

The Histology & Nature
of
Mixed Tumours

by

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The following short paper which I have the honour of presenting as a Thesis for the Degree of M.D. of Edin: University, deals with the subject of Mixed Tumours.

The paper is based upon two cases which came under observation about the same time, whilst I was acting as House Surgeon to the Cumberland Infirmary, Carlisle.

The cases occurred in two different situations in different individuals, the first cases connected with the kidney occurring in a woman of 55, the other connected with the coccyx in a foetus of 6 months.

The pathological examination of the first case has been already made in the Laboratory of the Pathological Dept. of the University of Edinburgh, so that I propose merely to detail the points of interest which contrast with those of the second case, submitting a characteristic microscopic specimen which I have prepared for comparison.

First Case.

The Clinical History.

A woman of 55 was admitted suffering from failure of compensation of an old standing mitral stenosis. After a temporary improvement, the patient died

from cardiac failure.

At the post mortem examination in addition to the diagnosed condition and its sequelae, there was discovered attached to the left kidney, a large tumour which subsequent microscopic examination showed to be a Mixed Tumour. (Specimen No. 5) The kidney itself was not invaded by the tumour, and no secondary tumours were discovered in any other situations after a complete examination was made.

With regard to this case then, I wish simply to point out the following outstanding features which distinguish it from the Second Case.

- (a) The site - Left kidney.
- (b) The age of the patient - 55 yrs.
- (c) The absence of symptoms due to the tumour.

Case 2.

Clinical History.

The clinical history of this case is of Gynaecological or Obstetric interest in that it is an example of premature labour associated with, and probably due to abnormality of the ovum, and of pelvic presentation due to malformation of the foetus.

The patient, a married woman, mullipara, 20 years of age, was admitted to the Medical Wards complaining of severe colic pains in the abdomen of two days duration. There was a history of amenorrhœa of

6 months duration. On examination it was evident that there was a pregnancy of 5 - 6 months, and that the patient was in labour. The pregnancy terminated on the evening after admission by the expulsion of a 6 months female foetus, placenta and membranes. The presentation was pelvic. The foetus died before delivery was completed. Nothing pathological was observed in the placenta or membranes; but the foetus presented a bulging prominence underneath the skin over the coccyx.

The entire ovum, minus the liquor amnii, was at once placed in 2% formalin for further examination, for which, however, a suitable opportunity did not occur till the present time.

Detailed Description of the Second Tumour.

Method of Examination.

Microscopical.

Paraffin Sections were made in the usual way.

Of these 4 characteristic slides are submitted, stained follows: -

1. Haemalum, Van Gieson.
2. " "
3. Haematoxylin (Erich) Rubin Orange.
4. Haemalum, Van Gieson.

Method of Description.

A preliminary examination of pieces taken from various portions of the tumour made it evident that

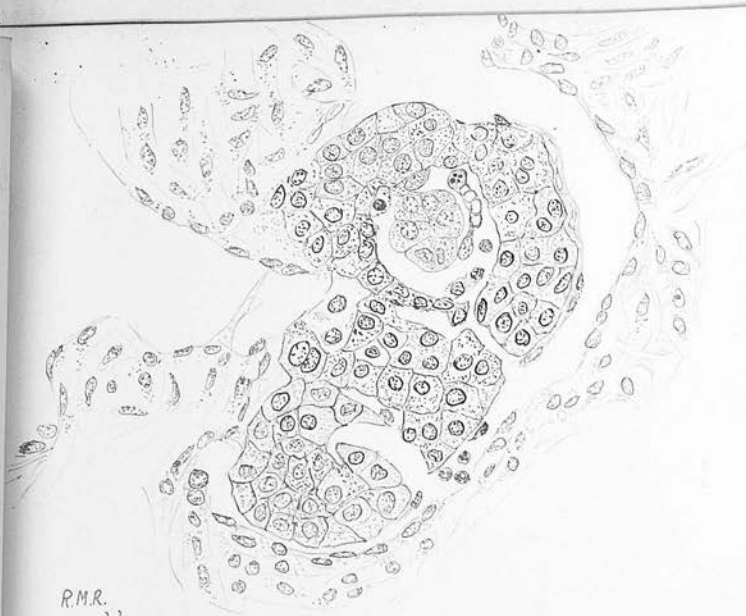
one had to deal with a Mixed Tumour composed of very dissimilar tissues in great variety. One considered that the tumour would probably be most efficiently described by a series of drawings presenting its characteristic appearances. In accordance with this plan, I have made a series of seven drawings. Each figure was drawn on black and white board from the preparation by means of the Camera Lucida. The drawing was completed on the work-table, constant reference being made to the preparation to ensure accuracy of minute detail; where necessary, details were verified by the Zeiss 2m.m. oil immersion and ocular 12, giving a magnification of 1,500 diam.

The colouring of the drawings is in some cases necessarily schematic, but as nearly as possible coincides with the various staining reactions of the different tissues figured.

N. Eye Examination.

The long interval between the preservation of the tumour and its present detailed examination detracted considerably from the value of the N.-Eye Examination.

The tumour was irregularly spherical in shape, 8. c.m. average diameter, lying behind the rectum in the Pelvic outlet and demarcated off from the surrounding tissues, but adherent to the back of the tip of Coccyx.



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Gland tissue. Resemblance to Liver

Compound Oc 2 x Obj 2mm
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Drawing 1. Slide No 1 mark ↑.

On section the cut surface was of very dark red colour, due mainly to diffused blood pigment.

Small nodules of cartilage were evident, but no bone was seen.

The tumour mass was soft and homogeneous, with here and there areas of more cystic structure, but no opinion could be hazarded as to the original nature of the altered contents of the cystic spaces.

The skin over the tumour was freely movable and easily separable from the tumour. There was a large accumulation of blood friable, unorganised, lying between skin and tumour over the most dependent portion of the swelling.

It is reasonable to suppose that this extravasation of blood from the tumour may have been the more immediate cause of the expulsion of the ovum.

Description of Drawings. No. 1. Slide No. 1.

v. Mark. ↑

A small portion of gland tissue surrounded on all sides by the undifferentiated stroma of the tumour. Similar gland tissue occurs passim throughout this slide of sections.

The drawing exhibits a portion of differentiated, fully developed, gland tissue, surrounded by the undifferentiated stroma. At one point there is difficulty in saying where stroma ends and gland tissue begins.

The Arrangement of the Gland Tissue.

The gland tissue is built up of columns of cubical granular cells possessing a large spherical, sharply-stained nucleus. The cell protoplasm is homogeneous and finely granular. The cell wall is distinct and each cell is clearly marked off from its neighbour. The shape of the cells is irregularly cubical, but here and there, where there is close packing, the outline is polygonal.

Ducts.

No ducts with differentiated lining cells are seen. There are indications of inter-cellular spaces which may not be due to shrinkage.

Vascular Elements.

At one point there is a definite capillary intervening between adjacent columns of cells and containing a few Red Blood Corpuscles and a leucocyte.

The surrounding stroma of the tumour contrasts sharply with the gland tissue and has the characteristics of loosely arranged connective tissue. The cellular element predominates, whilst the collagenous fibrils are few and delicate.

Nature of the Gland Tissue.

In the structure of the cells, and in their arrangement, the tissue most closely resembles Liver.



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Fig 2.

Stratified Squamous Epithel. Islet.

The wash represents diagrammatically the
Connective tissue Stroma of Tumour

Compens Oc. 2. Oil Immers. 2 mm
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The cells are not unlike those of pancreas; but upon the whole the compact columnar arrangement of cells remind one most forcibly of Liver.

Most probably it is impossible to decide, and indeed it is illogical, bearing in mind the common origin of both Liver and Pancreas, and the fact that one is not here dealing with a physiologically active gland.

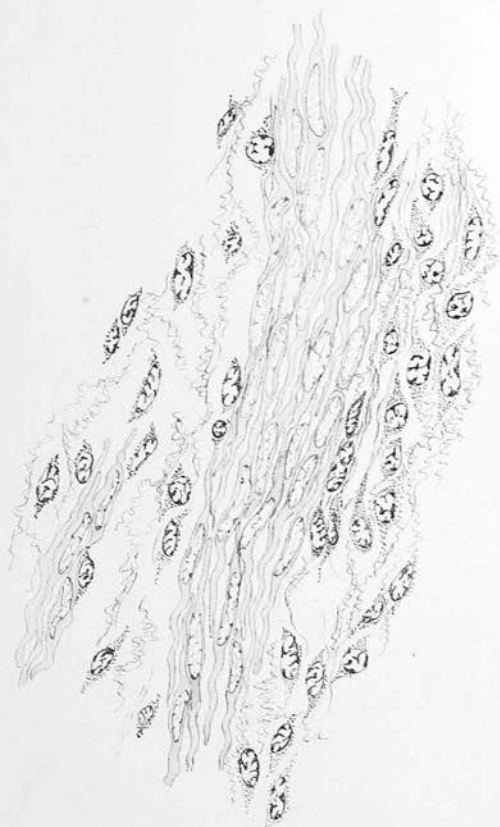
In slide No. 2 v. mark, as noted below under Drawing No. 3., this gland tissue occurs in larger masses and the general arrangement of the columns of glands cells, together with presence of capillary blood vessels closely resembles Liver.

Drawing No. 2. Slide No. 2. v. Mark. (S)

Stratified Squamous Epithelium.

A portion of fully developed stratified squamous epithelium occurs in the midst of the ordinary ^{tissue} connective stroma of the tumour, from which it is partially separated by shrinkage occurring in course of preparation.

The peripheral cells are small with relatively large nucleus. The intermediate cells are larger, and with the peripheral cells correspond to those of the stratum malpighi; while in the centre of the islet of Epithelium the nuclei are faint; reacting to the stain in a different way from that of the nuclei of



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Fig. 3.

A strand of unstriated muscle

Do the R. of the fig. lies a large acinus ~~100~~

C. Ocul 6 x of omnis 2 mm

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the intermediate cells. These most central cells are arranged in concentric rings, while at the most central point of the islet there is merely some cell debris.

The whole arrangement resembles a cell-nest occurring in Epitheliomata with feeble keratinisation.

This section was not taken from the surface of the tumour, so that there is no possibility of the islet being a mere involution of a fold of skin.

Drawing No. 3. Slide No. 2. v. Mark. (3)

A strand of unstriped muscle.

The portion figured lies in the stroma close to a large acinus lined with a single layer of cubical epithelium, not shown in the figure.

The surrounding area exhibits many other similar portions of unstriped muscle, cut transversely and obliquely.

It is worthy of note that the stroma here differs considerably from that surrounding the gland tissue of drawing No. 1.

Here it is less cellular and more fibrous, the collagenous fibrils being longer and more sinuous, as well as being present in larger numbers.

The cells of the stroma are very deficient in protoplasm, but their nuclei are deeply stained, contrasting with the fainter, large elongated nuclei of



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Fig 4.

Collection of Pigmented Epithel. Acinous arrangement
C.Oc. 6 x 01 immero 2mm $\frac{1250}{1}$

the muscle fibres.

This section is noteworthy in that it shows great numbers of alveoli of all kinds. Some lined with a single layer of cubical cells, some with 2 or 3 layers, and some possessing papillae of connective tissue covered with a layer of cubical cells, projecting within the alveolus.

Other tissues observed in this section include:

(a) numerous islets of hyaline cartilage, highly cellular, with scanty matrix.

(b) gland tissue similar to that shown in Drawing No. 1; but more closely resembling Liver in the arrangement of the cells; v.p. while the character of individual cells remains the same as above described. v. Mark. ←

Drawing No. 4. Slide No. 3. v. Mark.



An extensive collection of pigmented epithelium arranged in acini.

The portion figured shows an elongated space lined by cubical epithelium. The epithelial lining is much convoluted, producing several small diverticula at various points. Two of these diverticula have been cut through and appear as independent acini: while another is seen on surface view as a solid strand of slightly pigmented cells.

The cells lining the space are cubical, arranged in a single layer. The nucleus is large, the cell protoplasm contains a variable quantity of pigment particles.

The cells in the upper half of the figure contain most pigment, while least is observed in the portion where the cells lining the space are seen in surface section. On the right side of the figure again, the small alveolus is lined with cells which are extremely full of pigment particles.

Nature of the Pigment Particles.

With a magnification of 750 diam. (2 m.m. ol. immers and ocular 6) the particles appear as very short rods of dark yellow-brown pigment lying in the cell protoplasm.

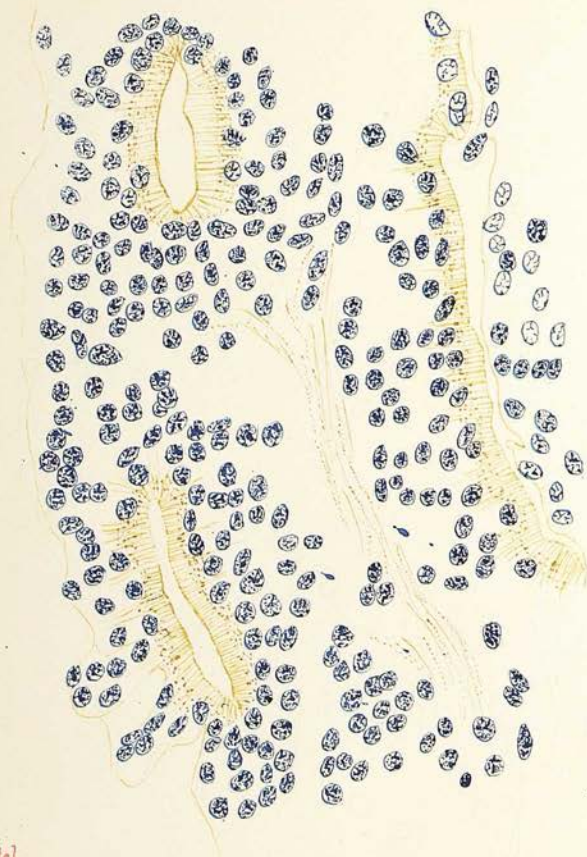
Where there is much pigment the whole cell appears black and the nucleus is obscured. The pigment is confined to the lining cells. No pigment is seen in the connective tissue cells of the stroma.

The Stroma.

In the neighbourhood of the pigmented cells the stroma is extremely cellular; collagenous fibrils are very few and extremely delicate.

Drawing No. 5. Slide No. 3. v. Mark. ↑

This figure is drawn from the same preparation as No. 4., and presents an appearance closely



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Fig 5.

A mass of epithelium - resembling develop.
:ing no neuro-epithelium.

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resembling a portion of developing neuro-epithelium.

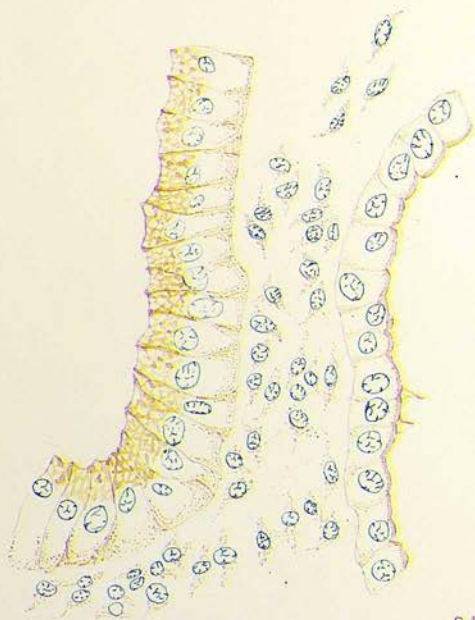
At a point marked (\uparrow) a similar portion of epithelium is seen to be in very close proximity to a patch of pigment cells identical with those figured in Drawing 4.

This proximity leads one to consider whether both do not belong to the same class of neuro-epithelium arising from a common portion of undifferentiated tumour stroma, the pigmented cells being analogous to the pigmented layer of the Retina.

In drawing No. 5. masses of cells containing very large nuclei and little protoplasm are grouped round a central lumen.

Three such lumina are present. Next the lumen there is a delicately striated border of protoplasm outside of which there is a dense arrangement of deeply stained nuclei.

In the centre of the figure separating the groups of nuclei belonging to the several lumina there is a strand of fine protoplasmic fibrils emerging from the upper mass of cells and lying obliquely across the field - an appearance one might interpret as a collection of developing axis cylinders.



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Fig 6. Gd. mucin secreting epithelium
lining a large acinus

C.O. 6 x 0.1 mm 2 mm $\frac{1250}{1}$

Fig. No. 6. Slide No. 3. v. Mark. ↑

This drawing is from the field immediately to the apparent right of Fig. No. 5. Large columnar cells are seen lining extensive alveoli which contain amorphous material presumably secreted by the lining cells.

The cells contain a granular material in the portion next the lumen, whilst the basal portion of the cell is occupied by the protoplasm. The nucleus is central in position.

The free margin of the cell is slightly cupped.

Thus in most of their features these lining cells closely approximate to the appearance of ordinary mucigen-secreting cells of the intestine.

Fig. No. 7. Slide No. 4. v. Mark. —

This drawing represents a field typical of the tumour.

The central feature is a large section of a nodule of hyaline cartilage. The nodule is surrounded by a definite ring of perichondrium.

The cartilage cells possess a large nucleus and a relatively small quantity of protoplasm, especially is this the condition close to the perichondrium; while in the centre the cell protoplasm is more abundant and vacuolated. The hyaline



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Fig 7. A typical field. Hyaline Cartilage. Various acini
C.Oc 6 x ol immes 2mm.

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matrix is small in amount and is readily distinguished by its different staining reaction from the cell protoplasm. Such nodules of cartilage occur in almost every section and exhibited the same characteristic features.

To the apparent right of the cartilage there is an alveolus lined with two or three layers of transitional epithelium.

Below the cartilage are two smaller alveoli lined each with a single layer of columnar cells with large nuclei closely resembling the cells of secretory epithelium.

Between the columnar celled alveolus and that with the transitional epithelial lining runs a capillary cut obliquely and exhibiting definite flattened endothelial lining cells in its wall. The lumen contains several blood corpuscles both red and white.

The tumour stroma has the following characters: -

Collagenous fibrils are scarce except round the alveoli and perichondrium; while connective tissue cells predominate.

Thus in this single field, differentiated tissues of very varied character - cartilage, transitional epithelium, secretory epithelium, pavement epithelium (endothelium) - are present in intimate association with each other.

THE NATURE OF THE TUMOURS.

CASE 1.

The tumour connected with the kidney like the coccygeal tumour of Case 2. contains a variety of tissues. It differs, however, essentially in nature. The tumour of Case 1. belongs to the class of Mixed Tumours (Mischgeschwülste).

General Description of Mixed Tumours of the Kidney.

Besides the large number of tumours of the kidney which are definitely Sarcomata or Carcinomata there are other tumours which partake of the characters of both. Sarcoma and Carcinoma. Such tumours have been grouped together by Wilms as a separate class called Mixed Tumours. (Mischgeschwülste)

Their characteristics have been fully described in a series of monographs by this author. Wilms Die Mischgeschwülste I. II. III.

This class of tumour is characterised by a stroma of Sarcomatous round and spindle cells in which lie acini of cells of adenomatous structure. The Mixed Tumours are further characterised, as a rule, by the early age of the individual in whom they occur. (v. infra p.4) The primary position of tumours of this class may be either intra-renal or extra-renal.

Intra-renal growths may attain considerable size. They may protrude into the pelvis of the kidney; or, on the other hand, the tumour may grow outwards and burst through the capsule of the kidney and appear externally, as was the condition in Case No. 1.

The kidney substance is displaced, compressed and may be atrophied. It is, however, not invaded by the tumour. A layer of demarcation is always recognisable and consists of compressed and altered kidney substance. v. slide. *N^o5.*

Extra-renal Growths.

The primary extra-renal variety is extremely rare. It grows in a similar manner, the adjacent kidney substance being displaced, compressed and atrophied by the pressure of the growing tumour.

In this variety also there is a zone of demarcation between new growth and kidney consisting of connective tissue partly derived from the remains of the connective tissue of the altered kidney substance and partly from the connective tissue elements of the tumour.

In both intra-renal and Extra-renal varieties the neoplasm may find its way into and extend along the blood-vessels by continuity of growth, and a

solid cord of tumour has even been observed to extend along the Renal Vein into the Inferior Vena Cava, and so to the Right Auricle (Enjelken, Merkel). Metastases have been reported in the Liver, Lung and Skin.

The local lymphatic glands also may contain secondary growths.

The Macroscopic Structure is that of a soft rapidly growing vascular tumour, often hæmorrhagic and sarcoma-like.

The Microscopic Structure.

The tumour is seen to contain young connective tissue with fibrils and delicate vessels.

Fat cells, cartilage, and gland tubules are also present. The tissues may be fully developed or in a more undifferentiated condition. Intermediate stages are met with ranging from a condition of undifferentiated tissue, viz: round and spindle-shaped sarcoma cells up to the fully differentiated tissues.

Description of Tumour of Case 1.

Microscopic Examination.

The specimen which is herewith submitted shows clearly the zone of altered kidney substance which marks off the new growth from the kidney itself.

Unfortunately the piece of tumour now in my possession is from the more superficial portion of the tumour only. It shows a purely sarcomatous structure - round and spindle cells and multinucleated giant cells. Some of the spindle cells closely resemble young muscle cells.

✕ The deeper parts of the tumour which contain large numbers of gland-like tubules is adenomatous in character. The stroma contains delicate fibrils supporting thin walled blood-vessels. There is evidence of considerable hæmorrhage having occurred at various points in the substance of the tumour.

A point of considerable interest is the age of the patient, from whom the specimen was obtained. These Mixed Tumours, though relatively rare, are commonest in childhood.

The age of highest incidence is from the 2nd. to the 4th. year. The oldest recorded case, according to Borst, ✕ occurred in a female patient of 18 years.

The present case may therefore be unique in that the patient was 55 years of age.

✕ A specimen exhibiting the structure of deeper portions of the tumour was obtained through the courtesy of Professor Greenfield, and accompanies this paper. *Specimen labelled Rd. Muir*

✕ Die Lehre von den Geschwülsten p. 961 band II.

Case 2.

The nature of the coccygeal tumour in this case is less easily settled. It presents features common to two varieties of tumour, viz: -

Teratoid

Teratoma

Before considering in detail these two classes of tumours, one may first briefly point out that there is an immense variety of neoplasms and tumour-like formations growing from the caudal end of the trunk. Many of these, however, have no bearing on the tumour under consideration. Such are the cystic expansions of the Central Canal of the Spinal Cord or of its meninges passing through a deficiency in the wall of the Spinal Canal - Spina Bifida in its various forms. These latter are not true tumours, though a Spina Bifida may contain a true tumour, e.g. glioma, or may be difficult to recognise owing to superaddition of inflammatory changes. Adjacent tissues may even come to be contained in this malformation, through a cystic out-growth enveloping a portion of adjoining tissue; a process which may ultimately lead to the inclusion of structures foreign to the Spina Bifida itself.

This coccygeal tumour has many characteristics in common with the two following classes of tumour.

1. Teratoid Tumours.

Teratoid tumours are not confined to the caudal end of the trunk. It is a matter of great significance, however, that a teratoid of the cephalic end never contains tissues of the caudal extremity. Similarly a caudal teratoid does not contain tissues characteristic of the cephalic end. They are thus distinguished from the Teratomata which exhibit no such limitation in the structures which may be present.

Teratoids are invariably covered by skin and contain a variety of highly differentiated tissues lying in a connective tissue stroma. All kinds of tissues have been described in these tumours: Liver, Central Nervous System; Skin; Epithelium of all sorts, ciliated, cylindrical, secreting, cubical etc. unstriped muscle, blood-vessels and cartilage.

While they contain a mixture of tissues, yet these tissues do not possess such a definite arrangement as would constitute the formation of organs. On the contrary the tissues are not correlated to each other, but are arranged indiscriminately, groups of liver cells, for example, being intimately associated with ciliated epithelium or masses of cells typical of the central Nervous System.

2. Teratomata.

This class includes neoplasms of which the structural formation may range from that of tumours containing merely a mixture of various tissues up to the development of double monsters.

A tumour of this class, however, always exhibits tissues more highly organised than those found in the Teratoid class, and the indiscriminate mixture characteristic of the teratoid does not occur.

Not only do the teratomata possess gland cells, but these cells are arranged in an orderly manner as a definite organ.

They may contain skin, but the skin often possesses the more highly differentiated skin derivatives, such as hairs or sweat glands which are not found in teratoids.

Similarly not only Cartilage is present as in Teratoids, but also bone. Teratomata, like Teratoids, may be found, situated in either cephalic or caudal half of the trunk. Unlike the Teratoids, however, in Teratomata the structures present are not limited to those peculiar to the end of the body where the tumour occurs. A cephalic Teratoma may contain caudal structures and vice versa, and it is only when this characteristic is present that one is able to recognise the tumour as a Teratoma and to distinguish it from a Teratoid.

A case described by Breslau and v. Rindfleisch illustrates this point very clearly (Borst bd. II. 912). The tumour was attached intra-cranially to the Sella Turcica and grew through an opening in the Sella Turcica from the Middle Cranial Fossa into the Pharynx and Oral Cavity.

It contained many tissues of the fully developed body, including portions of kidney and intestine. In a tumour so definitely connected with the cephalic end of the body the presence of kidney and intestine is sufficient to distinguish it as a Teratoma.

Theories of Origin.

Coccygeal Tumours.

Three main theories have been advanced regarding the origin of Coccygeal Tumours of the kind described in this paper.

1. Keith referring to the views of various embryologists states that the seat of origin is the Blastopore (Neurenteric Canal). (Keith Human Embryology and Morphology, p.12/)

Two main facts are adduced in support of this theory: -

(a) The position of the tumour corresponds to the site of the Blastopore at the caudal extremity of the neural canal.

(b) At the blastopore the epiblast layer is continuous with the hypoblast. This fact is important

as tending to explain the presence in the tumour of tissues derivable from epiblast and hypoblast.

2. Another theory is that the Coccygeal Body is the seat of origin. In support of this theory there is little evidence of value.

Almost the only fact that can be advanced is the corresponding situations of both tumour and Coccygeal Body.

But the Coccygeal Body is a derivative of the sympathetic collateral ganglionic system and therefore entirely epiblastic in origin. Obviously a tumour containing tissues derived from all three layers of the Blastoderm cannot arise from the Coccygeal Body.

3. A more probable theory is that the tumour arises as a variation of ordinary development; for example, as a second gastrulation in a single blastoderm. This theory is sufficient to explain the occurrence of the great variety of tissues present in the tumours.

The same theory is equally applicable to those cases of Teratoma which reach their highest development in a double monster.

There is thus no hard and fast line of demarcation between Teratoid and Teratoma as regards their mode of origin. All stages of development being met

with from a small Coccygeal tumour containing trilaminar tissues to a subcutaneous acardiac monster, or even a double monster.

Concluding Remarks.

When one compares the constitution of the Coccygeal Tumour, as exemplified in the series of drawings, with the description of Teratoid Tumours and Teratomata, one is in doubt as to the class to which it may justly be assigned.

The absence of higher differentiation of the tissues - for there are no organs or skin appendages present - inclines one to assign it to the class of Teratoids.

On the other hand, one finds in the tumour a tissue which is ordinarily derivable only from the cephalic end of the body, viz: pigmented epithelium closely resembling Retinal Pigmented Epithelium (drawing No. 4).

Were one able to say definitely that Retinal tissues are present, one must describe the tumour as a Teratoma, seeing that no Coccygeal Teratoid could contain a tissue proper to the cephalic end of the trunk.

At the same time one must remember that the specimen was obtained from a foetus at the 6th. month of intra-uterine life so early that one is not justified in assuming that the tumour had already attained

its full development and its tissues their final stage of differentiation.

In view of the theory of the common mode of origin of both Teratoid and Teratoma discussed above, one prefers to leave the question open, inclining, however, to the opinion that the tumour is in all probability a Coccygeal Teratoma.

The histological preparations and the drawings on which this Thesis is based are my own work, and I am solely responsible for the deductions drawn and opinions expressed in the text.

Dr E.F. Bashford of the Cancer Research Fund, London, very kindly placed the resources of his Laboratory at my disposal.