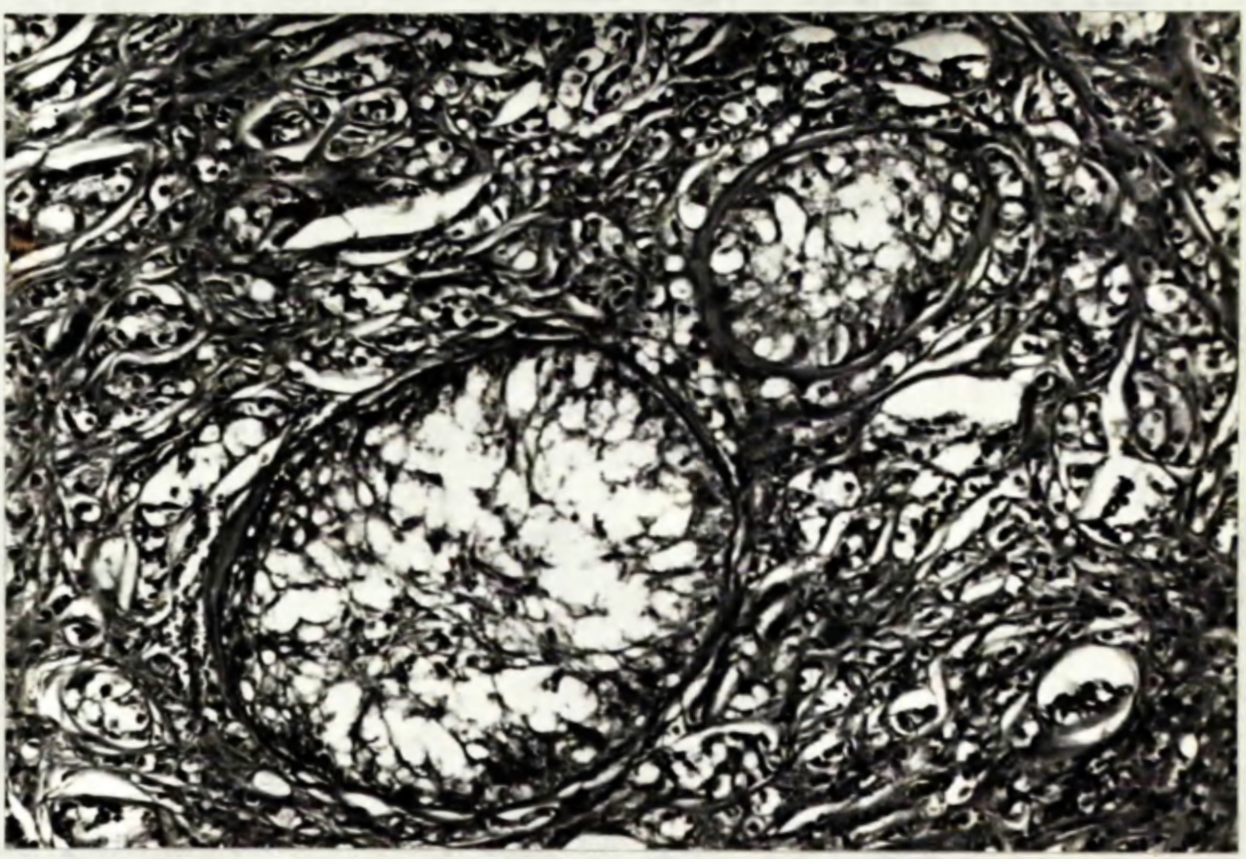


Fig. 70. Canine Sertoli-cell adenoma showing two cross sections of a large tubule lined by well differentiated Sertoli cells. The rest of the field shows a small tubular pattern. H & E X 130.

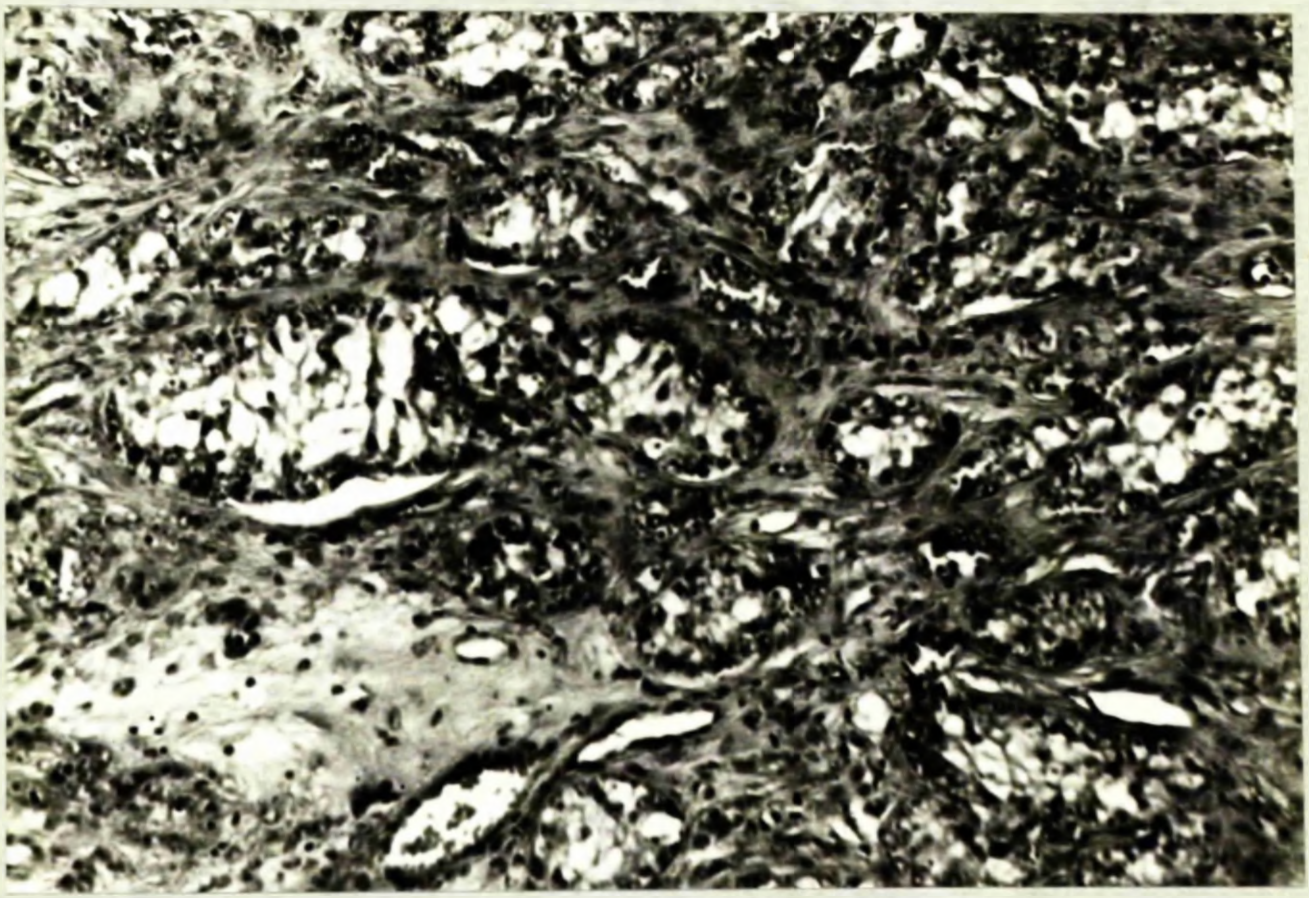


Fig. 71. Breakdown of regular tubular pattern in canine Sertoli-cell tumour is seen at the top right of the picture. Group of tumour cells are outwith the basement membrane of the tubule. H & E X 170.

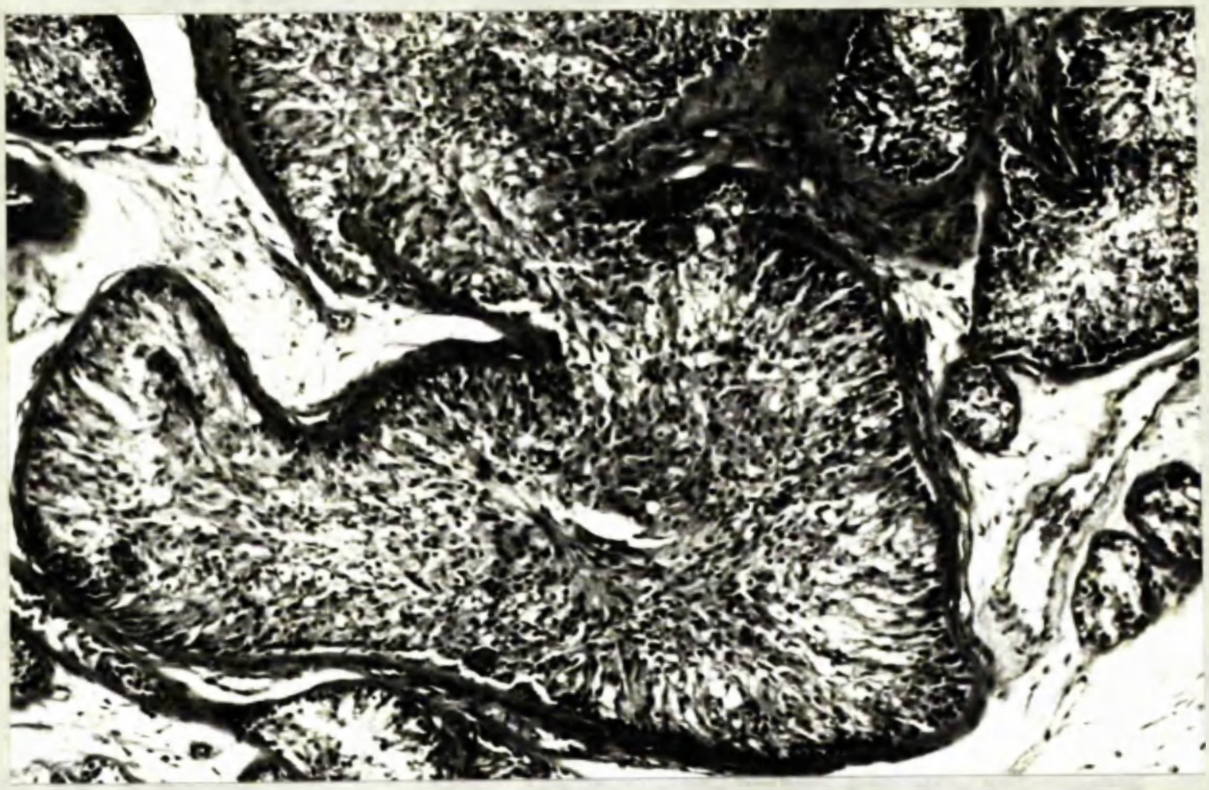


Fig. 72a. Canine Sertoli-cell tumour showing very large tubules filled with proliferating Sertoli cells, many of which show palisading. H & E X 116.

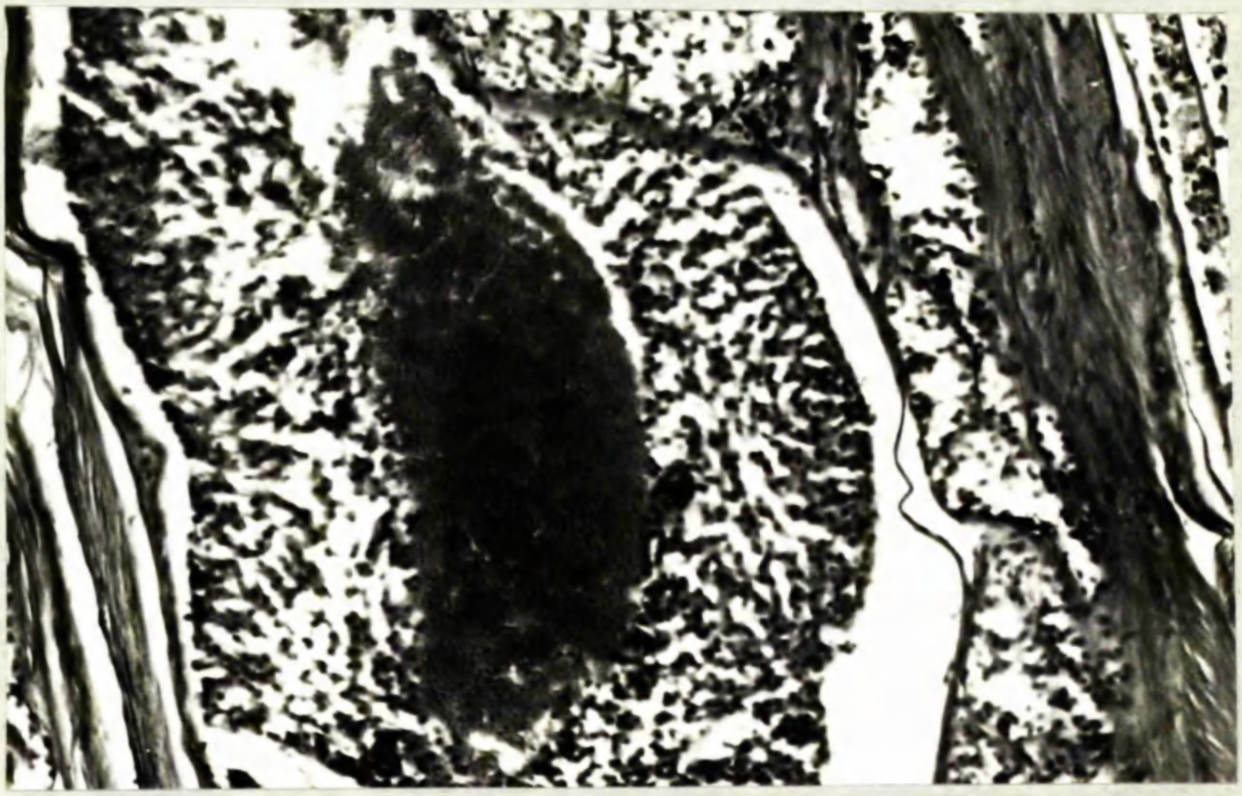


Fig. 72b. Central necrosis in the tubules of a canine Sertoli-cell tumour. H & E X 150.

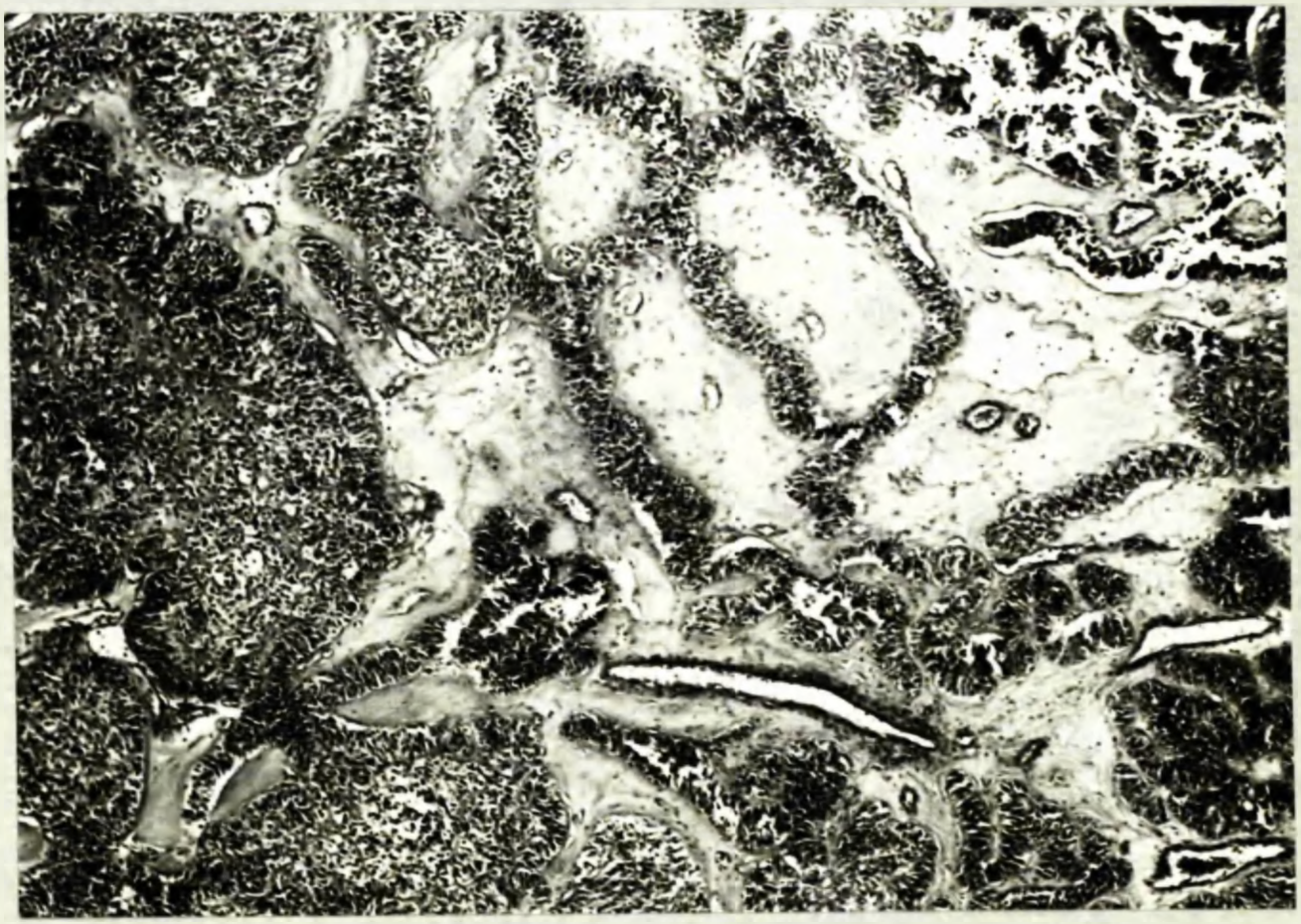


Fig. 73. Sertoli-cell tumour rather similar to that illustrated on Fig. 72a, but also showing a thick fibrous stroma in places. H & E X 67.

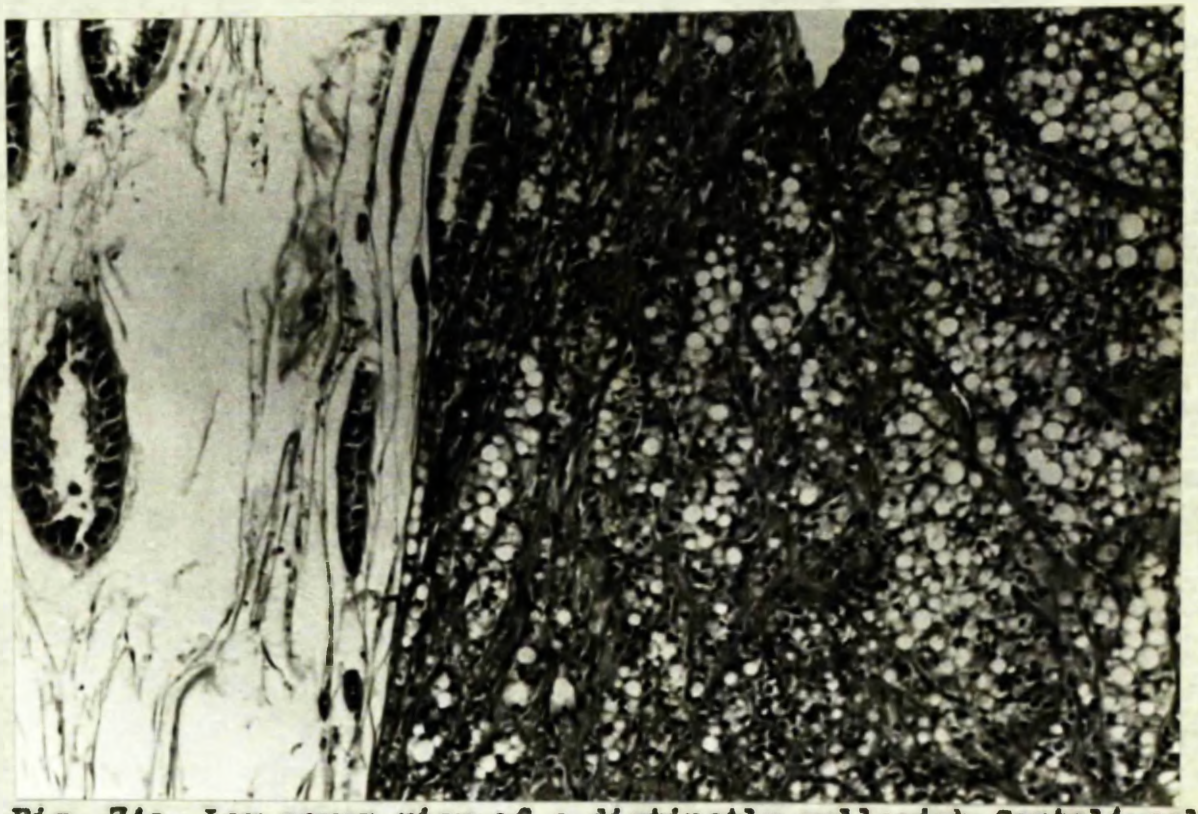


Fig. 74a. Low power view of a distinctly yellowish Sertoli-cell tumour showing the predominantly vacuolated nature of the cells. The seminiferous tubules on the left are atrophic. H & E X 120.

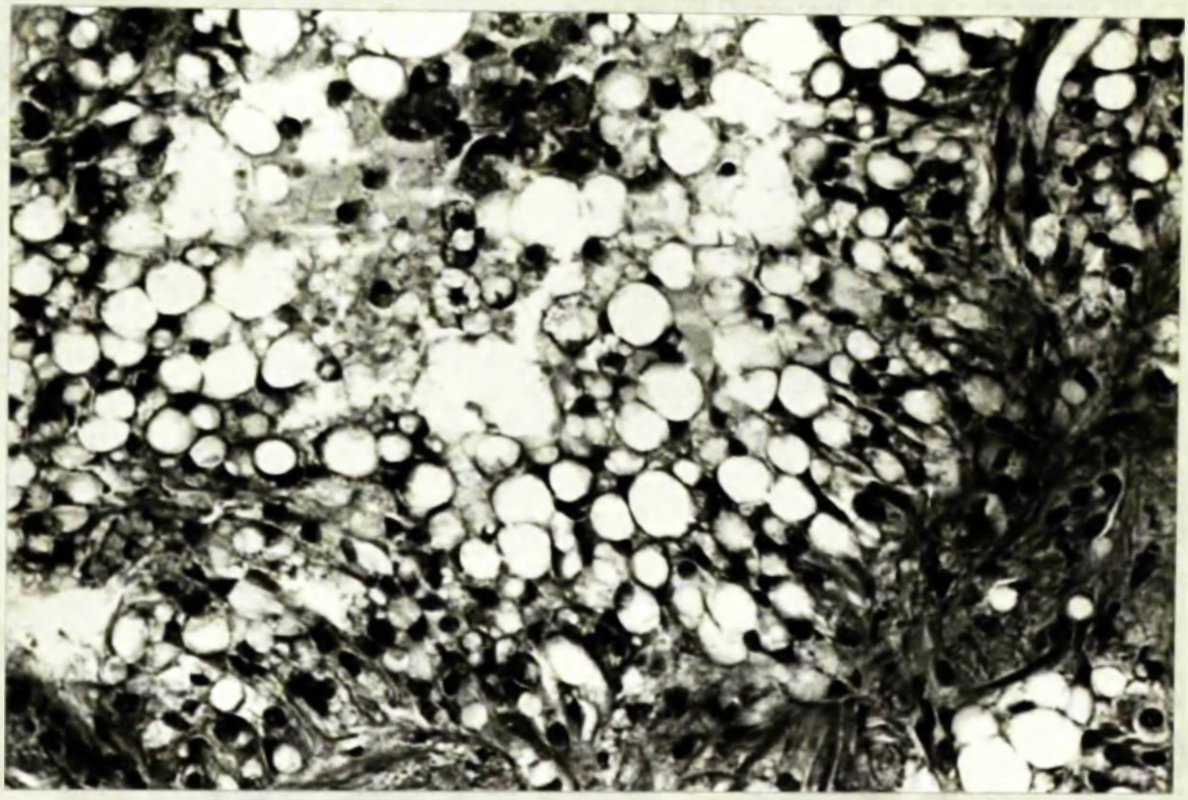


Fig. 74b. High power view of Fig. 74a. The vacuolation due to lipid and the resulting signet ring cells are clearly seen. H & E X 300.

Fig. 75. A yellowish brown interstitial-cell tumour found at post-mortem examination of an aged mongrel dog.

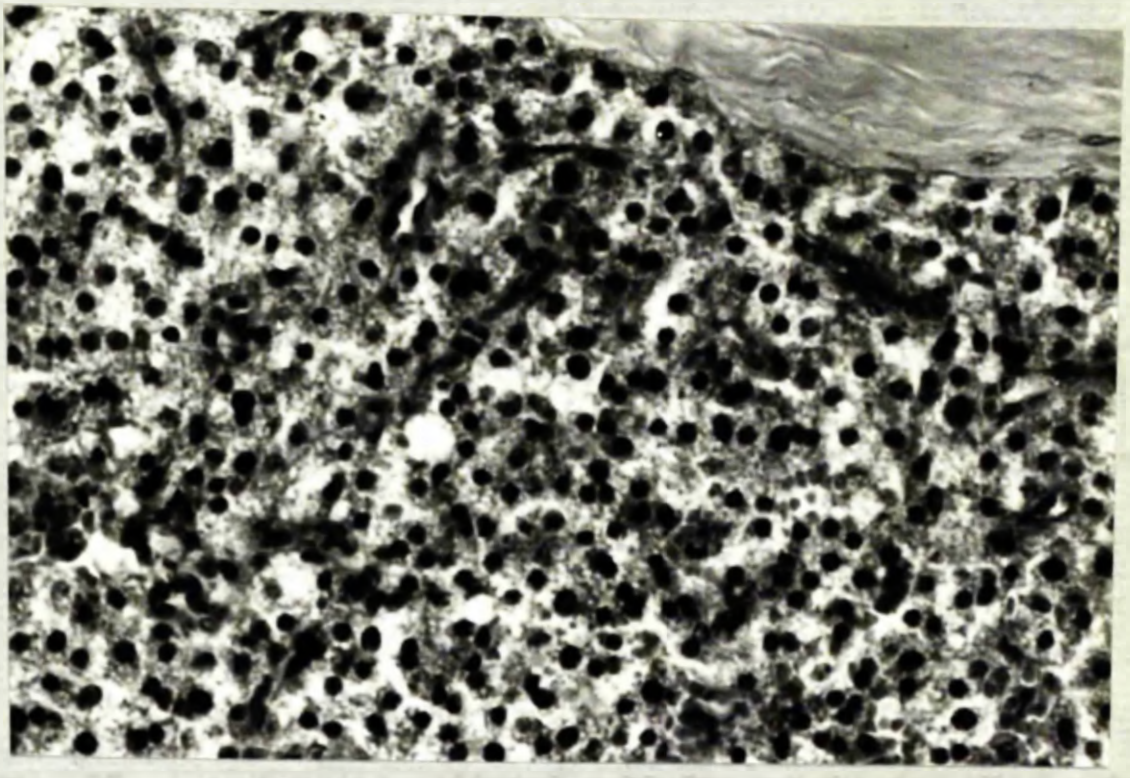


Fig. 76. A canine interstitial-cell tumour showing fine cytoplasmic vacuolation and granularity of the tumour cells. The nuclei are pycnotic. H & E X 410.

Fig. 77. Canine interstitial-cell tumour showing large cytoplasmic vacuoles. H & E X 580.

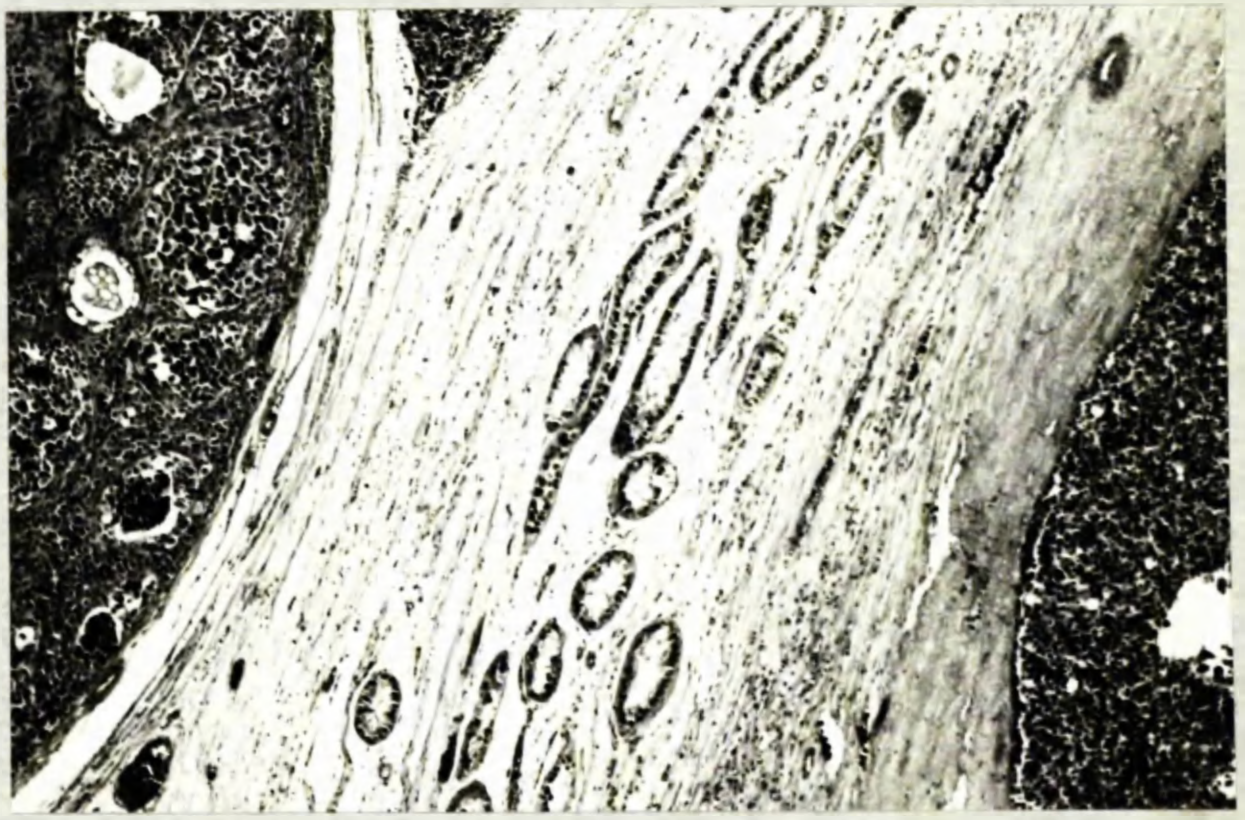


Fig. 78. Combined seminoma and interstitial-cell tumour in a canine testis. The seminoma is on the left and at the bottom left close to the tumour intratubular seminoma can be seen. H & E X 67.

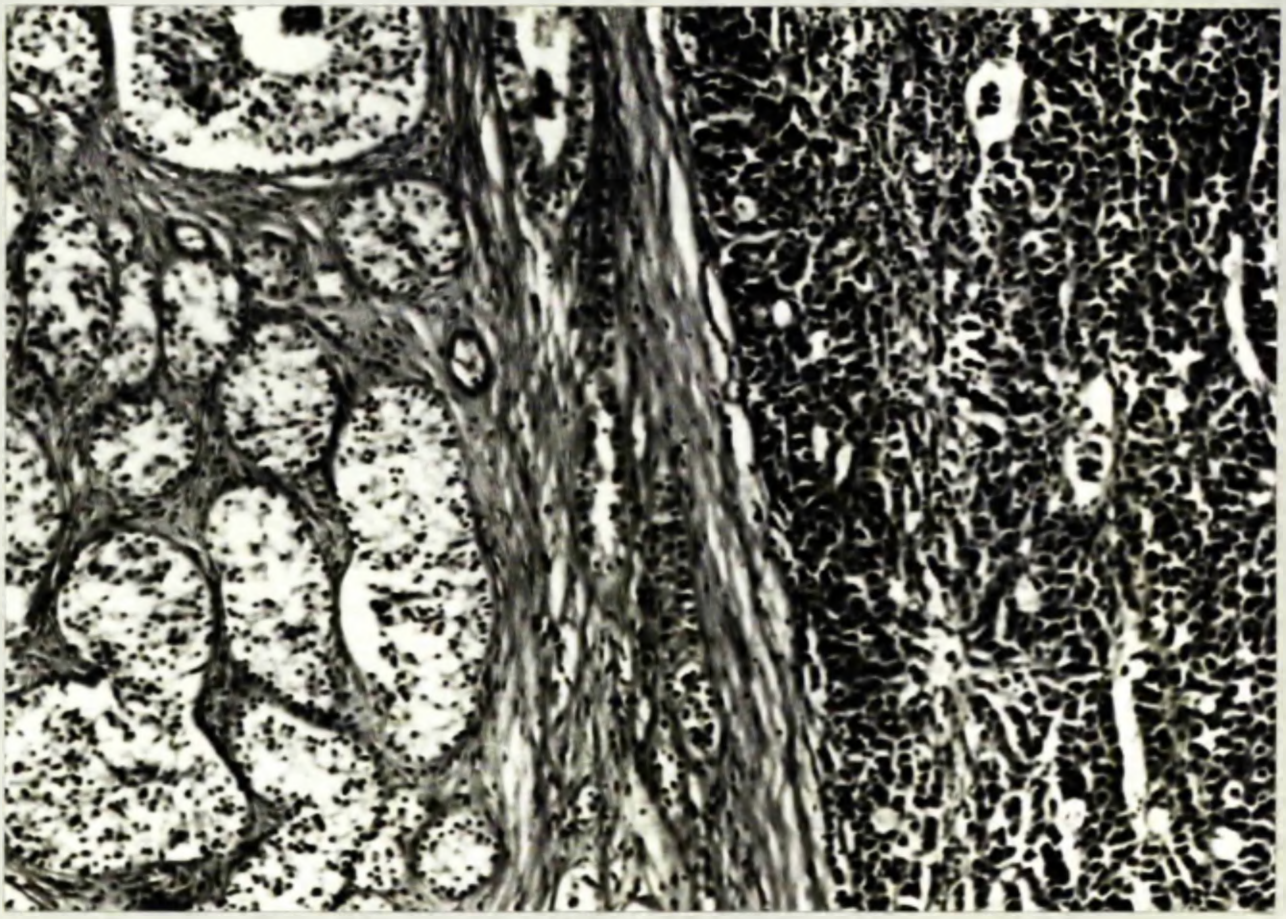


Fig. 79. Coexistent Sertoli-cell tumour and seminoma. The Sertoli-cell tumour on the left is fairly well differentiated. H & E X 66.

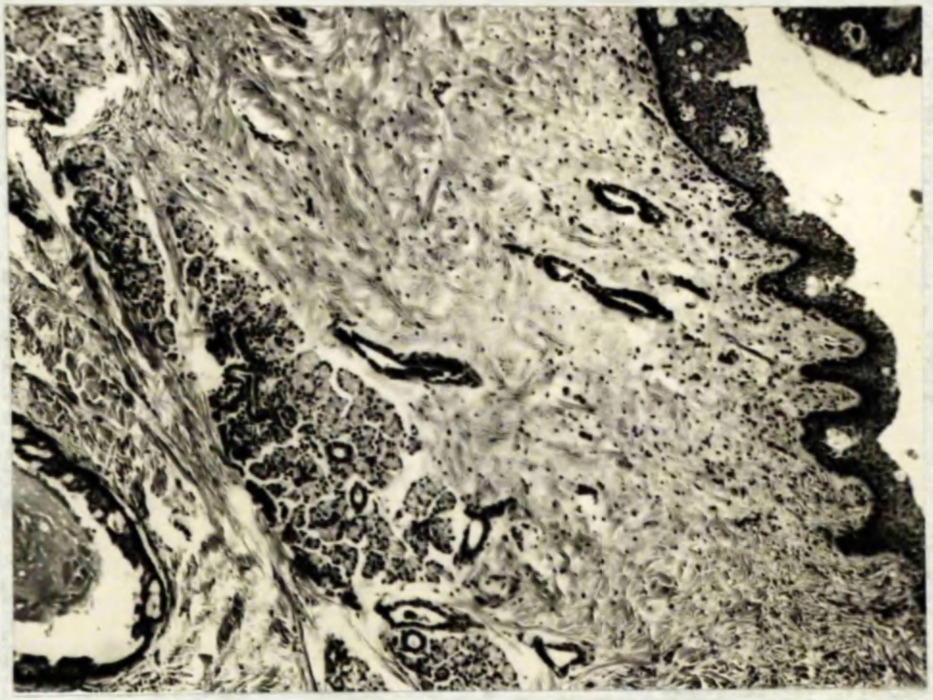


Fig. 80. Well differentiated teratoma in an equine testis. The cavity at bottom left is lined by respiratory epithelium and close to this are mucous glands and ducts. The centre of the field shows tubular structures lined by melanin pigmented cubical epithelium and on the right, part of a cavity is lined by stratified squamous epithelium. H & E X 25.

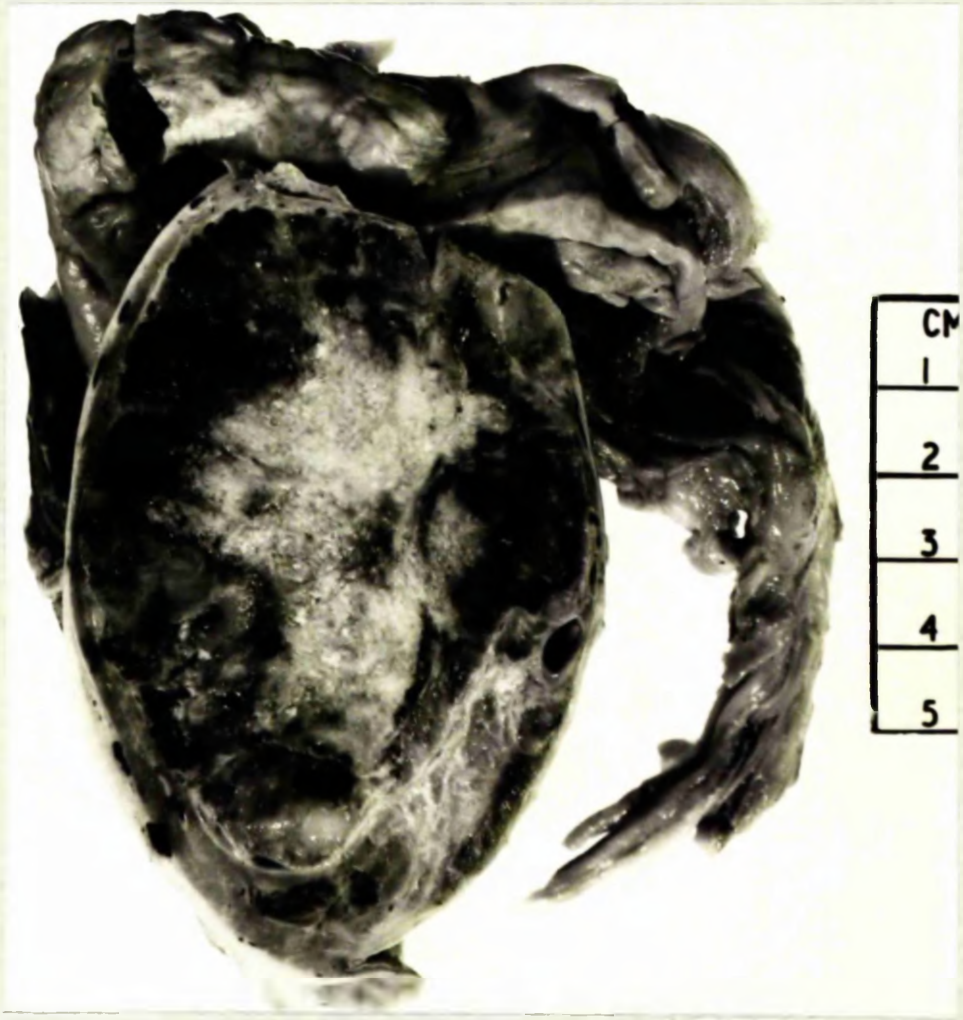
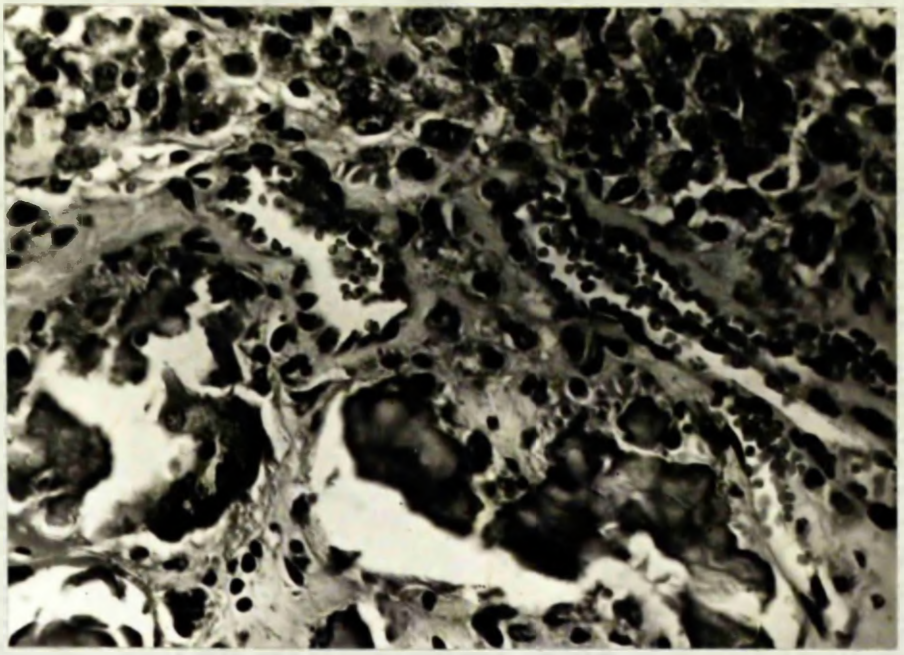


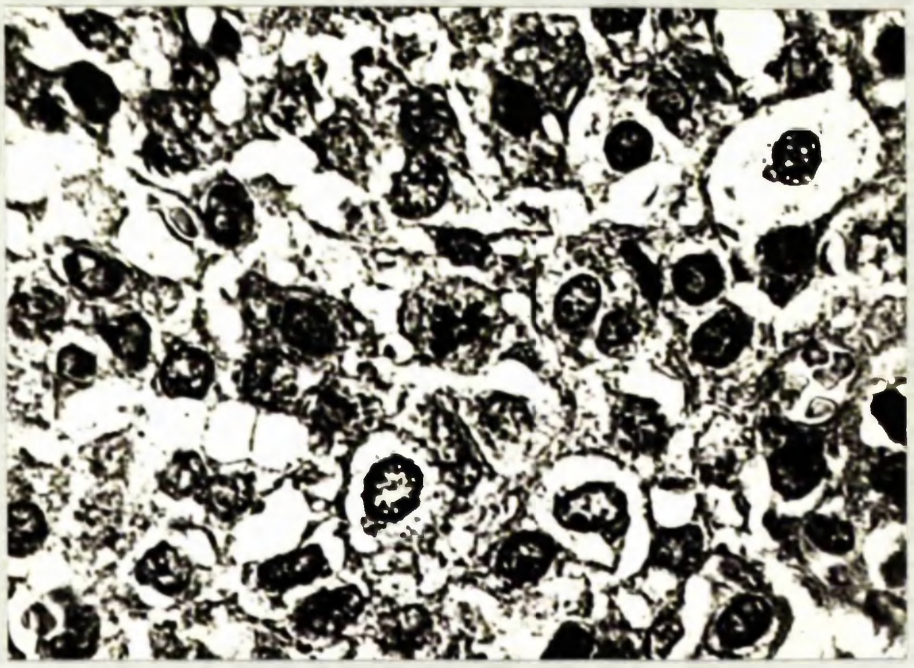
Fig. 81. Interstitial-cell tumour of right testis of antelope (Nyala). Note cystic areas and central necrosis.

Fig. 82. Interstitial-cell tumour of left testis of antelope (Nyala) illustrated in Fig. 81. The tumour has been bisected and opened. The large tumour of the right testis is seen in the background.



a

H & E X 500.



b

H & E X 950.

Figs. 83a and b. Sections of interstitial-cell tumour of antelope (Tragelaphus angasii) showing in (a) compact and granular interstitial cells and foci of amorphous calcification and in (b) foamy interstitial cells of high lipid content. A mitotic figure is seen in the centre of the field.

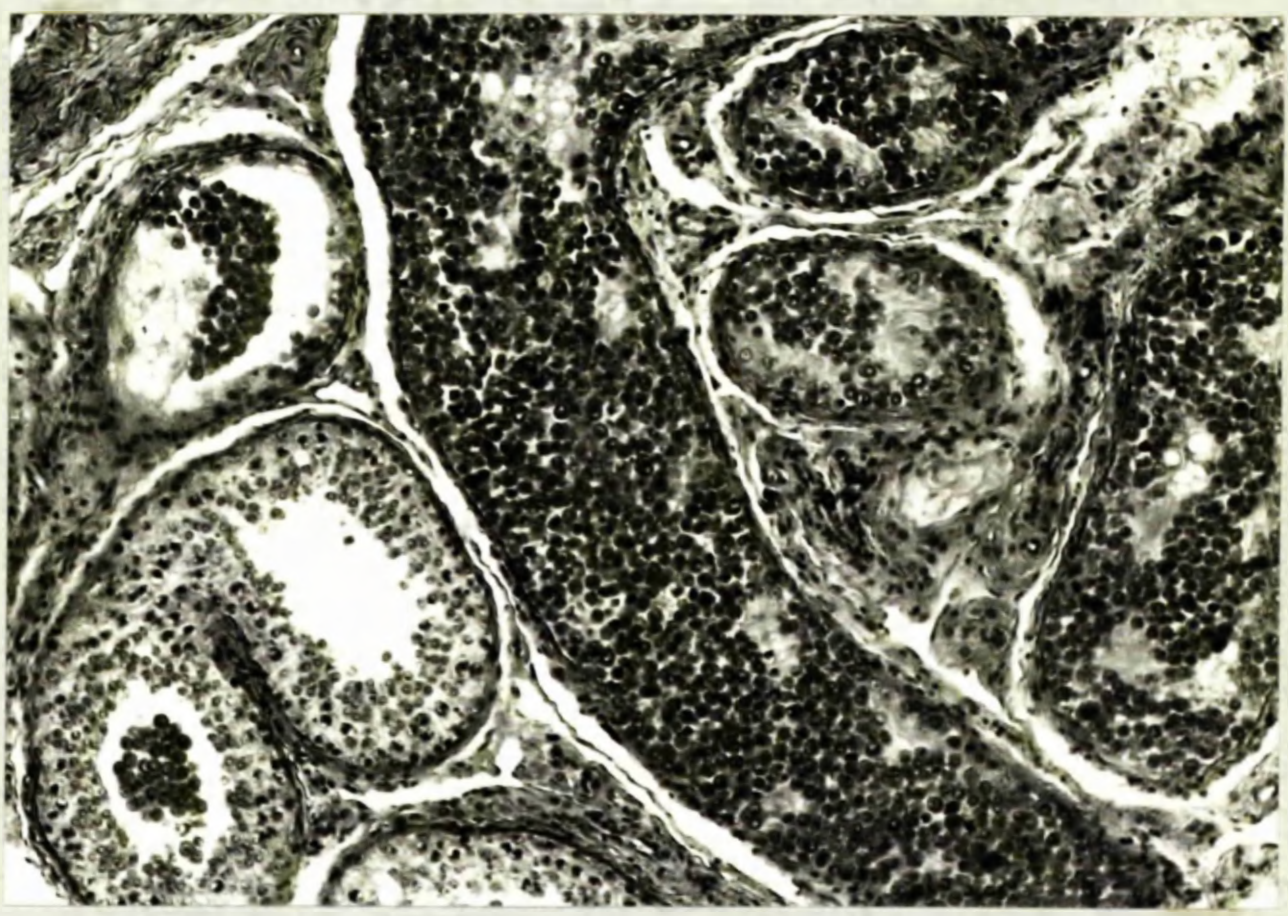


Fig. 84. Low power microscopic view of intratubular seminoma of ram showing seminiferous tubules filled with seminoma cells in the right two thirds of the picture. At the bottom left, spermatogenesis is present. H & E X 150.

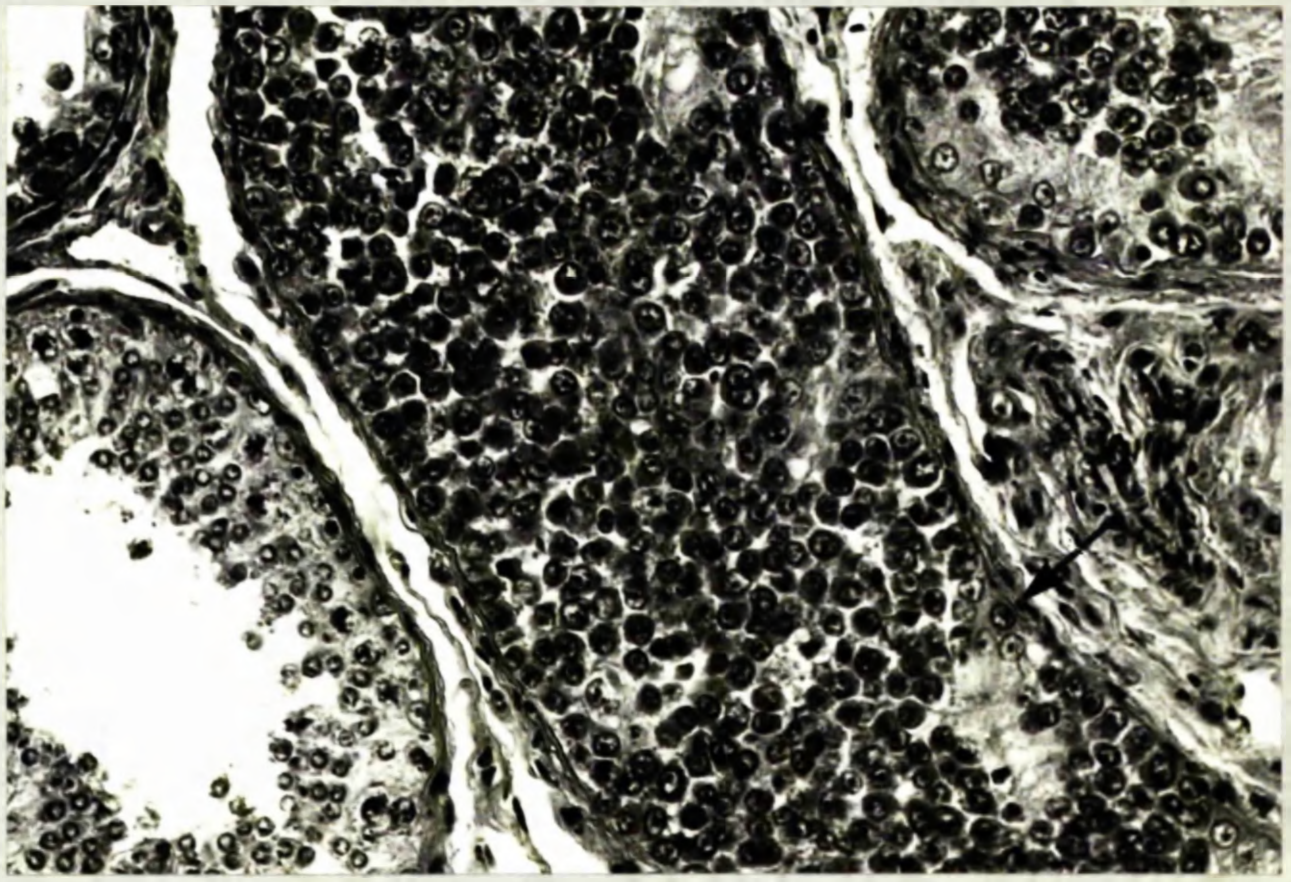


Fig. 85. High power view of part of Fig. 84. Note the almost complete replacement in the central tubule of the normal lining. Isolated Sertoli cells are seen. One is seen at bottom right hand corner. H & E X 290.

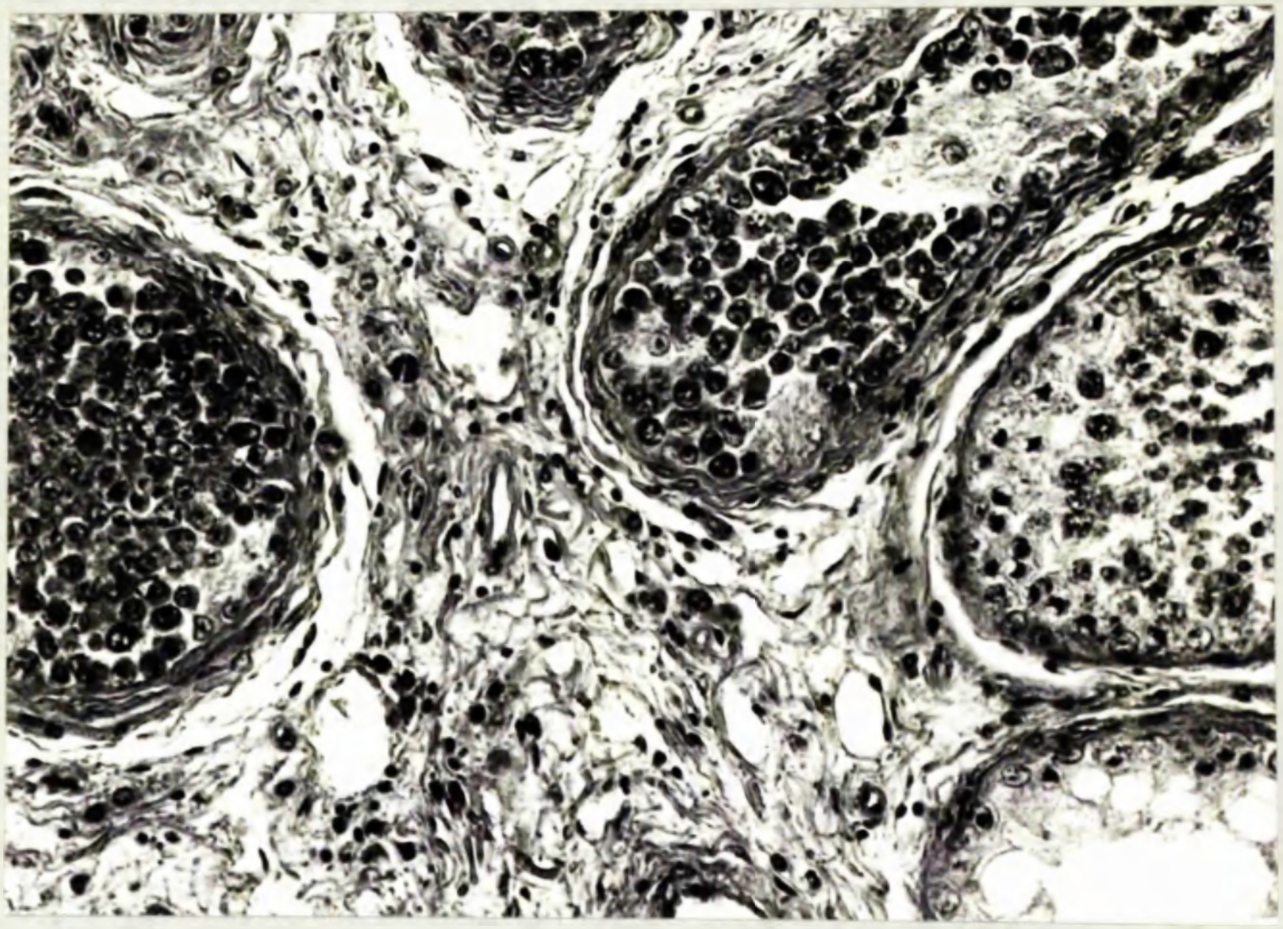


Fig. 86. Intratubular seminoma of ram in tubules on left and at top right. Spermatogenesis is present in the segment on the extreme right and at the bottom right an atrophic segment lined only by Sertoli cells is seen. H & E X 290.

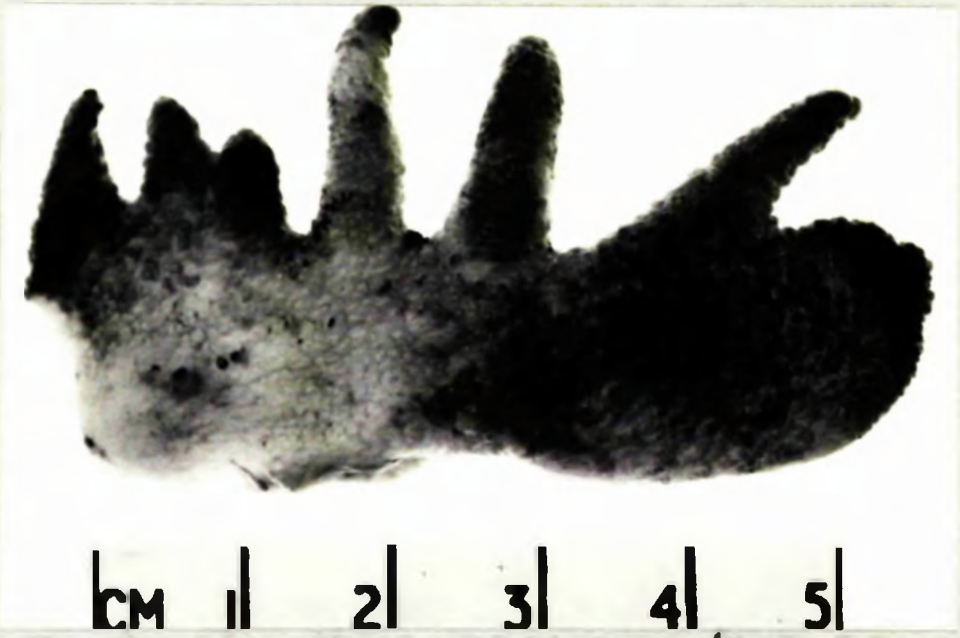


Fig. 87. The atrophic comb of a Light Sussex/Rhode Island Red hybrid cockerel bearing a spontaneous testicular teratoma.

Fig. 88. Cut surface of the spontaneous teratoma of right testis found in Light Sussex/Rhode Island Red hybrid cockerel. The attached left testis is small for June.

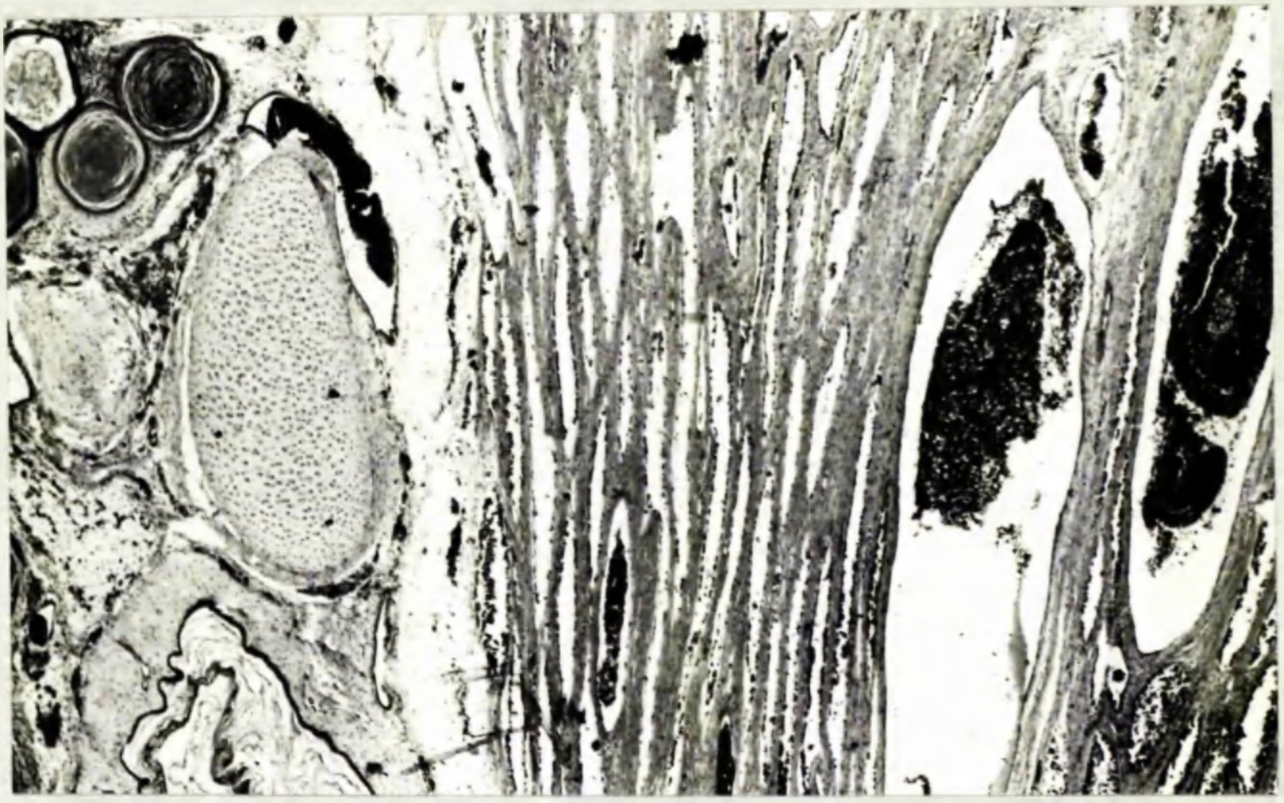


Fig. 89. Histological section from edge of spontaneous testicular teratoma illustrated in Fig. 88. Nodules of hyaline cartilage, horn cysts and other structures of the teratoma are seen on the left; the stretched and compressed seminiferous tubules and an engorged and tortuous vein on the right. H & E X 70.

Fig. 90. Slice of the left testis of the same cockerel, illustrated in Figs. 88 and 89, showing a small teratomatous nodule just below the capsule and to the left of this a small collection of horn cysts. A grey teratomatous nodule lies adjacent to the left edge of the specimen near the lower pole.

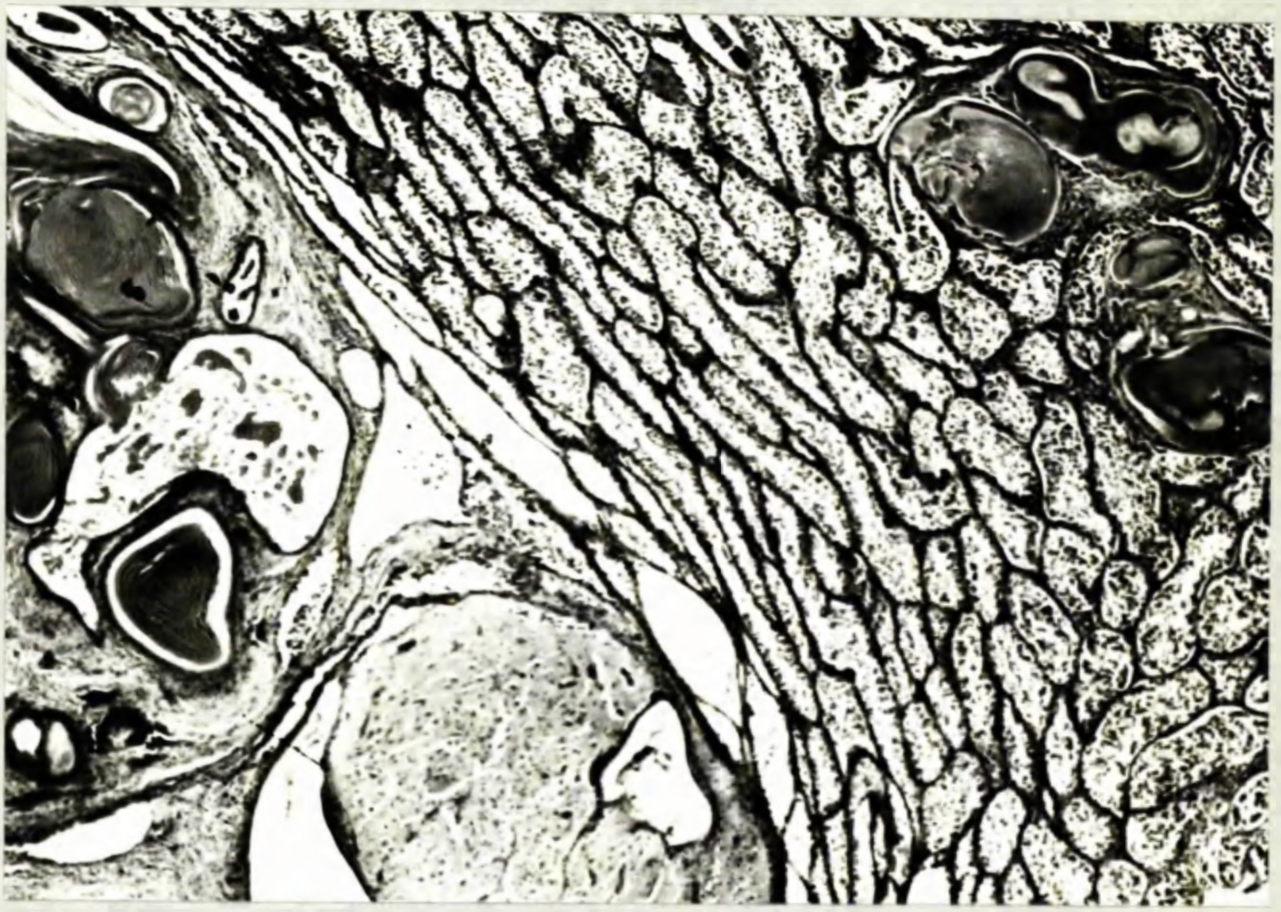


Fig. 91. The edge of a teratomatous focus illustrated in Fig.90 is seen on the left. At the bottom centre a spherical mass of neural tissue contains an ependymal lined cavity. Horn cysts are present in the main lesion and also separated from it by atrophic seminiferous tubules. H & E X 70.

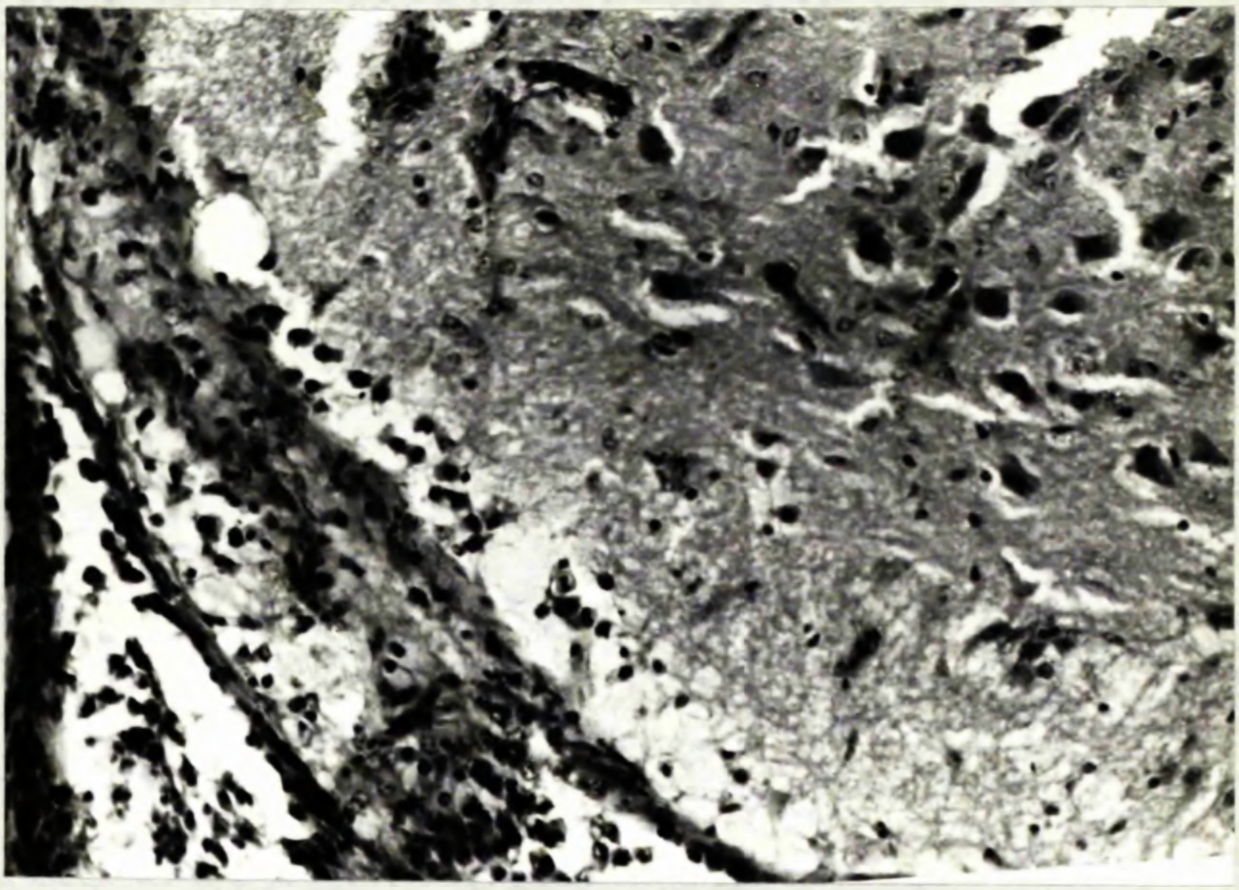


Fig. 92. High power view of neural nodule illustrated in Fig. 91. Large neurones and astrocytes are seen. H & E X 320.

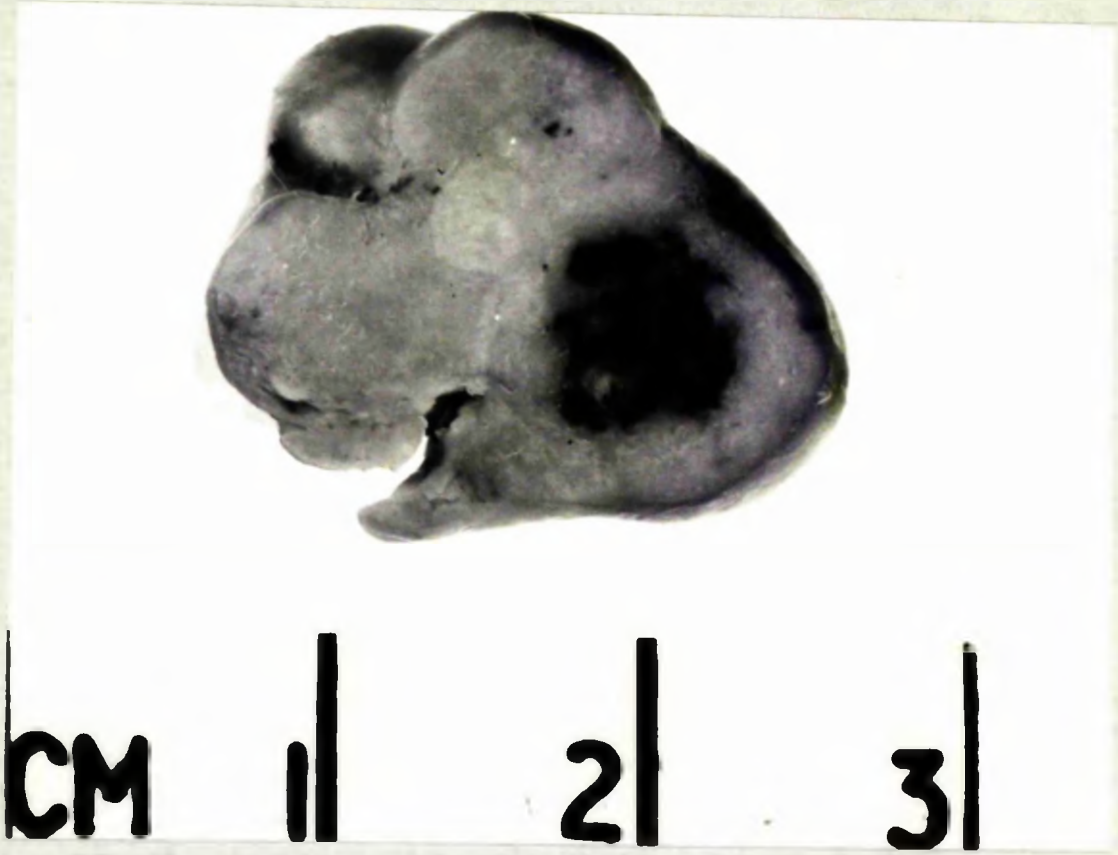


Fig. 93. The nodular yellowish interstitial-cell tumour of a budgerigar.

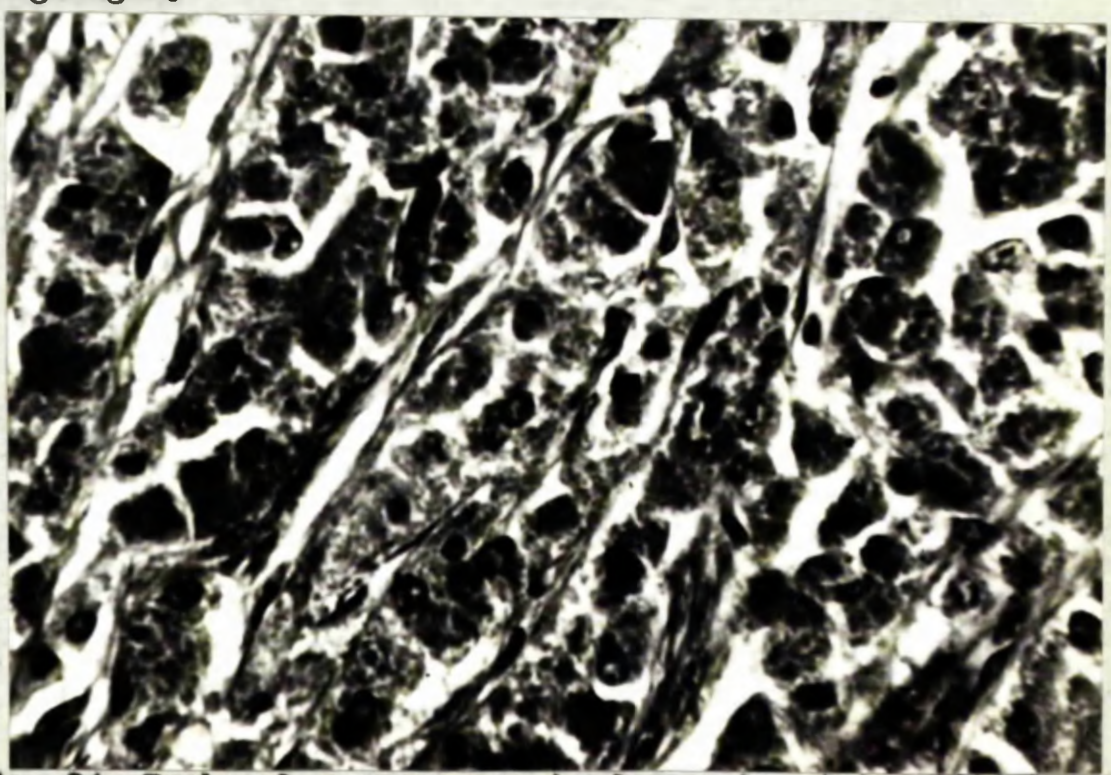


Fig. 94. Trabecular arrangement of granular interstitial cells in a testicular tumour of a 5½ year old budgerigar. H & E X 560.

Part III

Experimental Studies of Testicular Neoplasia.

A. Introductions to Experimental Studies.

The experimental approach to a study of neoplasia of a particular organ or tissue must initially be directed to the creation of an experimental model. Little progress can be made unless the tumours of the particular organ can be induced by experimental means. Prior to the discovery of pure carcinogenic compounds in the third decade of this century, tar was employed in attempts to produce tumours of various viscera with only occasional success (Woglom, 1926).

The carcinogenic activity of a pure hydrocarbon was first reported by Kennaway, (1930) with 1:2:5:6: - dibenzanthracene and with his co-workers he later reported the production of a transplantable sarcoma in mice and rats by means of subcutaneous injections of this substance in lard (Burrows, Hieger and Kennaway, 1932). Using the same substance inoculated into the testis of a rabbit, Lacassagne (1933) found a testicular tumour which he considered to arise from an adrenal rest.

Ilfeld (1936) obtained carcinomas of the kidney and other viscera following the implantation into them of cholesterol pellets containing dibenzanthracene, but no carcinomas of the testis. Other workers produced sarcomas of the testis: Nicod and Regamey (1938) with methylcholanthrene in the mouse, Gullotta (1939) with 3-4 benzpyrene in the rat and Spinelli (1941) with methyl-cholanthrene in the rat.

A different approach was suggested by Michalowsky's (1926)

accidental discovery of teratomas of the testis of domestic cockerels following inoculation of zinc salt solutions into the testis as a method of partial castration. Partial surgical castration produced seminomas in ducks (Champy and Lavedan, (1939), but as avian reproductive mechanisms are in some respects different from the mammalian it was felt that, initially at any rate, experimental use of a small mammal like the albino rat might lead to results more applicable to man.

It also seemed possible that a more gradual release of the carcinogen over a prolonged period might avoid the development of sarcomas and lead to intratubular tumours. Accordingly Ilfeld's (1936) method was adopted and cholesterol pellets containing methylcholanthrene were implanted into the testes of rats. In view of the alleged increased liability of the ectopic testis to malignancy, (Gilbert and Hamilton, 1940), methylcholanthrene was also implanted into testes previously fixed by sutures intra-abdominally. In one group the testis was fixed at one month after birth before normal descent and in another group in adult life. In other experiments adult rats received oily inocula of 2-amino-fluorene, 2-acetyl-amino-fluorene and aqueous zinc salt solutions into the testis. No seminomas were induced, but there were sarcomas and interstitial-cell tumours. This work is described in "Attempts to Produce Seminomata in the Albino Rat by Inoculation of Hydro-carbons and other Carcinogens into Normally Situated and Ectopic Testes" in "The British Journal of Cancer, 1956, Vol. X, 134-144".

The rest of the experimental work has been concerned with the teratomas induced in the testes of domestic fowl by direct injection of zinc salt solutions. These teratoma closely resemble in morphology the testicular teratomas of man. The unresolved problem of the cell of origin of teratomas, whether diploid or haploid and if haploid, whether some gametal fusion was involved, suggested study of the chromosomal constitution of these tumours. This particular study was stimulated by the finding by Hunter and Lennox (1954) of female nuclei in testicular teratomas in man, a discovery which itself stemmed from the discovery by Barr and Bertram (1949) of the sex chromatin body in mammalian interphase nuclei. The work was facilitated by the development of cytological methods for chromosome spreading involving pre-treatment with hypotonic solutions and squashing. The techniques of Makino and Nishimura (1952) and Ford and Hamerton (1956) were used with modifications. This experiment is described in "The Chromosomes and Genetic Sex of Experimental Avian Testicular Teratomas" in "Experimental Cell Research, 1962, Vol. XXVI, 304-311".

The next investigation was to ascertain if a particular functional state of the testis and adenohypophysis was necessary for the induction of these teratomas and to study the morphological sequence of events following inoculation of several zinc salts solutions or suspensions and hydrochloric acid. Although unlike wild avian species the domestic cockerel is usually fertile throughout the year, there is a seasonal upsurge of spermatogenic

activity in the early spring and it is within a fairly localised period that zinc injections are able to induce teratomas. One result of this work was the recognition of two distinct types of teratoma, a large partially differentiated teratoma and a dwarf type of growth predominantly embryonal carcinoma. The large type was associated with the right testis and the dwarf with the left. Analysis of the size and laterality of all the recorded experimental teratomas in fowl confirmed this association as frequent enough to be significant. The nature of the lesions in the testis following 5 per cent zinc chloride, 8.1 per cent of zinc acetate and an oily emulsion of 6 per cent zinc stearate were examined and the pituitary glands of tumour bearers and the other inoculated animals compared with intact controls. These observations together with a tabular record of all recorded experimental teratomas in fowl are described in "Observations on the Zinc Induced Testicular Teratomas of Fowl" in "The British Journal of Cancer, 1964, Vol. XVIII, 130-142".

Zinc chloride solutions as used in these experiments produced a zone of haemorrhage and necrosis around the site of inoculation in the testis. In view of the belief of Bagg (1937) and Falin (1940) that inductors or other substances liberated from the necrotic tissue induced teratomatous growth, the specificity of the metallic ion seemed open to doubt. Therefore the same volume of a normal solution of hydrochloric acid was injected into the testes of 45 White Leghorn cockerels. A strictly

comparable group of 46 cockerels had intratesticular injections of 5 per cent zinc chloride. Both types of injection produced similar areas of necrosis but only the zinc injections produced teratomas (Guthrie, 1964c). This work is fully described in "The Specificity of the Metallic Ion in Experimental Induction of Teratomas in Fowl (appended).

It is known from the work of Falin and Anissimowa (1940) that copper salts also produce teratomas. Copper (atomic no. 29) and zinc (atomic no. 30) are closely related transition elements in the periodic table. Cadmium (atomic no. 48) in the same group was shown by Parizek (1957) to have distinctive effects on the testis. More recently it has been shown to be a carcinogen (Haddow, Dukes, Roe and Mitchley, 1962, and Heath, Daniel, Dingle and Webb, 1962). It therefore seemed important to ascertain the effects of a direct injection of a cadmium salt into the avian testis. This work is described in "Histological Effects of Intra-testicular Injections of Cadmium Chloride in Domestic Fowl" in "The British Journal of Cancer, 1964, Vol. XVIII, 255-260.

The principal regulator of testicular growth is in all species the adenohypophysis with its gonadotrophins, follicle-stimulating hormone (F.S.H.) and luteinising or interstitial-cell stimulating hormone (L.H. or I.C.S.H.). In birds prolactin also plays a role apparently suppressive in nature (van Tienhoven, 1961). It seemed logical to explore whether a tumour retained the hormone dependence of its parent tissue. If so the effect of suppression of the hormones should be ascertained as this offers

a prospect of therapeutic control. This work is described in "The Effects of a Synthetic Antigonadotrophin (2-amino; 5-nitro-thiazole) on Growth of Experimental Testicular Teratomas" in "The British Journal of Cancer, 1966, Vol. XX, 582-587".

B. The Specificity of the Metallic Ion in the Experimental Induction of Teratomas in Fowl.

Zinc chloride solutions were employed by Michalowsky (1926) to produce partial castration in domestic cockerels. A surprising result was the production of teratomas in the injected testes when the injections were made in the spring. Other salts of zinc sulphate (Falin, 1940) and nitrate (Falin, 1941) and also copper sulphate (Falin and Anissimowa, 1940) produced teratomas of the testis. The necessity for the metallic ion seemed to be unproved. Falin and Anissimowa (1940) introduced hydrochloric acid, 10 per cent formalin and caustic substances into the testes of fowl, but produced only necrosis. The numbers and details of experiments are not given and it seemed advisable before further attempts at teratoma induction with other metals to investigate the effects of intra-testicular injections of a normal solution of hydrochloric acid (N.HCl.).

Material and Methods.

Forty-six White Leghorn cockerels, eight months old were each given bilateral intratesticular injections of 0.2ml. N.HCl., using the method previously described (Guthrie, 1962). A strictly comparable group of 47 cockerels each received 0.2ml. of 5 per cent zinc chloride solution (pH 3.2) into both testes. One of each group died within several weeks. These are excluded from the calculations.

Results.

Five teratomas arose in the zinc injected animals within two to four months. After the experiment had lasted six months, all the

fowl which had received injections of N.HCl were killed. No teratomas were found. Applying a Chi square test for small numbers gives a value of 7.4 and with one degree of freedom, P of less than 0.01. Both groups of fowl showed rather similar testicular scars, although the scars were larger and contained more ion and haemic pigments in the zinc injected animals. One cockerel which had received 5 per cent zinc chloride died 3 weeks after injection and one cockerel which had received N.HCl died 5 weeks after injection. The histological appearances at the edge of the necrotic zone are similar and are compared in Figs. 1 and 2.

The pituitary glands of the two groups were compared at post-mortem examination. No significant differences were noted between the two groups. They were not all killed at the same season and no partial castration effects were noted.

Discussion and Conclusions.

Similar areas of necrosis can be produced by injections into the testes of N.HCl and 5 per cent zinc chloride (pH 3.2). A different concentration of acid might have produced more necrosis and thus larger scars and it may be necessary to subject the testis to a wide range of acid concentrations in order to exclude such substances as inducers of teratomas. Nevertheless this experiment shows that necrosis alone does not induce teratomas in the adjacent testis.

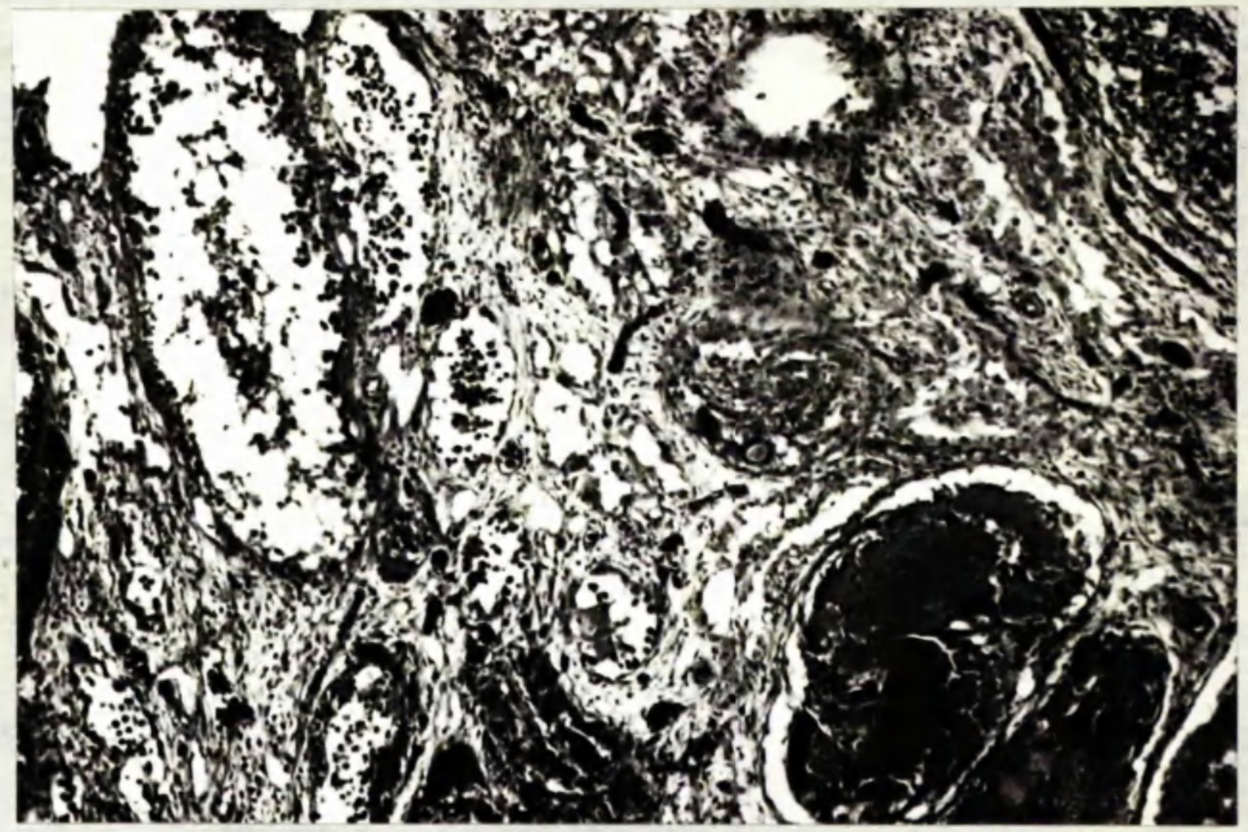


Fig. 1. Testis five weeks after injection of 0.2ml. N.HCl. Note necrosis on the right and early scar formation. H & E X 130.

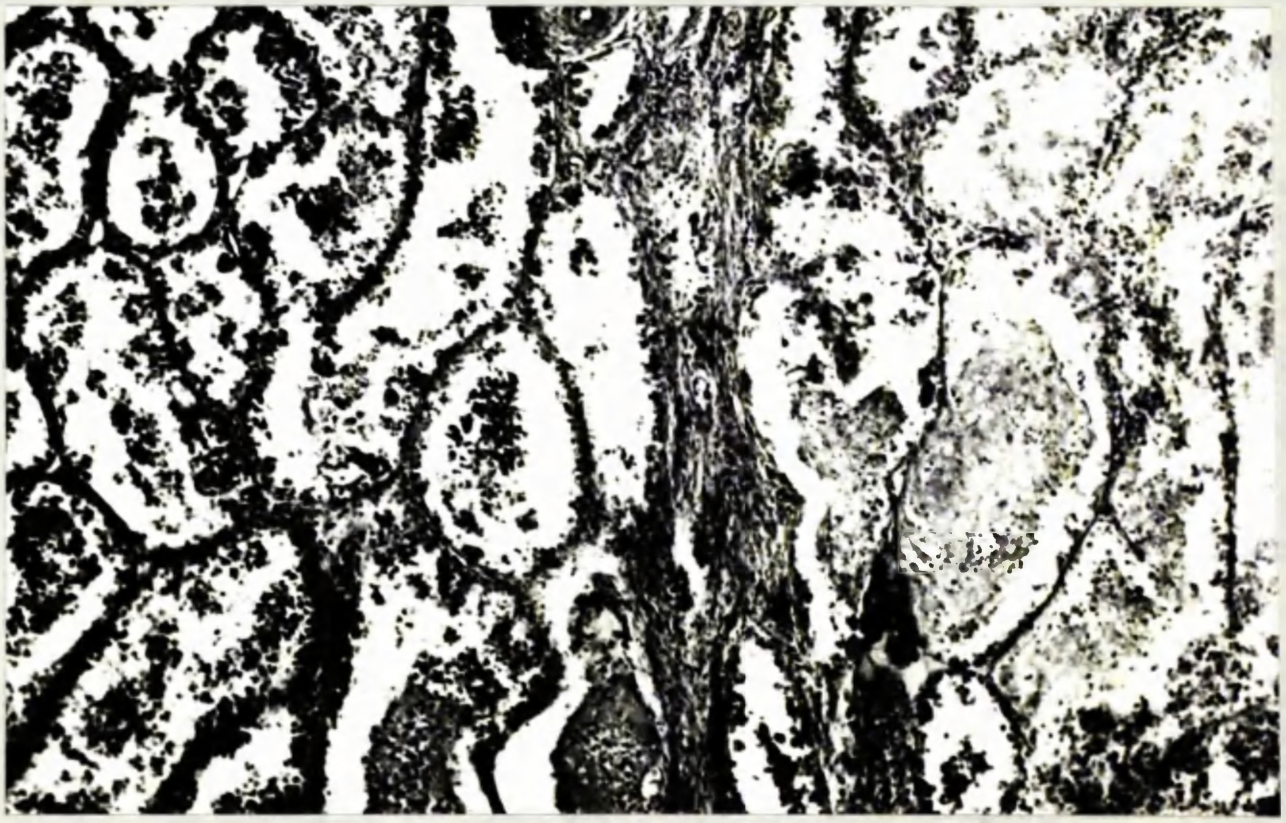


Fig. 2. Testis three weeks after injection of 0.2ml. 5 per cent $ZnCl_2$. Note necrosis on the right. H & E X 100.

General Discussion
of
Parts I, II and III and Conclusions.

General Discussion.

Although minor differences exist in classification and nomenclature, there seems to be general acceptance that teratoma, embryonal carcinoma and chorionepithelioma as defined by Dixon and Moore (1953) form part of the one tumour complex. The justification for the separation of the seminoma from the teratoma is perhaps still open to argument. Ewing's continued belief (1911 and 1940) in seminoma (or embryonal carcinoma in his terminology) as a one-sided development of teratoma has been attacked as causing prolonged confusion in the nomenclature (Willis, 1960). The work of Chevassu (1906), Nicholson (1907), Bell (1926) and others seemed to point to the seminoma as a distinct entity, presumably derived from the spermatogenic epithelium. This line of histogenesis is supported by Willis (1960), but detailed proof of this is still awaited.

In more recent years the clear histogenesis of canine seminomas from intratubular growths and the absence of teratoma in that species have been strong points in the argument against Ewing's hypothesis. Since foci of intratubular seminoma without invasive growth are seen as early stages of seminoma in both dog (Dow, 1962) and ram (Jensen and Flint, 1963), elements of a teratoma might be expected at this stage. But despite the high incidence of intratubular seminoma in dogs a canine teratoma has not been found (Cotchin, 1960). Nevertheless Brown (1964) accepts one-sided development of a teratoma as one of the three

histogenetic alternatives for testicular argentaffin carcinoma which generally exists as a pure neoplasm. Any sizeable tumour is almost certain to have destroyed its site of origin. It could be argued that if the teratoma is initiated by an intratubular embryonal type of growth, then some species specific factor might inhibit teratomatous development in certain species and differentiate the embryonal growth into seminoma. If the teratoma is evolved by parthenogenesis of primordial preneiotic germ cells through the intermediate stage of embryoid bodies (Peyron, 1939; Marin-Padilla, 1965 and Canina, 1966), then some intrinsic incapacity of the canine germ cell to segment and differentiate may be responsible for the absence of teratomatous development. Mulligan (1949) refers to the absence of twinning in the dog as a possible explanation for the absence of teratomas. He was clearly thinking of the teratoma as a congenital included twin, but it may point to a significant characteristic of the canine gonia.

Experimental studies of carcinogenesis in the animal testis have not solved the problem of relationship of seminoma and teratoma. The introduction of zinc salt solutions into the testes of domestic fowl in the early spring is a reliable method of producing teratomas, but as reviewed by the author, attempts to induce seminomas in small animals have met with little success and the occasional tumours described as seminomas have not borne a close resemblance to the human or canine tumours

(Guthrie, 1956) and their behaviour is unknown.

The experimental teratomas of fowl are related to the rapid seasonal growth of the testis and possibly increasing gonadotrophin activity (Guthrie, 1964a). Although contemporary domestic fowl are fertile throughout the year unlike wild avian species outside the tropical regions, there may be a seasonal variation in fertility (van Tienhoven, 1961) and the author's observations on White Leghorn cockerels on open range have shown increasing testicular size from January to March (Guthrie, 1964a). The majority of teratomas were produced at the period of maximal spermatogonial division between 4 and 7 weeks after the winter solstice. It may be that all teratomas are related to some kind of seasonal growth in the gonocytes. Most wild animals in temperate zones have annual breeding cycles and recently Conaway and Sade (1965) have described seasonal growth and atrophy in the seminiferous tubules of free ranging rhesus monkeys. There is some indirect evidence from seasonal birth fluctuations that there may be a seasonal variation in fertility in man (Pasamanick, Dinitz and Knobloch, 1960) although this is likely to be modified by social and economic conditions. Kihlstrom (1966) quotes a personal communication from Hornstein, who found a 4 week cycle in the exfoliation of cells from the human male urethra. More direct measurements of human fertility and studies of spermatozoal morphology and ultrastructure under varying climatic and seasonal conditions are therefore indicated. Information about rhythmic

variations in spermatogonial activity might be of value in controlling fertility as well as elucidating the critical timing of tumour initiation. It is conceivable that seminoma might be initiated at a different period in such a cycle or perhaps at a later age when cyclic activity has ceased. The role played by pathological periods of depression and activity should also be borne in mind in view of the possible relationship to mumps orchitis, undescended testis and previous atrophy (see Chapter II).

Most of the large series of human testicular tumours studied show more tumours in right than in left testes (see Part I, Chapter I). Pugh and Smith (1964) comment that although teratomas show a similar right to left ratio as testicular tumours as a whole (5:4), the more malignant growths, malignant teratoma anaplastic (M.T.A.) and malignant teratoma trophoblastic (M.T.T.) favour the left side. This would seem to correlate with the side preferences of the two types of experimental avian teratoma described by the author (Guthrie, 1964a - article appended). Further investigation is required of the essential differences between the left and right testes both avian and mammalian. As mentioned in the above article the left testis of the domestic cockerel is almost invariably larger than the right and has a lower mitotic rate. Comparison of the rates of D N A synthesis in each testis over a period is indicated.

The hopes that a morphological sex difference between host and tumour might demonstrate a gametal or haploid origin of

the teratomas (Hunter and Lennox, 1954) have remained in abeyance. The finding by Myers (1959) and others of complex mosaic patterns with areas of positive sex chromatin alternating with negative areas requires further investigations. The experimental teratomas of fowl show a diploid pattern and normal sex chromosome complement (Guthrie, 1962). The observations of Galton et al (1966) on human testicular teratomas also support an origin from diploid cells, although they do not rule out a gametal origin. Six of their eight teratomas showed marked aneuploidy and one or more marker chromosomes peculiar to each tumour, but they failed to detect dividing cells with an euploid chromosome complement compatible with the presence in the tumour of cells with sex chromatin. The difficulty presented by all the recent work on sex chromatin in tumours is in deciding whether the chromocenter seen represents an inactive X-chromosome with the implication that it is the second X-chromosome in the cell or whether it consists of a solitary X-chromosome or some other body. Study of very early teratomas for the detection of the initial chromosomal status may be necessary for the elucidation of the status of the cell of origin.

Once the zinc-induced teratoma has been initiated, its continued growth like that of the testis, may depend on the level of pituitary gonadotrophic hormones. The experiments using 5-amino, 5-nitrothiazole as a suppressor of gonadotrophic activity suggest that an antigonadotrophin may be of value in therapeutic control of this kind of tumour (Guthrie, 1966). An antiserum to avian

gonadotrophins might have a similar effect. It is possible that only parts of a teratoma at a particular stage of differentiation are hormone dependent and the possibility that growth hormone may accelerate differentiation in teratomas has already been mentioned in connection with the fully differentiated teratomas found in childhood. (Part I, Chapter III).

There have been no reports so far of the effects of either steroid or synthetic suppressants of hypophyseal gonadotrophins on human patients with tumours of the teratoma group. Clinical trials are indicated, as chemotherapy with cytostatic and anti-mitotic agents has only produced temporary benefit (Notter and Ranudd, 1964). In patients with embryonal carcinoma, mithramycin, an antibiotic of high toxicity has produced significant remission (Brown and Kennedy, 1965). It is, like actinomycin D, a potent inhibitor of RNA synthesis (Yarbo et al., 1966).

The basic problem of causation requires investigation at the ultrastructural and molecular levels. The metal induced teratomas are clearly related to the necrotic zone produced by the inoculum. Is the spontaneous teratoma related to a zone of tissue injury? Apart from iron the metallic content of such an area is likely to be of a trace quantity. It must also be remembered that the majority of human teratomas give no history of injury, but other causes of tissue necrosis may be present.

Conclusions.

1. The considerable experience gained by morphological studies using conventional histological techniques and light microscopy now allows recognition and classification of 99 per cent of human testicular tumours and in these the prognosis can be given. One must look to the electron microscope for further information. The author's clinico-pathological study confirms the much poorer prognosis of the teratoma group of tumours found by most recent investigators; an overall 6 year survival rate of 32.4 per cent for teratoma group as compared with 72.5 per cent for seminomas. Seminomas were the largest group, 42 per cent; tumours of the teratoma group comprised 37 per cent, and the combined seminomas and teratoma group 6 per cent.

2. Comparative studies have been most useful with regard to seminomas. Testicular tumours are rare in man, but are important as one of the commonest forms of malignancy in the young adult. Their equal or even greater rarity in animals makes comparative studies difficult. They are, however, common in the dog, which has afforded many examples of early seminoma-in-situ as well as Sertoli-cell and interstitial-cell tumours which are very rare in man. This study has shown constant association of seminoma-in-situ with atrophic seminiferous tubules. A spontaneous testicular teratoma in a domestic cockerel closely resembles the large partially differentiated teratomas induced by zinc injections.

3. Experimental studies seem to offer the greatest promise of solving problems of histogenesis and therapeutic control. The salt solutions of zinc and cadmium induce teratomas within a few weeks of their injection into the fowl's testis in the early spring months. The author's experiments have not demonstrated an intratubular origin as even in early growths small extratubular teratomatous structures of well differentiated and cystic nature were present. The chromosomal sex of these tumours was shown to be the same as the host. Even in the small percentage of tetraploid metaphases present, pairs of normal sex chromosomes were identified. This work, however, requires confirmation using better spreading techniques. Among the experimental testicular teratomas in fowl, two distinct types have emerged, a large partially differentiated teratoma and a dwarf embryonal carcinoma type with some differentiation. The dwarf type is significantly associated with the left testis and the large type with the right.

A synthetic antigonadotrophin, 2-amino, 5-nitrothiazole suppresses teratoma development when administered orally to domestic fowl after the injection of the metallic carcinogen. Initial experiments also suggest that it produces marked deceleration of teratoma growth.

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Summary

Testicular Tumours

A Clinico-Pathological, Comparative and Experimental Study.

A clinico-pathological study has been made of 157 human cases of testicular tumour. A classification based on this and previous studies was suggested.

Fifty-six animal tumours from 49 animals were studied and where possible each type was compared with its homologues in other species including man. Opportunities for comparison were most numerous in the case of seminomas and interstitial-cell tumours.

The experimental work was concerned with attempts to produce in animals those types of testicular tumour clinically important in man viz. seminomas and teratomas. The initial attempts to produce seminomas in the rat failed, but Michalowsky's work (1926) provided a suitable experimental model for the study of testicular teratomas. This was first used for the elucidation of the chromosomal structure of these teratomas in view of the interest at that time in the sexual dimorphism in the nuclei of teratomas in males (Hunter and Lennox, 1954). Subsequent studies were concerned with the varying structure of these teratomas and the possible relationship of this to the side affected.

Later work demonstrated that cadmium salts also produced teratomas and small Sertoli-cell nodules, but while hydrochloric acid produced similar localised necrosis of the testis, no teratomas were produced.

The gonadotrophs of the adenohypophysis were increased in numbers in many of the fowl which had received injections of zinc chloride, cadmium chloride and hydrochloric acid. This was considered to be a measure of the degree of partial castration achieved. The work also demonstrated that there was a critical stage in the annual spermatogenic cycle for the initiation of teratomas.

The dependence of the zinc-induced teratomas on pituitary gonadotrophins was investigated by the administration of a synthetic antigonadotrophin 2-amino, 5-nitrothiazole. This suppressed the development of teratomas when administered orally several weeks after the injection of zinc and also appeared to produce deceleration of the growth of an established teratoma.