TISSUE DIFFERENTIATION IN MALIGNANT SYNOVIAL TUMOURS

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"... the variety that is manifested in Human Nature and in human life and institutions is a superficial phenomenon which masks, without impairing, an underlying unity." A. J. Toynbee, The Study of History, Part III, C iii.

Tumours composed of different kinds of tissue show different characteristics in rate of growth, infiltration of surrounding structures, frequency of complications such as necrosis and haemorrhage, and development of metastases. Thus the prognosis, either natural or following treatment, of various neoplasms, differs. This applies obviously to tumours of different organs or structures, but is true also of tumours of related tissues. It is desirable, therefore, that we should clearly differentiate tumours which, though different, are apparently similar in kind or origin.

The recognition of the nature and, by inference, the origin of a tumour depends in ideal circumstances on a number of observations—the site of the primary growth, its relation to surrounding tissues, the gross features of the tumour mass and its histological characters. The last two go hand in hand but histological features provide the more important criteria.

The differences in normal tissues (for example, in a limb) are due to differences in the direction and degree of differentiation of their original cells, which may have given rise to fibrous tissue, bone, cartilage or synovial tissue amongst others. In the same way tumour cells may differentiate in different directions, and according to which preponderates so the tumour is named. A most important point here is that any conclusion as to the origin of a tumour is merely assumption, and that, though it is commonly stated in the literature that tumours have arisen from synovial membrane, it will be shown that such statements are unjustified and are liable to give rise to confusion.

Synovial tumours are now easily recognised and their principal clinical and pathological features are known. They constitute a group different and distinct, both clinically and pathologically, from other connective tissue tumours. This paper is intended to be a general review of them and also to emphasise one particular topographical sub-group which has been given inadequate attention.

HISTORICAL NOTE

A review of the literature shows a gradual development of understanding of the nature of these tumours, particularly in the last twenty years. Appreciation of some features was slow, not only because this depended on a thorough knowledge of the nature of synovial tissue itself, but also because, as they are not common, opportunities for examining a sufficiently large series seldom come within the ambit of one individual's experience.

Before 1910 many tumours arising in or near synovial membranes had been described, but these were all regarded simply as connective tissue tumours—the malignant examples usually being called spindle-cell sarcomata. Their diagnosis as synovial tumours depended solely on their close relation to synovial structures, usually of joints. In 1910 Lejars and Rubens-Duval reviewed a series of cases and described these as endotheliomata. They observed spaces in the tumours but regarded the cells lining them as being endothelial and, since the lining of the synovial tissue was regarded at that time as endothelium, this designation was appropriate. In 1913 Tourneux made abstracts of ninety-three cases of synovial tumours.
From this time on there were numerous reports of tumours in synovial membrane and most of these were designated endothelioma or some form of angioma, the characteristic histological structure of synovial membrane being overlooked.

In 1927 Smith made a notable contribution. He pointed out that some tumours contained cells arranged differently from those of ordinary connective tissue tumours and emphasised the characters of the former tissue by applying the term "synovioma" to them. A little later the author (King 1931) discussed the nature of tumours of this kind occurring in tendon sheaths, and emphasis was laid on tissue spaces found in them as a special tissue differentiation and the essential similarity of these to normal synovial tissue was shown. The spaces could be lined by only a few or by closely packed cells just as they occur in synovial membrane in different conditions. In the same year Sabrazes and de Grailly (1931) described several tumours and applied the term synovialoma, and Razemon and Bizard (1931) reviewed a mixed group of forty-five benign and twenty-nine malignant
tumours.

In 1938 Berger, in a valuable contribution, gave a classification of these tumours and emphasised both the presence of synovial spaces and areas of mucoid change. These were regarded as two kinds of differentiation of this synovial tissue. In 1942 Fisher reviewed a series of forty-two cases. He emphasised the presence of a definite lining of cells in the spaces of the tumours and applied the term sarcomesothelioma to these tumours. The importance of Fisher's paper is that it drew attention to a special type of tumour and furthermore it included members of a topographical group that is more or less ignored elsewhere. These are tumours which histologically are indistinguishable from those occurring actually in joints, bursae or tendon sheaths, but which nevertheless occur in other parts of the limbs.

Groups of cases have been recorded and reviews of the literature have been given by Knox (1936), Coley and Pierson (1937), De Santo et al. (1941), Briggs (1942), Lazarus and Marks (1943) and Haagensen and Stout (1944).

An important paper by Bennett (1947) reviewed a series of thirty-two cases of malignant synovial tumours encountered in the American army during the war and since. This material is well presented and magnificently illustrated. There is a clear statement of three main types of tissue found in these tumours. These types indicate various directions of differentiation and include: 1) the presence of spaces in the tumour; 2) "tufts" or groups of oval or polygonal cells; and 3) groups of masses of epithelioid-like cells. It is thus clear that the cytological and histological features of these tumours have gradually become better understood.

**CLINICAL AND PATHOLOGICAL MATERIAL**

Observations were made on twenty-one tumours, most of which were directly related to joints, bursae or tendon sheaths, although a few were quite distinct from them (Table I). These cases have been observed over a period of twenty-five years. Some of them were investigated and treated, though in others only the pathological material was personally studied. Some have been reported previously—a tumour of the prepellar bursa (King 1939) and a group of seven cases of malignant tendon sheath tumour (King 1941). These are indicated in the Table by the year in brackets after the case number.

All of the examples included in the present series were regarded as being of the malignant type and most of them proved indubitably to be so. Such examples as were clinically or histologically thought to be innocent, though showing similar features, were excluded since they are often not well defined from inflammatory states.

**GENERAL FEATURES**

As these tumours are not very common an individual is not likely, except over a considerable period, to see many of them. Furthermore, they vary considerably in gross and histological structure, so that examination of any small series may give a wrong idea of the general character of the group. This has been shown in several accounts in the literature.
In addition to the study of the cases tabled here, therefore, the descriptions of the various interested observers have been considered and the conclusions are derived from a scrutiny of material from both sources.

**Age incidence**—Most of the cases are found in the third decade and the average age in most groups is about thirty-five years. Differences in individual series are exemplified by the group, described by Bennett (1947), whose cases were largely derived from service personnel; the average age was twenty-eight years. In the description of a special histological group Fisher (1942) stated that cases did not occur under puberty; but in a general group cases have been described in children—for example, a child of seven years (Smith 1927) and a baby of nine months (Coley and Pierson 1937) amongst others. In the present series the age incidence was a little higher than that seen elsewhere (average thirty-seven and a half years) but the majority of the cases (thirteen of the twenty-one) occurred in the third and fourth decades. The average age incidence is lower than that of fascial and related sarcomata.

**Sex incidence**—In most groups studied there has been a predominance of male patients; thus Coley and Pierson (1937) give the proportion male to female as 9 : 4; Berger (1938) gives 13 : 8; de Santo et al. (1941) give 11 : 5; Haagensen and Stout (1944) give 62 : 41 and Lazarus and Marks (1943) give 42 : 33. The clear influence of extraneous factors in determining the relative numbers in any group is well shown in the overwhelming predominance of males in the cases described by Bennett (1947); among thirty-two cases, mostly from the services, there was only one female. In the present series there were twelve males and nine females. In the cases described by Briggs (1942) and reviewed by Fisher (1942) the sexes were affected equally. The conclusion is that any sex difference is not, in our present state of knowledge, of practical significance.

**Relation to trauma**—An injury to the area in which the tumour develops is described by a certain number of patients. It was concluded by de Santo et al. (1941) that such injury initiated symptoms rather than gave rise to the tumour, and Briggs (1942) remarked that the injury described was mild. In the present series there was a clear-cut history of injury in four cases and in three others a minor injury or sprain was regarded as having attracted attention to the condition. In all such cases it is important to appreciate that too much attention must not be given to such uncertain evidence as the memory of a patient who is often shown, in other particulars, to be untrustworthy in the memory of details. In general, it may be said that mechanical injury does not play any significant part in the development of these tumours.

**Signs and symptoms**—In the majority of cases the patient presents himself for examination and treatment because of the presence of a nodule or tumour which in most cases has been present for only a short time. Occasionally it may have been there for a considerable period; in cases in the present series a swelling was present for three years, four years and ten years respectively. It seems obvious, particularly in such a case as this last, that either the tumour changed its character and began to grow rapidly, or a malignant tumour developed in what had been an innocent tumour or ganglion.

Often the tumours are painless but occasionally, especially in those in close relation to joints, some discomfort is observed by the patient. Less commonly pain may be present and occasionally the mass may be tender.

**Location of tumours**—Tumours have been found rather more frequently in the lower than in the upper limb. This was remarked particularly by Briggs (1942) though Fisher (1937) collected nearly as many cases in the upper limb. The series recorded by Bennett (1947) shows a considerable predominance in the lower limb and in the present series fifteen of the twenty-one cases were found in the lower limb.

Tumours are usually found in close relation to joints, bursae or tendon sheaths, but though some of them are intimately incorporated in these structures it is important to appreciate that tumours may develop apart from the actual synovial membrane. This has been mentioned...
specially by Haagensen and Stout (1944) who indeed emphasised that the tumour does not usually arise in the actual synovial membrane. They referred especially to tumours which are actually in close propinquity to joints or synovial structures but this is important in those tumours which lie at a considerable distance from a joint or bursa. A tumour, for example, lying in a limb half way between joints, say, in the middle of the thigh, cannot be related to any normal pre-existing synovial structure. This distribution has a very important bearing on the proper understanding of the pathogenesis and nature of these tumours and will be discussed again.

MACROSCOPIC APPEARANCES

The tumours vary considerably in size, which depends on the rate of growth and the time between the inception and observation of the tumour. Tumours as large as 20 centimetres in diameter have been described but it is more usual for the patient to seek attention earlier; the tumours are frequently seen when about 4 or 5 centimetres in diameter.

The tumours may be either circumscribed or diffuse. It has been stated that they may be encapsulated, but in the malignant forms this is not so. Tumours grow rapidly and invade and compress surrounding structures and so induce the appearance of a pseudo-capsule which is common to so many, particularly connective tissue, malignant tumours.

In shape the circumscribed tumours are usually irregularly ovoid. They are moulded by surrounding tissues and this gives them a somewhat nodular external appearance. Though many of them consist of a single mass of tissue some are composed of what appears to be an aggregate of nodules. In some cases this seems to be due to separate foci of growth, but in others a similar appearance is produced by disintegration or poor growth of tissue between areas of more active proliferation. In the diffuse tumours there may be an ill-defined thickening of the synovial membrane and this forms a very characteristic type, particularly in tendon sheaths, where it may form a cuff of tissue (Case 10).

Tumours arising near synovial membranes grow away from them rather than into them. It is seldom that a circumscribed tumour projects into a joint and, even if diffuse, tumours cause a thickening of the synovial membrane without encroachment on the cavity; tumours of bursae, however, usually replace the bursa.

Tumours may be firm in consistence and, in areas of fibrosis or calcification, are hard; the more rapidly growing ones, however, are soft and may be friable. Where there is mucoid change or cystic development they are fluctuant. On cross section the tumours show a creamy or greyish homogeneous appearance but in some areas may be more fibrous and white in colour; others show mucoid change which may be of such degree that cystic development is prominent. This may take the form of numerous small cysts or a few larger ones. These large cysts contain a straw-coloured fluid which is sometimes blood-stained. Yellowish areas due to necrosis often occur in the more solid parts of the tumour and haemorrhage is common. Thus on the one hand there may be a tumour of uniform tissue, soft and creamy in colour or fibrous and somewhat whiter, and at the other extreme an irregular cystic mass with a relatively small rim of capsule, the content being mucoid or haemorrhagic. All gradations and variations between these two extreme forms are to be found, so that considerable differences in macroscopic appearances may be observed in this tumour group.

HISTOLOGICAL APPEARANCES

The variety of macroscopic appearances is reflected in the considerable variation in histological structure. The close relations of these various forms are shown not only by the obvious development of each of them from typical synovial tumour tissue but also by their simultaneous occurrence and intermingling in some tumours.

Simple synovial tissue is, of course, a modified connective tissue. A good deal has been made, in some papers, of the morphological distinction between synovial tissue and
Photomicrograph of a part of a section taken from Case 10. The material consists principally of mucoid tissue and resembles the early stages of a ganglion. Most of the tumour consisted of material of this kind and despite its benign appearance it was clearly malignant. The small collection of spheroidal cells (which were more numerous in other parts) indicates its activity (×180).

Photomicrograph of part of a section taken from Case 12. There is considerable mucoid change and the mucinous material is shown by well defined strands of stained material. There are many large spheroidal cells around the area and these merge into the adjacent spindle-cell tissue (×180).
Photomicrograph of a section of part of a tumour removed from Case 4. The tissue is predominantly spindle-cell in type but there is mucinous material in and between some of the cells. There is also an endothelium-lined space ($\times 400$).

Fig. 3
Photomicrograph of part of a section from Case 5. This shows mucoid change but there is a disproportionately large number of spheroidal cells as compared with the specimens shown in Figs. 1 and 2 ($\times 180$).

Fig. 4
spindle-cell connective tissue, as if these two were different kinds. Actually, of course, they indicate two directions of differentiation in these cells. Those near a surface will develop like synovial tissue whereas those away from the surface are of a more indifferent type. It is therefore important, ontogenetically, that we regard the connective tissue—that is, spindle cell tissue—as being the precursor of the other varieties and, indeed, this can be shown to be so.

We have thus a fundamental and pervading spindle-cell tissue and certain other forms differentiated from this. The various forms to be described are:

A. Spindle-cell tissue.
B. Special synovial tissues.
   1. Mucoid tissue.
      (a) Cystic form.
      (b) Cellular form.
   2. Synovial surface tissue (with typical spaces).
   3. Tissue with endothelium-lined and "gland" spaces.
   4. Spheroidal-cell tissue.
      (a) Small cell groups.
      (b) "Epithelial" cell strands.
      (c) "Epithelial" masses.

A. Spindle-cell tissue—The spindle-cell tissue occurring in these tumours is indistinguishable from that found in a sarcoma occurring in any connective tissue. If there should be no synovial differentiation in any part of the tumour, this cannot be regarded as being synovial but, though a tumour may be composed almost entirely of such spindle-cell tissue, even a small area of differentiation will justify the designation of synovioma.

B. Special synovial tissues—The various forms of differentiated tissue are so diverse that it is easy to understand how a few decades ago the various tumours were regarded as different. Gradations from spindle-cell tissue to these various forms have now been found, so that only the fully formed tissues will be described and, since their character is accepted generally, the accumulated evidence for their inter-relation will not be discussed.

1. Mucoid tissue—Mucoid material is found in synovial tumours in at least two distinguishable forms. Doubt has been cast by some writers on the mucoid nature of this material but they have overlooked the observation that synovial mucin is different in its staining (and therefore chemical) character from that, for example, of epithelium. Its gross characters, where such can be determined, the occasionally found positive staining reactions and the absence of positive tests for other protein or fatty material, make its nature certain. It is noteworthy that in such a large series as that described by Bennett (1947) tumours showing this kind of change should have been absent. They were, however, well described by Berger (1938).

(a) Mucoid cystic areas occur as the most easily recognisable form of mucoid change in these tissues (Figs. 2 and 3). Usually there is a transformation of spindle into polyhedral cells which contain considerable protoplasm in which droplets are to be found. These cells merge into a less cellular area in which dissolution of the tissue has occurred (Figs. 2 and 11). The cells become more swollen and less defined and amongst them there are threads and strands, which material (by its staining character) is typically mucin. Most of the material, however, fails to give staining characters of mucin.

When there is a relatively large amount of this mucinous material the appearances may resemble those of a ganglion (Fig. 1), but in some part there will be cellular areas and, if the condition be a true tumour, it will act as such and, despite its resemblance to a ganglion, will nevertheless recur, invade or metastasise. This occurred in Cases 10 and 15 of the present series.

(b) The cellular type consists of groups of large spheroidal or irregular cells containing a large amount of clear protoplasm in which there are droplets (Fig. 10). In other places the cells
High power photomicrograph of part of a section from Case 1. There is a well defined cleft in the tissue, one side of which is relatively acellular but the other side shows closely arranged large cells. Since the cells occupying the space are staining differently from the remainder and are separated from each other by more homogeneous and less solid material, the cleft appears to be in the stage of formation ($\times 650$).

Photomicrograph from a section of part of the tumour removed from Case 17. The tissue is cellular and there are large branching spaces running through it. In addition there are smaller epithelium-lined "gland" spaces ($\times 140$).
FIG. 7
Photomicrograph of section of part of a tumour removed from Case 19. The tissue is cellular and there are branching spaces through it (× 50).

FIG. 8
Photomicrograph of a section of part of a tumour removed from Case 6. The tissue is cellular, composed of large irregular spheroidal and polyhedral cells. There is an irregular space the lining of which closely resembles normal synovial membrane. It is noteworthy that this degree of differentiation should occur in what is clearly an otherwise anaplastic and rapidly growing tumour (× 140).
are irregular or stellate and lie in a widely spaced fibrillar stroma in the interstices of which there is non-staining mucoid material (Fig. 4). Case 5 of the present series was almost entirely of this type. This kind of tissue may merge into that described above, in which cystic spaces are found. It might be considered that these changes are merely those of mucoid development in connective tissues and not indicative of synovial differentiation; however, the relation of type (a), through ganglion, seems to be clear and, as mentioned, type (b) is related to (a) in some tumours.

2. Synovial surface tissue with spaces—Spaces found in tumours possess a lining which closely resembles synovial tissue; indeed they often show, in miniature, all the characters of synovial cavities; they may be so small as to be found only on histological examination but at other times may be sufficiently large to be obvious as macroscopically demonstrable splits in the substance of the specimen. Though often simple slit-like spaces or rounded cavities, at times they are complicated and branching (Figs. 6, 7 and 8).

The lining is different in different examples. The simplest form resembles an ordinary membrane—that is to say, it is a simple connective tissue surface, some odd cells being on the surface but most lying below it and connective tissue actually lining the surface. It is necessary to distinguish such spaces from those artificially produced. The presence of collagenous tags in artefacts and areas lined by cells in the true spaces make the distinction reasonably easy. Occasionally, early spaces, which indicate their mode of formation, are seen (Fig. 6). In other instances the tissue is more cellular and the cells are plump and relatively large. When numerous, the cells are orientated to the surface, their long axes being at right angles to it so that it closely resembles the membrane of inflamed joints.

Although in some cases tissue cellularity extends from the surface of these spaces out into the surroundings, in others there is a definite distinction, either in the number of cells or in their type, between the two. This gives a further tissue resemblance to synovial membrane. The cells are sometimes more definitely demarcated from their neighbours and resemble either an endothelium or even a columnar epithelium.

3. Endothelium-lined spaces and "glands"—For many years, even after adequate descriptions of synovial membrane had been given, considerable confusion occurred because its real nature was not appreciated and it was thought to be lined by a definite endothelium. For this reason the older name for the tumours of synovial membrane was endothelioma. It is important to appreciate now that occasionally the lining of the synovium may undergo change to one with cells indistinguishable from endothelium.

Whether these cells should be called endothelium or epithelium is largely a matter of definition of terms. Since the cells referred to here are spindle in form, have ovoid nuclei, lie along the surface, are derived from connective tissue, and furthermore, since the spaces resemble lymphatics or blood vessels, the term endothelium conforms with general usage (Fig. 13).

There is, however, a still further differentiation. Cells may become cuboidal or even columnar and are much better demarcated from the subjacent tissues than those previously discussed (Fig. 14). Also they are observed, in section, to line relatively small spaces (Figs. 14 and 15). The general form of the cells, particularly their distinction from the adjacent tissue, is one usually regarded as characteristically epithelial (Fig. 15). These occur in the group that Fisher (1942) described and designated sarcomesothelioma. While his arguments in favour of this term may be appreciated, it is doubtful whether, in view of its emphasising only one feature of a larger group of tumours, it has special value.

That these cells, despite their "epithelial" form, are actually connective tissue in origin and are closely related to typical synovial membrane cells is shown, as mentioned previously, by the association in some tumours of the epithelium-lined glands and synovial spaces.

It is sometimes suggested that the use of terms such as carcinosarcoma by some of the older observers is an indication of their lack of knowledge of the subject, but it is clear that,
Photomicrograph of section of part of a tumour removed from Case 7. In this area there are groups of closely packed spheroidal and polyhedral cells arranged in a more fibrous stroma. Other parts of the tumour showed synovial spaces ($\times 210$).

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Photomicrograph of section of part of a tumour removed from Case 2. There are groups of polyhedral and spheroidal cells lying in a fibrous stroma. In general form, this part of the tumour shows a resemblance to carcinoma ($\times 210$).
Photomicrograph of a section of part of a tumour removed from Case 15. The tissue was very cellular and is composed of spheroidal and polyhedral cells, closely packed together, showing a considerable amount of protoplasm. On one side they merge into mucoid tissue which was a striking feature of the tumour. This tumour differs from those shown in Figs. 1, 2 and 3, only by the relative amounts of cellular tissue and mucin (×70).

Photomicrograph of a section taken from Case 18. This is composed of small groups and strands of polyhedral and spheroidal cells lying in the connective tissue stroma. The resemblance of this kind of tumour to a scirrhouc carcinoma of the breast may be very strong (×210).
FIG. 13
Photomicrograph of a section of part of a tumour removed from Case 3. The tissue is cellular, being composed principally of spindle cells, the small spaces lined by "endothelium" (×400).

FIG. 14
Photomicrograph of a section of part of a tumour removed from Case 20. There are small circumscribed spaces lined by cuboidal and columnar cells which are well defined from the subjacent tissue and thus can be regarded as constituting an "epithelium" (×650).
on the contrary, within the limits of knowledge of histology at that time it showed a keen observation and appreciation of structure.

4. Spheroidal epithelium-like cell forms—Swollen cells of spheroidal, polyhedral or irregularly ovoid form are frequently seen in relation to spaces; in other cases, however, they are found separated from these surfaces. They occur in several forms which may be divided arbitrarily in a number of ways; here they are divided into three main types:

(a) Cell "tufts" have been described by Bennett (1947). These consist of small aggregations of closely packed ovoid, spheroidal, polyhedral or even spindle cells (Figs. 9 and 10). These may be found producing projections into spaces (Fig. 13) or they may occur as small masses in the surrounding connective tissue. The cell margins are not well defined; the principal feature suggesting epithelium is the absence of a demonstrable intercellular substance. They are important, however, in so far that they merge into the next groups.

(b) Epithelium-like strands—Spheroidal and polyhedral cells may be scattered through the tissue in strands, often two or three cells thick (Fig. 12). The resemblance of such a tissue, at first

sight, to a scirrhous carcinoma of the breast may be striking. This similarity was remarked on by Lejars and Rubens-Duval (1910) and a similarity to other carcinomata has been mentioned.

(c) Cell masses are sometimes large, when they are composed of swollen spheroidal cells which have a well defined cell margin and are clearly demarcated from each other and from the surrounding tissue (Fig. 11). These cells usually show a more voluminous protoplasm in which clear droplets are to be seen and they may merge into large mucoid areas such as were described above.

The various cell types and tissue arrangements described here have been segregated and described separately for reasons of clarity. It happens sometimes that one type predominates and may be almost ubiquitous in a particular tumour but more frequently various forms are to be found in different parts of the same growth.
DISCUSSION

As has been shown, tumours of the synovial type may occur in a number of quite different forms. As a result of the special attention that has been paid to them in the last few years these various types are well recognised as being related to synovial structures.

These tumours are not very common and the various features will only be encountered if a number of cases be examined. It is understandable, therefore, that most authors should have described some features whilst omitting others, but if several papers be examined it will be found that they are complementary and that amongst them all the various features will be discovered.

An important feature of these growths is that a proportion of them may be found away from joints or other recognisable synovial structures. This is emphasised in the present series by the segregation of four cases from the others, these cases not being related obviously to any synovial structure; cases of this type were described also by Fisher (1937). This development of "synovial" tumours in connective tissue away from synovial membranes has an important bearing on the nature and origin of these tumours.

It may be thought to be of academic rather than practical importance how we name tumours; however, the very fact of attempts at classification involving assemblage of similar conditions emphasises its significance. The question is then, how do we classify these tumours? Is it on their nature or on their origin? That there is confusion on this point is shown by reference to the literature. Several authors quite clearly state that it is a matter of the origin of the tumours from synovial tissue. Thus Knox (1936) states that "... a relatively small group [of connective tissue tumours] take their origin from the specialised connective tissue cells which form the synovial linings"; Coley and Pierson (1937) say that "their origin from synovial membrane is now established"; de Santo et al. (1941) stated: "Synovial sarcomas originate in synovial tissue and thus are found in joints, periarticular bursae and in tendon sheaths"; Briggs (1942) referred to "tumours which take their origin from the synovial lined structures" and Lazarus and Marks (1943) stated "synovial sarcomas originate primarily in synovial tissue, and for this reason are found in joints, bursae and tendon sheaths." It will be seen particularly in two of these statements that, because the tumours are named from their assumed origin, they must therefore arise in specific locations.

On the other hand Haagensen and Stout (1944) have "pointed out that, whereas these tumors are composed almost certainly of mesothelial cells, it is very questionable whether or not they are derived from the normal lining cells of joints, tendon sheaths and bursae, because the tumors are usually outside of these structures although often in close proximity to them." It is emphasised here that, though these tumours are often in close proximity to synovial structures, there are the examples which lie at a distance from these and yet give a histological picture which is indistinguishable from those occurring close to the joints. The tumours, however, are not classified on any topographical basis but, irrespective of their position, are grouped together according to their histological structure.

It is obvious then that the opinion that these tumours come from a synovial membrane is pure hypothesis. The only thing of which we can be certain is that they are composed of particular tissues which are microscopically demonstrable. It is important then that we should understand that we classify these tumours according to their histological appearances rather than their presumed histogenesis.

It can be shown readily in these tumours that the various kinds of cells are closely related to each other and may be transformed into each other. Just as in bony tissue bone, cartilage, fibrous and mucoid cells may all arise from one kind of cell, so here we have a similar state of affairs. From the position of some of the tumours it is also clear that these various cells may arise from the ordinary connective tissue in the cells of the limb at a distance from the ordinarily formed synovial membranes.
### TABLE I
**Predominant Features in Twenty-one Cases of Malignant Synovial Tumour**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age</th>
<th>Site of lesion</th>
<th>Duration</th>
<th>Macroscopic form</th>
<th>Histological type</th>
<th>Trauma</th>
<th>Treatment</th>
<th>End-result</th>
<th>Time of death</th>
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<td><strong>J O I N T T U M O U R S</strong></td>
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<tr>
<td>1</td>
<td>M</td>
<td>32</td>
<td>Knee</td>
<td>4 years</td>
<td>Irregular, ovoid, cystic 6 × 4 centimetres</td>
<td>Spaces, &quot;glands&quot;</td>
<td>—</td>
<td>Amputation</td>
<td>Metastases in lungs</td>
<td>3 months</td>
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<tr>
<td>2</td>
<td>F</td>
<td>26</td>
<td>Knee</td>
<td>18 months</td>
<td>Irregular, ovoid, fibrous 5 × 4 centimetres</td>
<td>Spaces, epithelium</td>
<td>—</td>
<td>Amputation</td>
<td>Metastases in lymph nodes</td>
<td>?</td>
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<tr>
<td>3</td>
<td>M</td>
<td>41</td>
<td>Elbow</td>
<td>14 months</td>
<td>Ovoid, fibrous 5 × 3 centimetres</td>
<td>Spaces, epithelium</td>
<td>—</td>
<td>Excision</td>
<td>Metastases in lungs</td>
<td>1 year</td>
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<tr>
<td>4</td>
<td>M</td>
<td>29</td>
<td>Knee</td>
<td>6 months</td>
<td>Irregular, ovoid, soft 7 × 3 centimetres</td>
<td>Spaces, mucoid tissue</td>
<td>+</td>
<td>Excision and radium</td>
<td>Recurrence</td>
<td>?</td>
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<tr>
<td>5</td>
<td>F</td>
<td>34</td>
<td>Knee</td>
<td>18 months</td>
<td>Nodular, fibrous 6 × 5 × 3 centimetres</td>
<td>Spaces, mucoid tissue</td>
<td>—</td>
<td>Excision and radium</td>
<td>Recurrence</td>
<td>?</td>
</tr>
<tr>
<td><strong>B U R S A L T U M O U R S</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6</td>
<td>M</td>
<td>35</td>
<td>Prepatellar</td>
<td>3 months</td>
<td>Ovoid, soft 6 × 6 × 4 centimetres</td>
<td>Spaces</td>
<td>—</td>
<td>Excision and radium</td>
<td>Metastases in lungs</td>
<td>2 years</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>61</td>
<td>Prepatellar</td>
<td>10 months</td>
<td>Ovoid, firm, whorled 6 × 5 × 3 centimetres</td>
<td>Spaces, epithelium</td>
<td>—</td>
<td>Excision</td>
<td>Small recurrence after 3 years</td>
<td>?</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>26</td>
<td>Acromial</td>
<td>7 months</td>
<td>Ovoid, fibrous 5 × 4 × 2 centimetres</td>
<td>Spaces, &quot;glands&quot;</td>
<td>—</td>
<td>Excision</td>
<td>Still well after 5 years</td>
<td></td>
</tr>
<tr>
<td><strong>T E N D O N S H E A T H T U M O U R S</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>9</td>
<td>M</td>
<td>46</td>
<td>Flexor carpi radialis</td>
<td>6 months</td>
<td>Ovoid, fibrous 5 × 4 × 3 centimetres</td>
<td>Spaces</td>
<td>+</td>
<td>Excision</td>
<td>Metastases in lungs</td>
<td>10 months</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>51</td>
<td>Flexor carpi radialis</td>
<td>12 months</td>
<td>Irregular cuff of tissue 4 × 1 centimetres</td>
<td>&quot;Epithelium,&quot; mucin</td>
<td>+</td>
<td>Excision</td>
<td>Local rapid recurrence</td>
<td>?</td>
</tr>
<tr>
<td>No.</td>
<td>Sex</td>
<td>Age</td>
<td>Tumor Site</td>
<td>Duration</td>
<td>Ulceration</td>
<td>Spaces</td>
<td>Treatment</td>
<td>Metastasis</td>
<td>Survival</td>
<td></td>
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</tr>
<tr>
<td>11</td>
<td>F</td>
<td>54</td>
<td>Flexor digitorum pedis</td>
<td>12 months</td>
<td>Ovoid, fibrous 3 x 2 x 2 cm</td>
<td>Mucin, spaces</td>
<td>Amputation</td>
<td>Recurrence in lymph nodes</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>38</td>
<td>Peroneal</td>
<td>2 years</td>
<td>Ovoid, fibrous 3 x 2 x 2 cm</td>
<td>Mucin, spaces</td>
<td>Amputation</td>
<td>Metastases in lymph nodes and lungs</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>57</td>
<td>Flexor carpi ulnaris</td>
<td>10 years</td>
<td>Ovoid, fibrous 5 x 4 x 3 cm</td>
<td>Spaces, mucin, epithelium</td>
<td>Excision</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>52</td>
<td>Extensor digitorum</td>
<td>3 years</td>
<td>Ovoid, fibrous 5 x 4 x 2 cm</td>
<td>Mucin</td>
<td>Excision</td>
<td>Recurrence</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>34</td>
<td>Flexor carpi ulnaris</td>
<td>8 months</td>
<td>Ovoid, cystic 2 x 1 cm</td>
<td>Mucin, epithelium</td>
<td>Excision</td>
<td>Cure (12 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>21</td>
<td>Lateral malleolus</td>
<td>6 months</td>
<td>Irregular, ovoid, fibrous 5 x 3 x 2 cm</td>
<td>Spaces, glands</td>
<td>Excision</td>
<td>Cure (14 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>28</td>
<td>Tendo calcaneus</td>
<td>2 months</td>
<td>Ovoid, soft, cystic 10 x 7 x 3 cm</td>
<td>Spaces, epithelium</td>
<td>Excision</td>
<td>Metastases in lungs</td>
<td>1 year</td>
<td></td>
</tr>
</tbody>
</table>

**Others**

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Tumor Site</th>
<th>Duration</th>
<th>Ulceration</th>
<th>Spaces</th>
<th>Treatment</th>
<th>Metastasis</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>M</td>
<td>25</td>
<td>Inner thigh (middle)</td>
<td>14 months</td>
<td>Irregular, ovoid, fibrous 8 x 5 cm</td>
<td>Epithelium</td>
<td>Excision</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>28</td>
<td>Inner thigh (upper)</td>
<td>20 months</td>
<td>Irregular, ovoid, cystic 10 x 7 cm</td>
<td>Spaces</td>
<td>Excision</td>
<td>Metastases in lungs</td>
<td>3 years</td>
</tr>
<tr>
<td>20</td>
<td>F</td>
<td>41</td>
<td>Inner thigh (middle)</td>
<td>4 months</td>
<td>Irregular, ovoid, mucoid 10 x 4 x 3 cm</td>
<td>Epithelium, glands</td>
<td>Amputation</td>
<td>Metastases in lungs</td>
<td>4 months</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>31</td>
<td>Groin</td>
<td>5 months</td>
<td>Irregular, ovoid, fibrous 7 x 4 cm</td>
<td>Glands</td>
<td>Excision</td>
<td>Metastases in lungs</td>
<td>8 months</td>
</tr>
</tbody>
</table>

* The various clinical and pathological features of the series of cases which form the basis of this paper. Cases previously recorded are indicated by the number of the case and year of publication in brackets. Sex incidence, male : female, was 12 : 9. Average age incidence was thirty-seven and a half years, the greatest incidence being in the third decade. Duration of symptoms, in general, was only a few months. Most of the tumours were small when first seen. The histological types refer to the predominating features and correspond with the subdivisions given in the text.

This series is described to portray the pathological features of this condition and it is not intended to draw conclusions from the results of treatment, but it is noteworthy that good results were obtained in at least three cases treated by conservative measures. The progress of the tumour and the liability to metastases seem to depend on the nature of the growth rather than on a special method of treatment.
That synovial tissue is more likely to develop in some parts of the body than others in normal circumstances was emphasised by Floderus (1920) when he referred to joints as being developed from an "arthrogenous blastema," but what has become apparent from observations on various conditions, other than tumours, is that this area is not confined to certain localised regions; indeed, experimental embryology shows that the position of tissues in a limb and their relation to other structures is much more important, in determining whether they will give rise to synovial tissues, than any predetermined cellular character.

This of course is a well known phenomenon in ordinary circumstances. False bursae may form in various parts even where normal bursal tissue is not found, for example, on the top of the head. A false joint may be formed in the middle of a bone. These tumours, therefore, which develop at a distance from synovial tissues are thus strictly comparable with these unusual synovial structures.

It may be concluded from this, apart from any other available evidence, that the view that synovial tissue can be formed only from special synovial cells is much too rigid an attitude. Given the appropriate stimulus it seems that connective tissue cells anywhere are capable of this particular kind of differentiation. If we accept this point of view then the occurrence of synovial tumours in areas away from joints and bursae is easily understandable.

In some of the accounts of these tumours they are described as having certain distinct components, commonly a synovial and a fibrous tissue component. This is quite true descriptively and helps to elucidate the complex histological picture, but the suggestion that these are really fundamentally distinct and different is misleading; the fibrous portion of the growth may differentiate into synovial tissue and vice versa.

The term mesothelium, for cells lining some of the spaces in these tumours, has been used by some writers but it is doubtful whether such terms have any real value. These have an embryological significance but their use as applied to structures developing in the adult is rather like applying the terminology applicable to the first four Egyptian dynasties to present day affairs. The tumours show features peculiar to adult normal or inflamed synovial tissue or to other conditions of this tissue (for example, ganglion) and should be named from this rather than from a presumptive and doubtful precursor.

Study of synovial tumours shows that the tumour cells demonstrate many of the potentialities that are present in more "normal" circumstances. In addition they show others that are not often or even ever seen elsewhere, thus demonstrating potentialities which otherwise would not be known. It is now recognised that a neoplasm is not something extraneous, such as a parasite, but is derived from and is part of the body tissues. Thus tumours may give evidence of capacities of cells and provide confirmatory evidence of what has been recognised in other circumstances, that ordinary connective tissue cells in unlikely places are able to differentiate in the direction of synovial tissues.

A principle generally applicable to malignant tumours is that the more differentiated the cells of a growth the less malignant it is. This does not appear to apply, however, to the synovial tumours, because we find a high degree of differentiation of the types described in some of the most malignant tumours. This appears to be due in part to the independence of the degree of cell differentiation and the development of tissue patterns; thus, we may find that in a growth in which there are well developed synovial spaces the tumour cells may nevertheless be anaplastic and atypical. This is well shown in Figure 8. As is found in other tumours the malignancy of the condition is that of the most actively growing and atypical part, so that in assessing the malignancy of any particular tumour it is necessary to consider the characters of any group of rapidly growing cells rather than the general degree of differentiation found throughout the tumour. For the present, therefore, observations on these forms of differentiation are of considerable general pathological importance but in the present state of our knowledge do not help us to differentiate prognostically between different members of the group.
CONCLUSIONS

Synovial tumours constitute a distinct group of connective tissue growths possessing clear-cut clinical features, fairly uniform gross structure and characteristic histological appearances.

The histological appearances vary greatly but they are all due to variants of cell form and variations of tissue pattern which are all derived from changes in simple connective tissue cells. The tissues do not arise from special synovial cells but are due to differentiation of connective tissues which were not of any special type. These tumours, therefore, are connective tissue tumours which show some or other of a series of differentiations in a direction of synovial spaces, fluid (mucin) and special cell groupings. It is thus obvious that they are named from their component tissues and not from an originating tissue.

The appreciation that the classification of these tumours is on the basis of this differentiation, that is, of their structure, rather than of their origin (that is to say, it is histological rather than histogenetic) is fundamental in understanding their distribution and form.

SUMMARY

1. A series of twenty-one cases of synovial tumour is tabled and the histological appearances are discussed.
2. The characteristic histological forms, (a) mucin formation, (b) synovial spaces, (c) endothelial and "gland" spaces and (d) epithelium-like tissue, are described.
3. These all arise by differentiation of connective tissue cells which occur throughout the connective tissue part of the limbs.
4. Though more commonly found in regions where synovial membrane is present, they are not confined to such special areas.
5. The tumours are classified on a histological and not a histogenetic basis.

REFERENCES


King, E. S. J. (1931): Concerning the Pathology of Tumours of Tendon Sheaths. British Journal of Surgery, 18, 594.

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