"Prognosis in Sarcoma of the Uvea"

T H E S I S

for

the Degree of M. D.

by

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D E C L A R A T I O N

I hereby declare that

1. All the work required for this Thesis was done by me at the Royal London Ophthalmic Hospital (Moorfields) City Road London.
2. This Thesis is entirely composed by me.

M. B. , Ch. B. , D. L. O. , D. O. M. S.

C O N T E N T S

Prefatory Note - In Acknowledgement

The subject of this Thesis is so difficult, that it would have been impossible of accomplishment without the help of a Pathologist and a well-equipped laboratory. This help was forthcoming from Mr. C. Dee Shapland the then Pathologist and now an Honorary Surgeon in Royal London Ophthalmic Hospital (Moorfields) London E. C. 1. He did everything possible to help me by giving me the free use of his laboratory, the benefit of his guidance, and throughout he has taken very keen interest in the progress of this work. Richard Sutton known to one and all as 'Dick' the laboratory Assistant at Moorfields did all that was required of him to help me to prepare the microscopic sections.

I have also to thank Mr. Goulden the Dean, and Miss Lloyd-Jones the Secretary of the Medical School of Moorfields, for giving me permission to carry out this work at the hospital, Mr. Ridley the Registrar, and his Secretary Miss Paddington supplied me with various lists, figures, and other particulars required by me, and also for permitting access to the records of the various patients.

I have to thank all the Honorary Surgeons of Moorfields for giving me permission to make use of their records and clinical notes on all the patients used for this investigation.

And lastly my acknowledgements are due to the authors of all the papers and books which I have quoted in the text, a complete list of these will be found on succeeding pages.

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I - Introduction and Plan of this Work.

During recent years considerable amount of literature has been written regarding the prognosis in sarcoma of the uvea. Several statistics have been published regarding the incidence of this disease, the number of deaths from metastases, the time interval between the occurence of the disease and the time of the death. A list of all the important papers and references on the subject is given in the bibliography of this paper, and on going through all of them the work of*E. von Hippel, Callander**, and Callander & Wilder*** draws special attention, E. von Hippel's for his very careful statistics about the cases which he has been following for a number of years, some of them for over 20 years, and which he has been checking and rechecking time and again. Callander's, and Callander & Wilder's for suggesting new ways of evaluating the prognosis in sarcoma of the uvea.

Among the publications of these three authors three new ways of arriving at the prognosis in this disease are suggested, and this paper is written to investigate the claims of two of them.

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*See Reference No. 17, 18, 19, 20

**See Reference Nos. 2, 3

***See Reference No. 4

The three methods are :-

*1. Prognostic Significance of the quantity of Reticulin found in a section of the growth after enucleation.

Callander and Wilder first published the details of this method in the American Journal of Cancer October 1935. They showed how the Reticulin fibre distribution not only varies in different growths, but also in different areas of the same growth. H & E staining give no indication regarding the quantity of Reticulin or correspondence to presence of its fibres. Special silver staining methods are required to demonstrate its presence. And they showed that the prognosis becomes progressively worse as the quantity of Reticulin becomes less. They of course clearly state that this method by itself is not reliable, the original method described by Callander** of Cell Typing still holds good, but a very much more accurate prognosis can be given, if this method is used as an aid to Cell typing.

The details of this method will

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*See Reference No. 4,
**See Reference No. 2.

be discussed in a later chapter.

2. Prognosis as judged by Histological Cell-Types.

Callander* describes how each sarcoma can be classified in one of the following 4 groups according to the type of cell found in it, they are 1. Spindle Cell (Sub-type A or B), 2. Fascicular Type, 3. Epitheloid Type, 4. Mixed-celled types, and he goes on to describe that each particular type differs in malignancy, whereas spindle typea are comparatively benign, the others become progressively more malignant in the order named above. They have published statistics from a very large number of cases in support of above.

Other authors (Terry & Johns†* Mckee***) have also published their cases supporting the above classification with some variations.

The details will be described in a later chapter.

3. E. von Hippel**** has recently published a new method of determining the prognosis in sarcoma based on the method of Klein of Ludwigshafen. This method is based on the fact that the serum of non-carcinomatous individuals is capable of destroying the cells of

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*See Reference No. 2,3. **See Reference No. 34.
***See Reference No. 23. ****See Reference No. 20.

malignant tumours, while that of sarcomatous or carcinomatous individuals is not. Therefore every case of sarcoma should be tested with this reaction before enucleation. The positive reaction which is to be expected may become negative after the operation. If this change takes place in about two months after the operation, the prognosis should be considered favourable, but if the reaction still remains positive for three months or later after the operation, an enquiry will probably show that the patient has probably died from metastases. The test should be repeated at intervals, and the patient should be kept under observation for at least 10 years. Further research and cooperation between many workers is required before it can be stated that this method is of clinical use in determining the prognosis in uveal sarcoma.

In this paper I have endeavoured to investigate the clinical applicability of the first two methods, that is, "Is it possible by the Reticulin Content of a growth, or by the type of Cell found in a growth, to give an accurate prognosis, after enucleation as to whether the patient will remain free from, or succumb to

metastases". The results given in subsequent chapters speak for themselves.

I do not propose to follow the third E. von Hippel's method any further, I have only mentioned it for the sake of pointing out all recent work on the subject.

During the years 1930 and 1935 both inclusive, that is for a period of six years, 100 patients suffering from sarcoma of the uvea were admitted in The Royal London Ophthalmic Hospital (Moorfields). For the purposes of this investigation I chose the cases from the above six years 1930 - 1935 for the following reasons :-

1. In the hospital class of patients considerable difficulty is experienced in tracing the patients after a lapse of long time, and this period is not too long, even in this period as I shall presently show a certain number of cases could not be traced.
2. The majority of the cases in this series were operated upon more than five years ago, and none less than three years ago. So sufficient time has elapsed to conclude that the majority of patients who have escaped metastases so far, have in all probability escaped from them permanently.
3. This period has furnished 100 cases, which

number is large enough to make the results of some value.

From these 100 cases, for some reason or other, 4 patients were not treated at Moorfields, and in the case of one private patient no attempt was made to trace him as his records were not available, so that left me with 95 cases to carry out my investigations from.

Unfortunately from the 95 eyes that were removed 23 blocks were missing, so there were only 72 blocks from which the investigations on the significance of Argyrophile fibres (Reticulin) in determining the prognosis in sarcoma of the uvea were made. The sections of these 72 blocks were prepared and stained with special silver staining methods described elsewhere, and then they were grouped in different categories according to the amount of Reticulin found in each section. Then the prognosis, solely from the Reticulin content, as well as in conjunction with the Histological Types was judged, and the results are recorded in a later chapter.

Side by side the H & E section of each patient was examined and classified according to Callander's* classification, that is whether it was purely Spindle Cell Sub-type A or B, Fascicular, Epitheloid, or mixed celled growth, if last which was

*See Reference No. 2.

the predominant type of cell. In a certain number of slides some difficulty was experienced to group them in their respective classes, the resons for these difficulties and the way they were overcome are described elsewhere. The prognosis in each case was judged according to the type of cell found in each growth (in case of mixed tumours by the predominating cell). From the 95 eyes removed at Moorfields, 3 H & E sections were missing, so only 92 slides could be examined, and the results as found are recorded in the chapter dealing with the subject.

After the preparation and classification of all the sections, the attempt to get in touch with the 95 patients was made, and the following procedure was adopted.

A questionnaire with a stamped addressed envelope was sent out, it asked for the following :-

1. Their general health since the operation.
2. The condition of the socket
3. If they have had any serious illness since the operation, if so the diagnosis, and the name of the hospital or the private practitioner who attended them.
4. Change of address if any.

No further action was taken on the replies which showed that the patient was alive and

well,but in the cases where the relatives of the deceased wrote that the patient had died,a further letter asking them the exact cause of death if known to them,the date of death,and the name of the doctor or the hospital where the patient had received medical assistance for his last illness,was sent out. Then if necessary an enquiry was made from the patient's doctor or the hospital in which the patient had died to find out the exact cause of death.

In several cases there was no reply in spite of weekly reminders,and also several letters were returned by the Post Office as undelivered,an attempt was made in all these cases to get in touch with them by calling at the addresses as shown in the books of the hospital.Enquiries were made from the present tenants of the addresses,the neighbours,or the local doctors,and if necessary which it was in many cases,calls were made at the new addresses received from these sources,thereby whereabouts of many patients were traced.This last was a very tedious and laborious work,and it took two months of daily running about to accomplish.

In spite of all these efforts,in a certain number of cases,as is inevitable in an investigation of this character,no trace of the patient could be found,so these cases are recorded as patients lost or untraced.The exact number of these cases is 10.

The results of all these investigations are described elsewhere,here it is sufficient to mention that the 95 cases which I attempted to trace,I found :-

1. Patients Alive.....51

2. Patients Dead From metastases 27

Other Diseases 4

Unknown Cause 3

Total.....34

3. Patients lost or untraced.....10

Total.....95

I have also included in this paper a chapter on statistics,to show the incidence of sarcoma of the uvea to all eye diseases - Out-patients and In-Patients,indidence as regards age and sex are concerned,and the various parts of uvea affected.

A warning here about the time limit in judging the prognosis in sarcoma of the uvea,this question is a very vexed one.So far as published records go there does not seem to be any time limit after which secondary growths do not take place.At present most of the authorities are agreed that if metastases have not taken place within five years of enucleation,in a large majority of cases they probably will not take place at all.However,there

are so many cases reported where secondary growths have taken place after five years, and a few after 10 years, that von Hippel's* conclusion that "there is no limit after which a certain cure can be assumed" seems to be justified. On the other hand, the number of patients who develope metastases after 5 years is so small, that if a patient has remained free for so long, he may within reason be expected to remain free from them for all time. So whenever any conclusions on the prognosis in this disease are judged, this fact should always be borne in mind. So wherever required I have divided the list of my cases living in my tables in two categories,

1. Those who are alive for more than 5 years.
2. Those who are alive from 3 to 5 years.

During the follow-up of these patients, I discovered that one of the patients although alive was suffering from metastases, she has been classed among the patients dead of secondary growths in all the tables.

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*See Reference No. 17

II - Reticulin

In the intracellular elements of connective tissue three kinds of fibres are found, i. Collagen fibres, ii. Elastin fibres, iii. Reticulin fibres. It is with the study of the last named that we are concerned with, that is with the quantity of Reticulin found in a given section of the sarcoma of the eye-ball, and whether a definite prognosis can be given from the quantity of reticulin valuated.

1. Reticulin Staining.

Reticulin is not demonstrable by ordinary stains, it only takes up silver stains, hence its fibres are called argyro-phile fibres. With silver stains its fibres appear as prominently black branching extensively against brownish stains of the tumour cells and their nucleii.

Several silver staining methods have been described such as Ranson-Ramon-Y-Cajal Method, Bielschowsky Method and others, Foot's Method for General Laboratory purposes as modified by Wilder is the one used by me for staining my sections *. This method has made the process a short one without the loss of detail. For the sake of brevity and also because of the fact that considerable discussion on staining methods is out of place I shall only describe the method with which all my sections were stained with, that is the one described by H. C. Wilder in the American Journal of Pathology Sept. 1935, this method

is a modification from Foot's Method and is simple, quick, and efficient. It stains the finest reticulin fibres with great precision, no heat is required. Prior to exposure to ammoniacal silver (Foot's Silver Di-amino-Hydroxide) sections are sensitized with Uranium Nitrate solution. The exact Technique of impreganation is as follows.

1. Sections. Made in usual way, that is paraffin, celloidin, or frozen. Then sections are cut the required thickness, 4 to 30 micron thick. Thicker sections give better idea of density, the thickness used by me was about 18 microns.

2. Pre-treatment. Place section in 0.25% Potassium Permanganate solution for 30 minutes in the sun, or at a temperature of 39 degrees for a few minutes, or (in 10% Phosphomolybolic Acid for one minute). Rinse in distilled water and place the section in Hydrobromic Acid (Merck's concenterated 34% 1 part, and distilled water 3 parts) for one minute.

Hydrobromic Acid may be omitted if Phosphomolybolic Acid is used.

3. Sensitization. Wash in tap water, then in distilled water, and dip the section in 1% Uranium Nitrate (Sodium free) for 5 seconds or less.

4. Silver Impreganation. Wash in distilled water for 10-20 seconds and place it in Silver Di-amino-Hydroxid

for one minute.

Silver Di-amino-Hodroxide is prepared as follows, to 5 c.c. of 10.2% Silver Nitrate add Ammonium Hydroxide drop by drop until the precipitate which forms is just dissolved. To this add 5 c.c. of 3.1% Sodium Hydroxide and just dissolve the resulting precipitate with a few drops of Ammonium Hydroxide. Then add distilled water to make this solution up to 50 c.c.

5. Reduction. Dip quickly in 95% Alcohol, and reduce for one minute in a solution consisting of Distilled water 50c.c., 40% Neutral Formalin (neutralised by Magnesium Carbonate) ½ c.c., and Uranium Nitrate 1% 1.5 c.c.

6. Toning. Wash in distilled water, and place the section in 0.2% (1/500) Gold Chloride (Merck's) for one minute. Rinse in distilled water and place the section in 5% Sodium Thiosulphate for 1-2 minutes.

7. Counterstaining. Wash in tap water, and the sections if required can be counterstained with Haemotoxylin, or Haemalum and Eosin.

The sections in this series were not counterstained.

8. Mounting. Dehydrate with i. Methylated Spirit, ii. Carbol Xylol, and mount the sections in Canada Balsam.

Alcohol up to 95% may be used but never absolute alcohol.

Note. Solutions can be used repeatedly for several days, they keep well without disintegrating if kept in Amber coloured stppered bottles indefinitely.

Summary. Bromuration as pretreatment is better than Pyridine pre-treatment for reticulin staining. In this method Reticulin is shown as sharply black. Apart from soaking the section in Potassium Permanganate solution, because of the sensitization with Uranium Nitrate the whole process can be carried out in a very short time, leaving the section in Silver Nitrate solution for days is not required.

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* References Nos. 11, 12, 13, 14, 15, 35.

III. Reticulin Content of a growth.

Reticulin fibre content varies in different growths from complete absence to dense intracellular network, any gradation between these two extremes is met with. It may also varies in different parts of the same growth, or even in different parts of one section. For accurate assessment several sections from different parts of a growth should be prepared, but for the purposes of this work one complete microscopic section of the growth was used as a basis for classification. In several cases other sections were prepared, but no marked change was recorded, but one complete section gives approximate valuation only.

The sections so prepared and examined are divided in three groups.

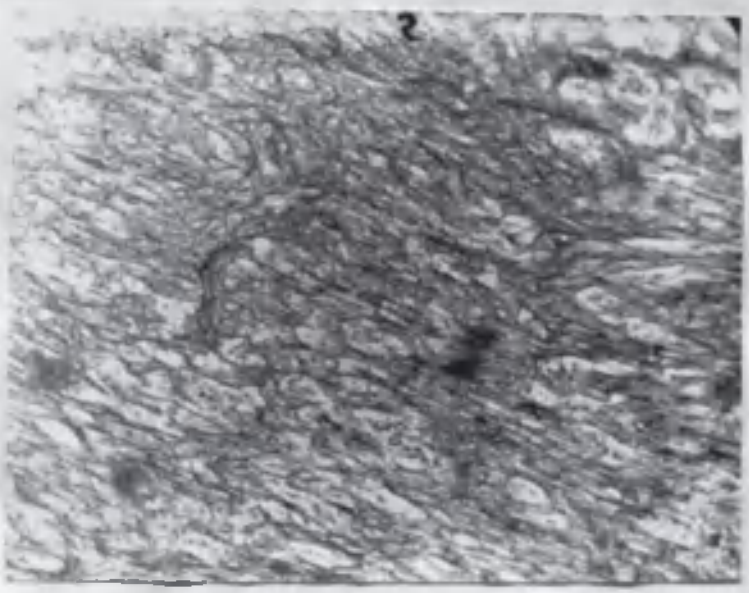
Group 1. In which large quantities of Reticulin fibres were found throughout the growth.

Group 2. In which in some areas Reticulin fibres were in large quantity, in others small or totally absent.

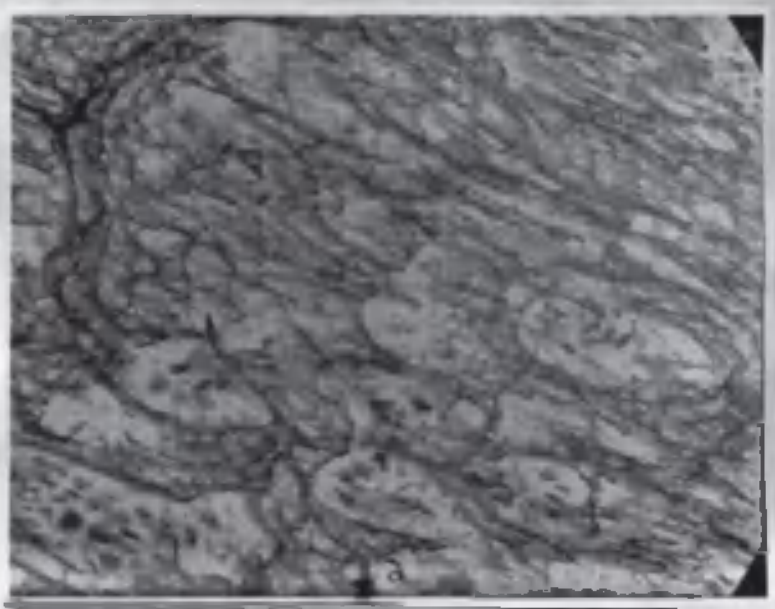
Group 3. In which Reticulin fibres were totally absent except at the periphery of the growth or at the periphery of the lobulated masses of cells, but they did not penetrate the cells.

Group 1. The slides classified under this group not only

showed large quantities of Reticulin fibres between lobules of cells, but their branches penetrated, between individual cells of the growth, some idea of the quantity of Reticulin can perhaps be obtained form the following micro-photographs.

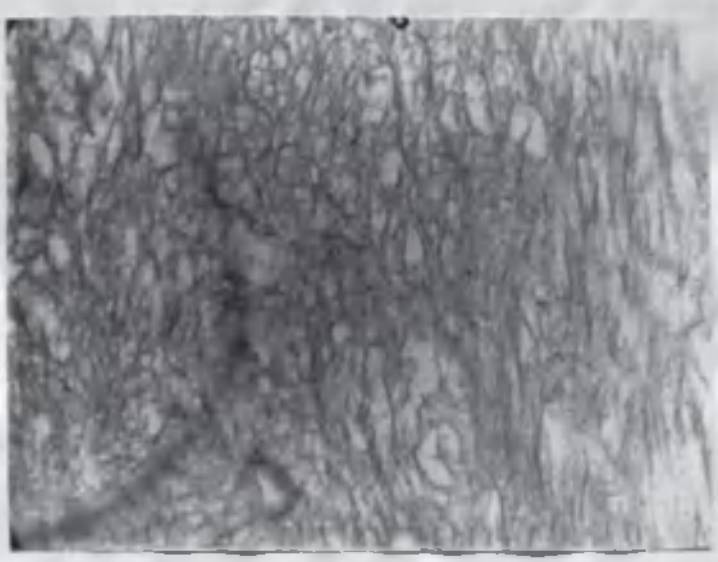


Mic Photo 1. showing dense Reticulin fibre network. Low Power x 110.

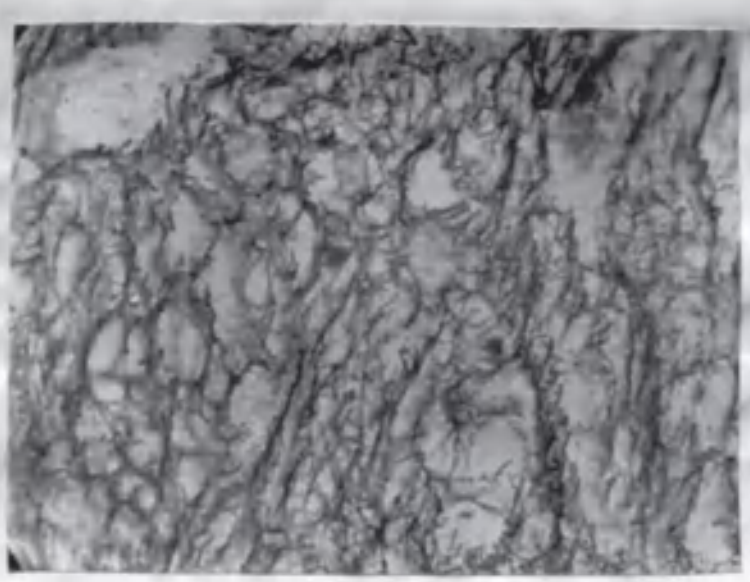


Mic Photo 2. showing same as 1. but under high power x 340.

In the Photograph No. 2 it will be seen that the Reticulin fibres are branching extensively and they are penetrating the individual cells. In this section very large quantity of fibres were met with.

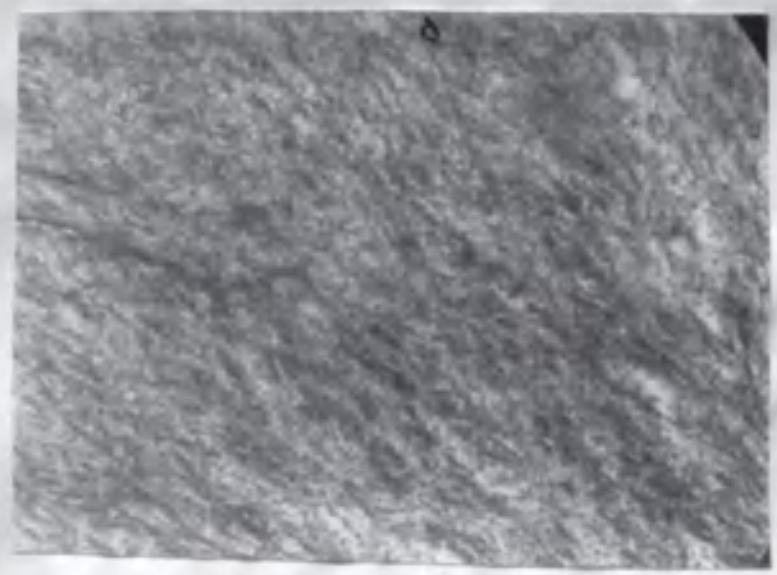


Micro Photograph 3. showing dense Retculin fibre network, but not so dense as in Photo No. 1. Low Power × 110.

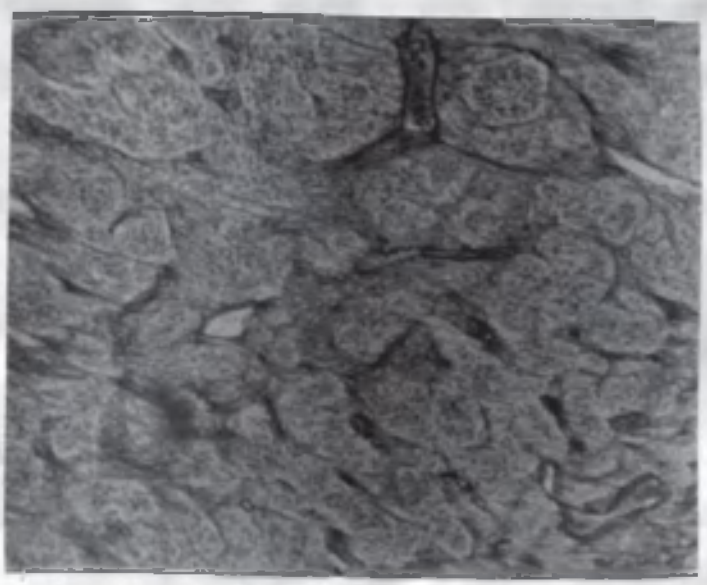


Mic. Photo 4. same as No. 3 under High Power × 340. Note extensive branching and fibres penetrating the tumour cells.

Micro Photograph No. 5 showing dense Reticulin fibre Network, The fibres in this growth are very fine and they are branching extensively, at one place their origin from the blood vessel is noticed. Low Power × 110



Mic Photo 6. Same as No. 5 but under High Power. Very fine fibres between each cell are seen, the fibres are in focus the cells are not, but their nucleii can be recognised as dots, these are nucleoli.
High Power × 340



Micro Photograph No. 7. The Reticulin Network is not so dense as in the preceding ones, the fibres are branching extensively, in some clumps of cells they have penetrated between individual cells, in the others they havenot.

Note the origin of the fibres from blood-vessels. Magnification x 110

The above are some of the pictures to, illustrate the type of growth in which large quantity of Reticulin is found.

This type of section is specially liable to be found in the Spindle Cell variety, Spindle Cells show fibre formation more extensively than other varieties of Sarcoma, in my series 20 sections showed this type,

that is that they belonged to Group I. From this statement it must not be assumed that this type - large quantities of Reticulin are only found in spindle-cell variety, because they are found in other type of sections also. In this series on 20 cases belonging to Group I, 12 are from spindle cell variety, 3 fascicular, 3 epitheloid, and two from the mixed-cell type.

The main criterion by which a section is placed in this group is the fact that Reticulin is not only found in large quantities, but it also penetrates among individual cells almost throughout the growth.

Group 2. In this group Reticulin is found in some parts of the section in small or large quantities, and is absent in other parts. For the purposes of classification under this group Reticulin found at the periphery of sections was not taken into account.

This group is further sub-divided in three sub-groups.

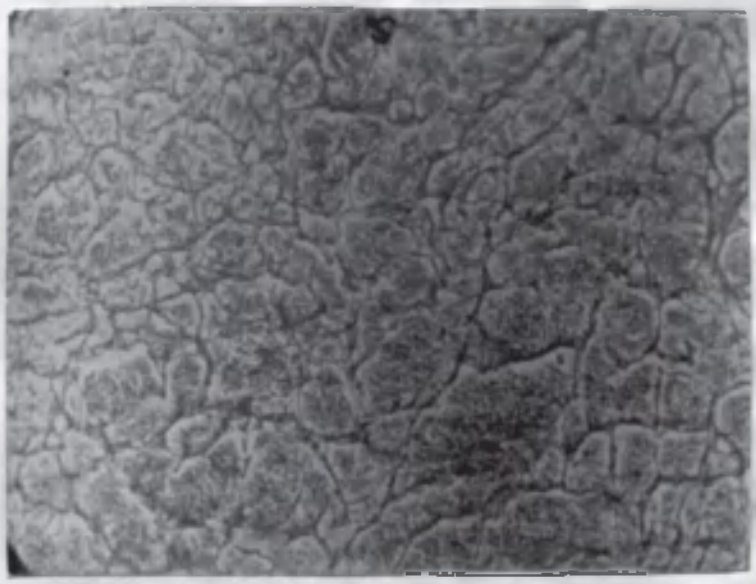
A. In which Reticulin is found in major part of the growth, that is if it can be definitely stated that it is present in quantities in more than half of the growth.

B. In which it is difficult to say that whether the areas with Reticulin are

more or less than the areas without Reticulin. That is that Reticulin is present in about half the growth.

C. In this group areas without Reticulin preponderate over the areas with Reticulin, that is that Reticulin is only present in less than half the section looked at.

To illustrate the type of section which is classified in this group.



Low Power x 110

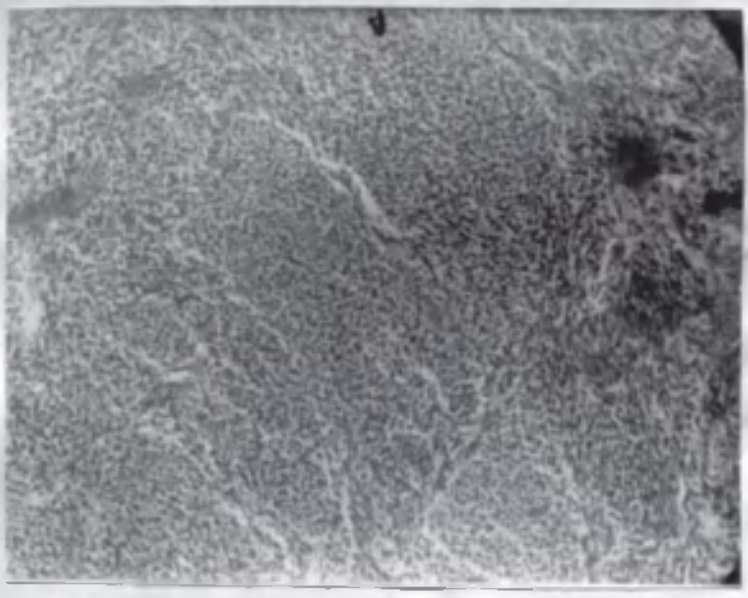
Micro-Photograph 8 -It will be noticed that Reticulin is present round clumps of cells, altho' it is branching, but the branches are not abundant, and their extension between individual cells are not marked. To get an idea that this slide is from mixed variety, see Photo No. 9 & 10.

Out of a total of 72 sections examined by me, a very large number belonged to this group, to be exact 45, and out of

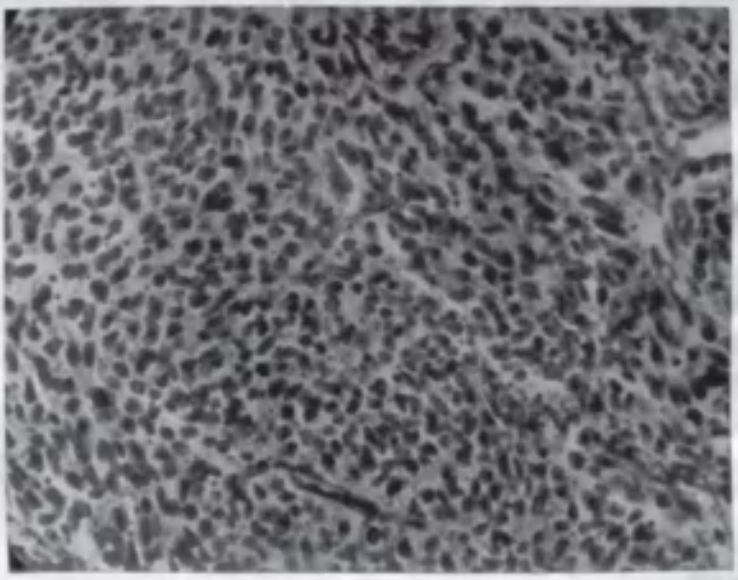
these 16 belonged to Subgroup A,10 to B,and 19 to C.

Again it is noticed that Spindle Cell variety show greater tendency to fibre formation than other varieties,In sub-group A cases,8 are spindle-celled,1 fascicular,1 epitheloid,5 mixed-celled cases,and 1 not classified .In subgroup B,1 spindle-cell,4 epitheloid, and 5 mixed-celled,a total of 10.Sub-group C,3 Spindle-celled,3 Fascicular,5 Epitheloid,and 8 Mixed-celled type,a total of 19 cases.

Group 3. In this group Reticulin is almost completely absent except at the periphery of the growth,a few strands round the bloodvessels may be seen,but that is about all.



Micro-Photograph 9 - This is a silver stained section to show complete absence of Reticulin fibres,a few strands here and there can be recognised.This photograph is from the same slide as No.8,one part of the section contained Reticulin,the other did not. Low Power X 110



Micro-Photograph 10 - Same as No. 9 under High Power to show total absence of Reticulin fibres. Magnification x 340

In this series of 72 sections, only 7 belonged to this group, one spindle-celled, one fascicular, five epitheloid, and none from mix-celled variety.

Summary

Reticulin Groups.	Total No. Slides
Group 1. (++++).....	20
Group 2. A. (+++-).....	16
B. (++--).....	10
C. (+---).....	19
Group 3. (----).....	7
Total No. slides	72

IV - Retculin Content and Prognosis of Sarcoma of the Uvea

Callander and Wilder in the American Journal of Cancer* first published the prognostic significance of Argyrophile fibres, and they came to the conclusion that the presence of Reticulin was a very good prognostic significance. They recorded

No deaths in Group, 1

22% in Group 2 A.
76% in group 2 B. } 68%
87% in Group 2 C.

100% in Group 3

They came to the conclusion that if in addition to the cell type classification, Reticulin classification is also used a very much more accurate prognosis can be given, and they stated that growths can be further sub-divided in groups of relative malignancy, and that deaths in spindle-celled groups can be explained by presence of areas containing no argyrophile fibres.

In main during this investigation my findings are more or less the same as theirs except that there is a difference in the percentages they have recorded, both as regards the incidence of various types and the the number of deaths from each group. There is no doubt that in the cases which are full of Reticulin whether they

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* See Reference No. 4

belonged to spindle-cell type or other groups the prognosis is good, and it became progressively worse as the quantity of reticulin decreased.

To analyse these findings in greater detail, out of the 100 cases which reported at Moorfields as suffering from Sarcoma of the uvea during the years 1930 and 1935 both inclusive, 51 are alive, 10 could not be traced, 27 died from metastases, 4 died from other causes, 3 died from unknown cause, in case of 4 the eye was not excised at Moorfields, and one private case no attempt was made to trace him.

Alive	51
Patients Lost	10
Deaths 1. due to metastases	27
2. Other Causes	4
3. Unknown Cause	3
Total	95
Eyes not excised	4
Not attempted to trace	1
Total	5
Grand Total	100

Cases Alive. In the cases which are alive I am dividing them in two groups, one which are alive more than 5 years, that is the ones which were operated during the years 1930 and 1933, and the second group which are alive from 3-5 years, that is the ones which were operated upon during 1934 and 1935. In the first group there are 29 cases and in the second there are 22, the

Reticulin content of these cases is as follows.

Groups	Over 5 years	3-5 Years	Total
Group 1. (++++)....	12	6	18
Group 2. A. (+++-)..	7	4	11
B (++--)..	3	4	7
C (+---)..	1	1	2
Group 3. (----)....	-	1	1
Eyes Missing	6	6	12
Total	29	22	51

It will be noticed from this table that out of the 39 cases alive whose eyes have been sectioned and examined (there are 12 missing),29 belong to Group 1,and Group 2 A.,while only 10 belong to other groups,it will also be noticed that there is only one patient alive from group 3,and that case was operated upon in 1935,that is only 3 years ago. It is also seen from above that the number of cases alive falls as we descend in the Reticulin content scale.

Deaths & Reticulin. I have recorded above that out of the 88 cases traced, 27 died from metastases,4 from other causes,and 3 from unknown cause.The Reticulin

analysis of these cases is as under :-

	Deaths Metastases	Deaths other cause	Deaths Unknown cause	Total
Group 1.(++++)....	-	-	1	1
Group 2.				
A.(+++-).....	3	-	-	3
B.(++--).....	3	-	-	3
C.(+---).....	14	1	-	15
Group 3.(----)....	3	2	-	5
Eyes Missing.....	4	1	2	7
Total....	27	4	3	34

Here again it will be noticed that there is not a single death from Group 1.which can be definitely ascribed to secondary growths,despite repeated enquiries the cause of one death recorded could not be ascertained.The majority of deaths from secondary growths are found in Group 2.C,that is that major portion of the growth did not contain Reticulin,and as the amount of Reticulin dimnishes the chances of secondary growths taking place increase.

It is mentioned above that out of the 95 eyes excised at the Royal London Ophthalmic Hospital (Moorfields) during the years 1930 and 1935,23 were missing,and therefore I was able to prepare the

sections of 72 eyes only, and these were stained with silver stain described above, and their Reticulin content and the results of follow-up are as follows :-

	Total	Cases Alive				Cases Dead					Un-traced
Group Classification	Total	Over 5 Years	3-5 Years	Total Alive	% Alive	Metastasis	Unknown Cause	Other Cases	Total Deaths	% Deaths due to Metastases*	Un-traced
Group 1. (++++)....	20	12	6	18	90	-	1	-	1	5	1
Group 2. A. (+++-)..	16	7	4	11	69	3	-	-	3	19	2
B. (++--)..	10	3	4	7	70	3	-	-	3	30	-
C. (+---)..	19	1	1	2	10	14	-	1	15	74	2
Group 3. (----)....	7	-	1	1	14	3	-	2	5	43**	1
Total	72	23	16	39	54	23	1	3	27	33	6

*Deaths due to unknown cause are included in the percentage deaths due to metastases, as it is assumed that they have died of Metastases.

**Owing to deaths under other causes and one untraced patient this percentage is lower than it otherwise should have been.

It will be noticed that the percentage of patients alive falls as we descend in the Reticulin scale, and the percentage of Patients dead of Metastases increases as we descend in the Reticulin scale. I have mentioned it above that the patient alive in Group 3 was operated on in 1935, that is that he is just alive for three years, and this fact shoud be taken in account when judging the percentage of cases alive in that group. It will be interesting to follow that patient after a year or so.

For comparison the percentages as recorded by Callander and Wilder as regards the incidence of Metastases are as follows

	Callander & Wilder	Present Series.
Group 1.	None	5%
Group 2. A.	22%	19%
B.	76%	30%
C.	87%	74%
Group 3.	100%	43*%

*See note below the table on Page 37.

Differences in the above percentages can probably be explained by the fact that the figures of the above authors are worked out from the cases which they have followed for five years or longer, and they have not included in their total the cases untraced, or died of

other causes.

Conclusions. From the preceding tables and description there is no doubt about the fact that a definite prognostic significance can be attached to the quantity of Reticulin found in a growth, the more the Reticulin the better the prognosis, and if a case belongs to Group I then a good prognosis can be given with reasonable certainty, on the other hand if the slide belongs to group 3 or to Group 2 C. a bad prognosis can be given with equal certainty, in that case it can be assumed that the patient will probably succumb to metastases.

This question shall be discussed in greater detail after description of the 'Cell Type Classification'.

Summary

	Alive	Dead	Untraced	Total
Group 1.	18	1	1	20
Group 2. A.	11	3	2	16
Group 3 B.	7	3	-	10
C.	2	15	2	19
Group 3.	1	5	1	7
Total	39	27	6	72

V - .Relation Between Type of Cell found in a growth and Reticulin Content.

I have already indicated above that Spindle Cells show greater tendency to fibre formation than other types of growths, although this is not invariably the case, as there are cases in this series belonging to spindle celled group yet showing total absence of Reticulin, and there are also cases of Fascicular, Epitheloid, and Mixed-celled variety which belong to Group I of Reticulin classification. In studying the relation of Reticulin and the Cell type following figures were arrived at.

Reticulin Groups	Spindle A & B	Fascicular	Epitheloid	Mixed-celled Growths		Total
Group 1. (++++).....	12	3	3	2		20
Group 2.						
A. (+++-)...	8	1	1	5		16*
B. (++--)...	1	-	4	5		10
C. (+---)...	3	3	5	8		19
Group 3. (----).....	1	1	5	-		7
Toatl	25	8	18	20	+1*	72

*Includes one case not classified under cell classification.

From the above table it is obvious that beyond the fact that spindle-cell type growths in majority of

cases show greater quantity of Reticulin, and Epitheloid growths show usually small quantity of Reticulin, no other relation can be established. But what is important is that the Malignant growths like Epitheloid growths when they do show a large quantity of Reticulin they become less maliganant, this aspect will be discussed in the next chapter.

VI - Classification of Sarcomas of the Uvea by Histological types

Callander in describing the histological types in Transactions of American Academy of Ophthalmology 1931* states that all malignant melanomas of the uvea can be grouped histologically in four definite types. He describes the following :-

1. Spindle Cell Type
2. Fascicular Type
3. Epitheloid Type
4. Mixed Cell Type

1. Spindle Cell Type. This is the most commonly found type of cell, either solely by itself or in mixed tumours, The cells are arranged in sheets, whorls, or irregularly, Cells are long, spindle shaped, ends appear to terminate in fibres, thereby resembling fibroblasts. Cells are closely packed, and they have long oval nucleus.

According to the type of the nucleus the purely spindlecell growths are further divided in two sub-types

Sub-Type A. In which the nucleus has a delicate reticular structure, and the nucleolus is not well defined, these growths contain a fair amount of pigmentation. This type is found in choroidal growths only.

Sub-Type B. In these there is a sharply defined deeply stained small round nucleolus near centre of nucleus in coarse nuclear

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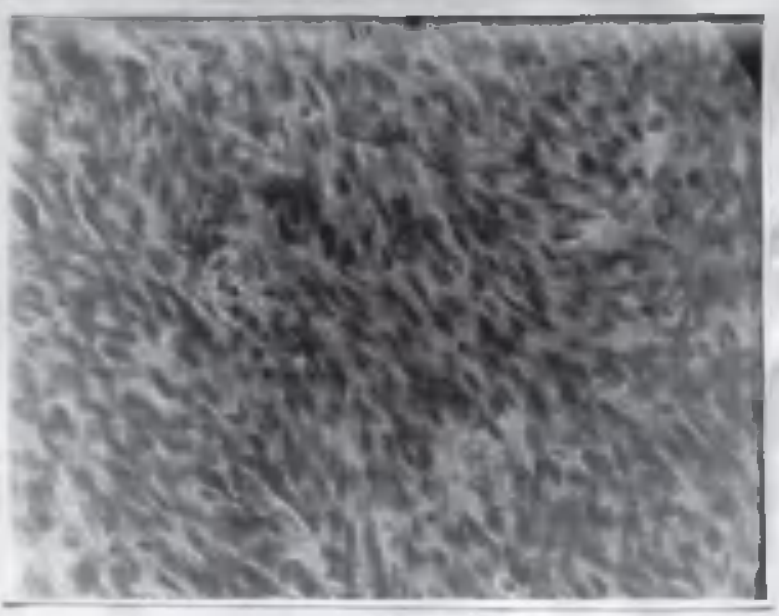
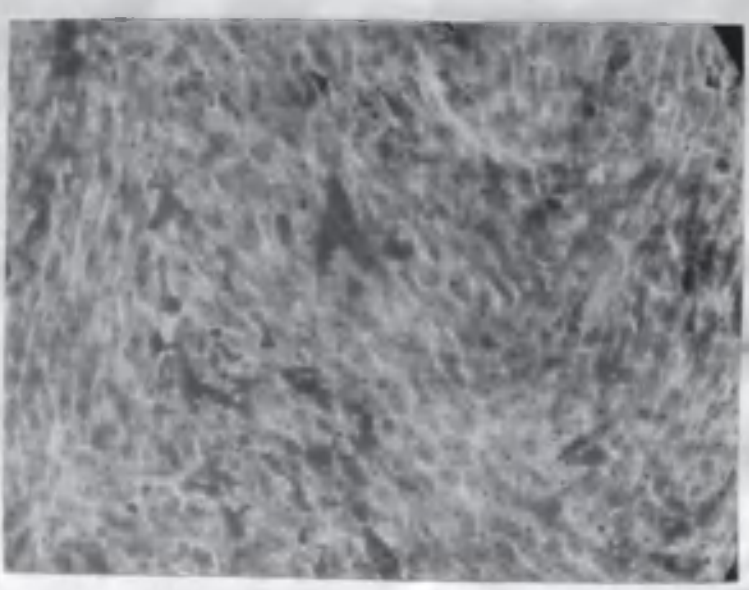
*See Reference No. 2

network. These tumours are generally lightly pigmented, and many of them are white tumours or leuco-sarcomas. This type is often found in mixed celled tumours, and in growths of choroid and ciliary body.

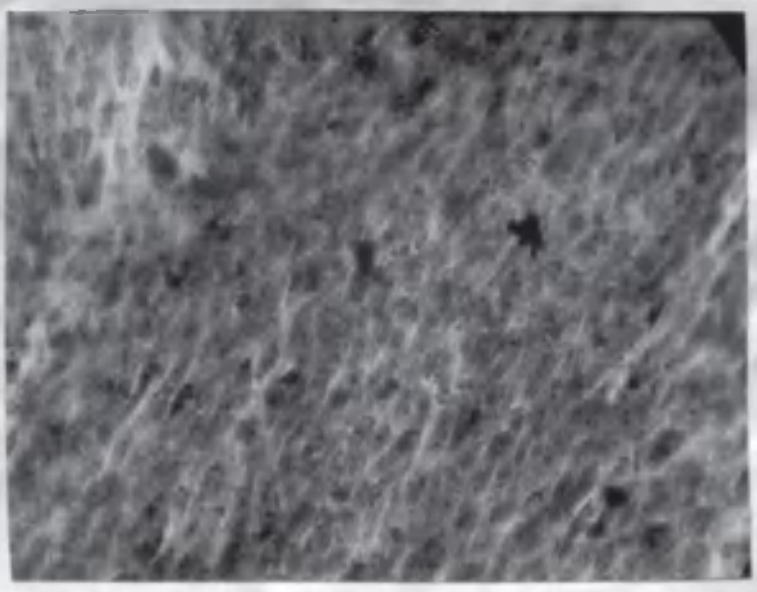
Micro-Photograph No. 11 - showing a spindle celled growth, this particular section belongs to sub-type A. Magnification x 110



Micro-Photograph 12 showing sub-type A type of cell, no distinct nucleolus can be recognised Magnification x 340

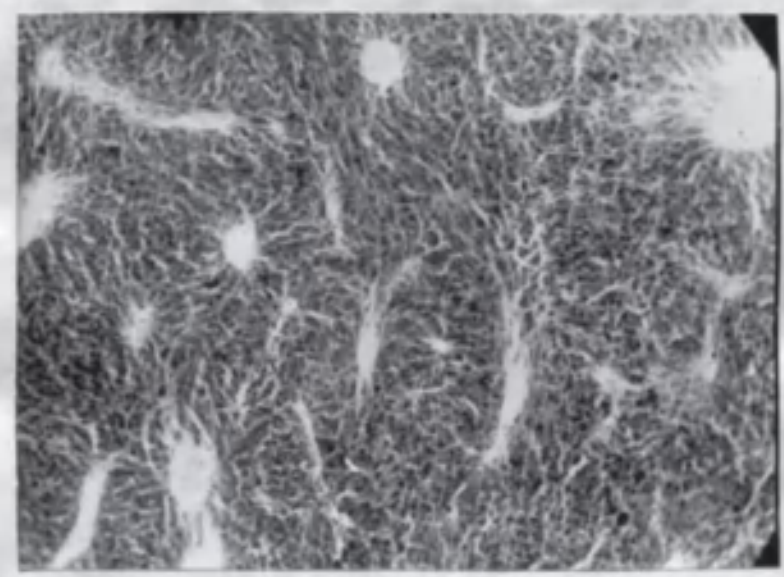


Micro-Photograph 13 - showing Spindle Cell sub-Type B, this photograph is from a mixed cell growth, but spindle cells with prominent dot nucleolus can be recognised. Magnification X 340

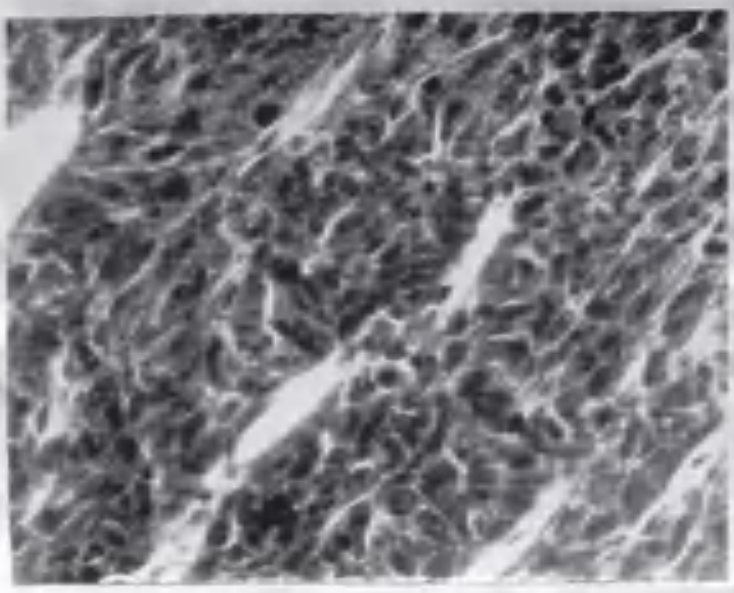


Micro-Photograph 14 - Also showing Spindle cell Sub-type B, prominent nucleolus can be seen. Magnification X 340

2. Fascicular Type. This type is not distinguished so much from the shape of the nucleus, or the shape of the cell, as from the arrangement of the cells. The majority of the cells are arranged in columns or fasciculi, the long axis of cells is at right angles to that of the column, and they radiate out in a palisade manner from a lymphatic or blood vessel, in cross section they give the appearance of a pseudo-rosette. The cells are elongated fibrelike, there is an oval nucleus with a prominent nucleolus resembling that of Spindle Cell Sub-Type B.

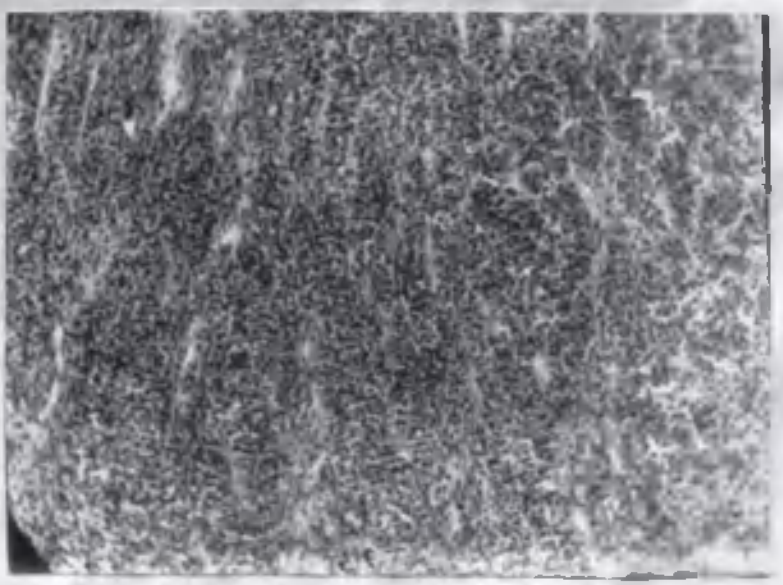


Micro-Photograph 15 - showing a faecicular type of section, note the arrangement of cells radiating out from blood vessels. Magnification x 110

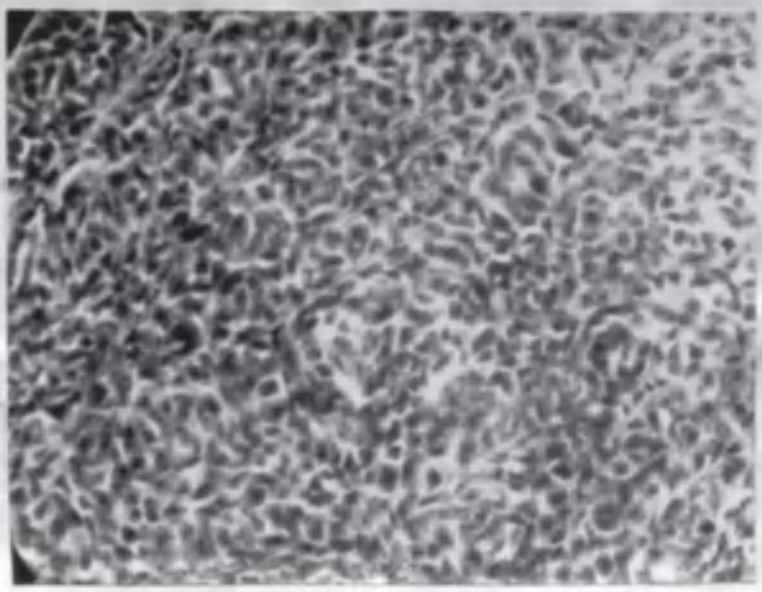


Micro-Photgraph 16 - Same as No. 15 showing fascicular type of cells. Magnification x 340

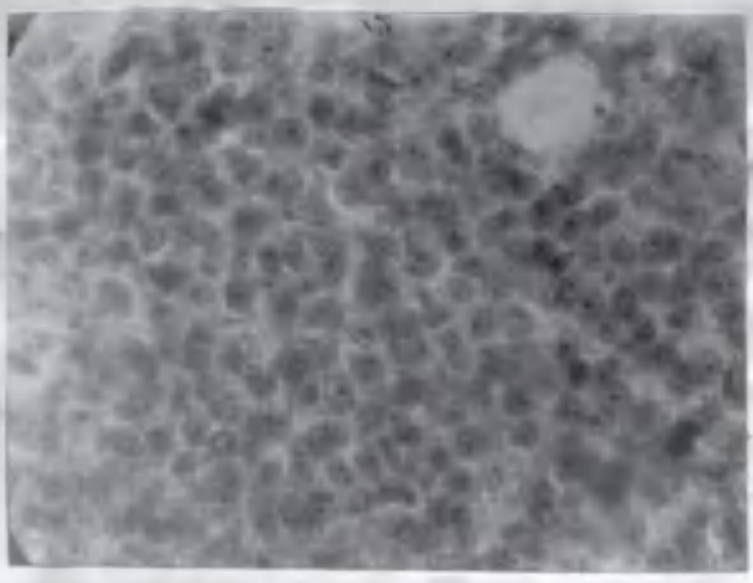
3. Epitheloid Type. The cells are polygonal, they are relatively large, although their size varies considerably in different growths. The cells have a large nucleus round or oval, with one or two distinct nucleolus. This type of cell is also commonly found in mixed celled growths.



Mic-Photo-17-showing Epitheloid type of growth under Low Power. x 110



Micro-Photograph 18 - showing Epitheloid Growth under High Power X 340



Micro-Photograph 19 - showing Epitheloid Growth under High Power. This cells in this particular photograph are very large ones, Compare this size with those of the cells in the Photograph No. 18.

Magnification X 340

4. Mixed Cell Type. These are the commonest melanotic tumours of the eye, there is an irregular mixture of spindle and Epitheloid cells, with occasional areas of fascicular type. Commonly there are small areas composed entirely of one or other cell type, but sometimes various types of cells are mixed in close association. Usually these growths are heavily pigmented

II. The Incidence of various types.

G. R. Callander in the Transactions of American Academy of Ophthalmology and Laryngology* gives the following figures from 237 cases

Spindle Cell	Sub-Type A	31
	Sub-Type B	54
Epitheloid		17
Fascicular		12
Mixed		123
	Total	237

Terry & Johns** from a series of 65 cases record almost similar incidence, their exact figures being :-

Spindle Cell	Sub-Type A	6
	Sub-Type B	12
Epitheloid		8
Fascicular		8
Mixed		31
	Total	65

Mckee's figures*** on the other hand vary very considerably from these authors. From a series of 27

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*See Reference No. 3
**See Reference No. 34
***See Reference No. 23

cases he records

Spindle Cell Sub-Type A.....	14
Epitheloid.....	7
Fascicular.....	4
Mixed.....	2
Total....	27

He makes no mention of Sub-Type B. As my own figures also differ from these of Callander,& Terry & Johns,so I am not going to attempt any explanation regarding the divergence in percentage recorded by Mckee and the other authors quoted above.

In the present series as already explained above,only 95 eyes were excised out of a total of 100 cases reported during the six years under review, out of these 95,three sections were missing,and the other 92 were classified in the various histological types as described by Callander*. It must not be assumed that the classification was easy,in most of the cases it was,but in certain cases it was found to be very difficult as to which type a slide belonged to. Owing to the age of the slides under examination this difficulty was further increased. To get over this difficulty after classification by me every slide was very kindly seen by Mr. D. Shapland the Pathologist of Royal London Ophthalmic Hospital,and the final classification recorded is the one of which he approved. After a series of examinations the 92 slides mentioned

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* See Reference No. 2

above were classified as :-

Spindle Cell Sub-Type A.....22

Sub-Type B.....7

Epitheloid.....25

Fascicular.....9

Mixed.....29

These figures differ from those of Callander, in that the incidence of Spindle Sub-type A is very much higher than that of B, while he records as the Sub-Type B being the commoner of the two, also in this series Epitheloid percentage is higher at the expense of the mixed-celled type. the latter fact, however, is of no consequence as both varieties are almost equally malignant.

III. Histological Types and amount of Pigment.

From the study of these 92 sections following results were arrived at :-

		Quantity Pigment			
	None	Slight	Moderate	Heavy	Total
Spindle A....	5	5	11	1	22
Spindle B....	3	2	1	1	7
Fascicular...	1	1	5	2	9
Epitheloid...	1	1	10	13	25
Mixed.....	4	1	14	10	29
Total..	14	10	41	27	92

Apart from the fact that Spindle cell varieties show less pigment, and Epitheloid and Mixed Cell Types have a tendency to greater pigmentation. I do not think any further comments are required.

VII - Histological Types And Prognosis.

Callander in his original paper* on the histological classification of the sarcoma of the uvea states that in order of maliganacy various types rank as follows :-

1. Epitheloid type-most malignant
2. Fascicular - next
3. Spindle Type B - more malignant than A
4. Spindle Type A - least malignant.
5. Mixed - malignancy varies with the type of cell preponderating, it is the presence of Epitheloid cell which is resposible for the metastases, this type claims the largest percentage of deaths from metastases.

The same author when giving the record of 237 cases in a later paper** gives the following figures :-

Type Cell	No. Cases	No. followed	Deaths Metastases	% Dead of Metastasis
Spindle A...	31	25	-	0.00
Spindle B...	54	44	3	6.81
Epitheloid..	17	14	3	21.42
Fascicular..	12	12	3	25.00
Mixed.....	123	101	37	36.64
Total.....	237	196	46	23.47

*See Reference No. 2

**See Reference No. 3.

From the point of view of malignancy this author* divided the uveal sarcomas in two groups

1. More malignant group consisting of Epitheloid, Fascicular, and Mixed Cell types.
2. Comparatively benign group Spindle Type A & B.

Terry and Johns ** discussing the same question from a study of 94 cases disagree with Callander as regards Spindle Cell B is concerned, they state that Spindle Cell Sub-type B is just as malignant as Epitheloid and Fascicular types, they grade these tumours in three groups :-

Grade I - comparatively benign Spindle A.

Grade II - next in order of malignancy, Spindle B, Epitheloid, and Fascicular.

Grade III- most maignant, Mixed Cell type.

They give the following percentages form 65 cases which they have followed for more than 5 years

Type Cell	No. Cases	Deaths Metastases	% Dead of Metastases	
Spindle A....	6	-	0.00	
Spindle B....	12	5	41.5	
Fascicular...	8	5	41.5	copied from his table.
Epitheloid...	8	3	37.5	
Mixed.....	31	16	51.6	
Total.....	65	29	41.5	copied from his table

*See Reference No. 4
**See Reference No. 34

In the 92 cases of this series the deaths from Metastasis and the percentage from the total cases are as under :-

Type Cell	No. Cases	No. Followed	Deaths Metastasis	% Deaths of Metastasis
Spindle A...	22	22	-	0.00
Spindle B...	7	4	-	As three cases are untraced out of 7, therefore no % can be given
Fasicular...	9	7	4	44.5
Epitheloid..	25	22	9	36.00
Mixed.....	29	27	13	45.00
Total	92	82	26	28.26

To compare the percentage deaths from the present series with those of Callander, and Terry & Johns,

	Present Series	Terry & John	Callander
Spindle A.....	0.00	0.00	0.00
Spindle B.....	None given	41.5	6.81
Fascicular.....	44.5	41.5	25.00
Epitheloid.....	36.00	37.4	21.42
Mixed.....	45.00	51.6	36.64
Total....	28.26	41.5	23.47

The percentages of Terry & Johns of course are only

taken from the cases which they had followed for more than five years, my figures are from the cases that were operated upon 3 to 9 years ago.

Table - Showing details of 95 cases according to Histologicl Types.

Cell Type	Total No. Cases	Cases Living				Cases Dead					Cases Untraced
		Over 5 Yeras	3-5 Yeams	Total Living	% Living	Metastases	Cause Unknown	Other Causes	Total Dead	% Dead due to Metastasis only	
Spindle A....	22	15	7	22	100	-	-	-	-	-	-
Spindle B....	7	2	2	4	57	-	-	-	-	*	3
Fasicualar...	9	2	1	3	33	4	-	-	4	44.5	2
Epitheloid...	25	4	5	9	36	9	1	3	13	36.0	3
Mixed.....	29	5	6	11	38	13	2	1	16	45.0	2
Sections lost	3	1	1	2		1	-	-	1	-	-
Total.....	95	29	22	51	53	27	3	4	34	28.5	10

*This percentage cannot be given as explained above.

From the preceding table it can be reasonably deducted that 1. Spindle A growths have a very good prognosis, in my series, and from the series of the other authors quoted, no death from secondary growths has been recorded in this group.

2. Fascicular, Epitheloid, and Mixed Cell growths each show approximately a mortality of 40 % from the primary cause, the mixed cell growths being rather worse than the other two.

3. I am unable to give an opinion regarding the Spindle B growths, owing to the relatively large number of cases untraced. But assuming that some of these cases are dead from meatstasis, as they probably are, that the Spindle B tumours should be classed mid-way between the other two groups from the point of view of prognosis.

With these deductions I agree with Terry and Johns in grading these growths in three groups, but I do not agree with these authors in placing

Spindle B Growths in parity with Fascicular,Epitheloid, group from malignaney point of view. I also disagree with Callander with regard to the same type of growth wherein he states that Spindle B Growths are slightly more malignant than Spindle A growths. I would suggest following grades

Grade I - Spindle Sub-type A, with few or no metastases.

Grade II - Spindle B, the exact percentage of deaths from secondary growths I am unable to state.

Grade III - Fascicular, Epitheloid, and Mixed Cell growths, with a mortality of about 40 %, the Mixed Cell growths being slightly more malignant than the other two.

The total mortality from secondary growths in cases operated upon form the cases which are traceable being in the neighbourhood of 30 %.

VIII - Prognosis from combined study of Reticulin Content and Histological Types.

Obviously the next question which arises is that can an accurate prognosis be given in Spindle B, Fascicular, Epitheloid, and Mixed Cell tumours from the Reticulin Content of these growths ? It is presumed from the description given in the previous chapter that Spindle A growths have a uniformly good prognosis. To answer this question a detailed study of all the cases who have died from metastases and of all the cases who are alive is required,

Cases known to have died from metastases

These tables are only prepared from those cases in which both Retculin sections and H & E sections were available.

Type Cell	Reticulin Content					Total
	++++	+++-	++--	+---	----	
Spindle A	-	-	-	-	-	-
Spindle B	-	-	-	-	-	-
Fascicular	-	-	-	2	1	3
Epitheloid	-	1	1	5	2	9
Mixed	-	2	2	7	-	11
Total	-	3	3	14	3	23

From the above table it will be noticed that 20 out of 23 cases show a Reticulin content of half or

less than half, and 17 out of these 23 were definitely less than half.

To compare above with the cases which are alive, that necessarily requires two sets of figures, that is the cases who are alive for more than five years, and the cases who aee alive for 3-5 years.

Cases who are alive. These figures are only taken from those sections in which both, results were available.

Type Cell	Total	Reticulin Content: Alive more than 5 yrs. ++++	+++-	++--	+---	----	Alive 3 to 5 years ++++	+++-	++--	+---	----
Spindle A	18	6	4	-	1	-	3	2	1	1	-
Spindle B	4	2	-	-	-	-	1	-	-	-	1
Fascicular	3	1	1	-	-	-	1	-	-	-	-
Epitheloid	5	1	-	2	-	-	1	-	1	-	-
Mixed	8	2	1	1	-	-	-	2	2	-	-
Total	38	12	6	3	1	-	6	4	4	1	1

Total of the above separate figures

Type Cell	++++	+++-	++--	+---	----	Total
Spindle A	9	6	1	2	-	18
Spindle B	3	-	-	-	1	4
Fascicular	2	1	-	-	-	3
Epitheloid	2	-	3	-	-	5
Mixed	2	3	3	-	-	8
Total	18	10	7	2	1	38

Some interesting facts emerge from the study of these tables, these are that there is only one patient alive with total absence of Reticulin, and as I have recorded elsewhere that patient was operated on as recently as 1935, so one may be permitted to be dubious about his future, there are only two patients alive with Reticulin less than half (+---), both these belong to Spindle Sub-type A which I have shown above as a rule gives 100 % good prognosis. All the other patients who are alive contain either half (++--) or more than half (+++-), (++++). From the comparison of the tables of cases who are alive & dead, it seems reasonable to deduce that Reticulin Content examination can aid considerably the Histological Classification in arriving at a prognosis.

To summarise

1. Spindle Cell A growths have generally a very good prognosis.
2. Spindle Cell B growths when aided with Reticulin which is half or more than half give a good prognosis.
3. Fascicular, Epitheloid, and Mixed-Celled growths good prognosis can only be given when the Reticulin content is definitely more than half, that is that it must be ++++, or +++-, the more the

Reticulin better the prognosis. If the Reticulin content is about half that is ++--, in that the prognosis becomes doubtful as some cases survive, and the others succumb to metastasis. And when the Reticulin content falls below half, that is +---, or totally absent ----, in that case a definitely bad prognosis can be diagnosed.

On the next page in a table I am summarising results of follow-up of all 95 cases both from Histological classification and from Reticulin content examination. The information that table yields has been discussed above, it differs from the above tables in that whereas they contained only the results of cases in which both classification were available, this table contains the results of all the cases in which an attempt was made to trace. To complete that table the deaths recorded should be further divided in the deaths due to Metastasis, Unknown causes, and those due to other causes. They are as under

Deaths due to other causes Total No. 4

	Cell Type	Reticulin	Remarks
1.....	Epitheloid ...	----	Even all these
2.....	Epitheloid ...	----	cases belong to
3.....	Epitheloid ...	Missing	malignant celltypes
4.....	Mixed	+---	with low Reticulin content

Deaths due to Unknown Cause... Total No. 3

	Cell Type	Reticulin
1.....	Mixed.....	Missing
1.....	Epitheloid ...	++++
2.....	Mixed	Missing

Reticulin Classification	Spindle A				Spindle B				Fascicular				Epitheloid				Mixed				Total*			
	Living	Dead	Untraced	Total	Living	Dead	Untraced	Total	Living	Dead	Untraced	Total	Living	Dead	Untraced	Total	Living	Dead	Untraced	Total	Living	Dead	Untraced	Total
Group I --- (++++)	9	-	-	9	3	-	-	3	2	-	1	3	2	1	-	3	2	-	-	2	18	1	1	20
Group II A (+++-)	6	-	-	6	-	-	2	2	1	-	-	1	-	1	-	1	3	2	-	5	*11	3	2	16*
(++--) B	1	-	-	1	-	-	-	-	-	-	-	-	3	1	-	4	3	2		5	7	3	-	10
(+---) C	2	-	-	2	-	-	1	1	-	2	1	3	-	5	-	5	-	8	-	8	2	15	2	19
Group III- (----)	--	-	-	-	1	-	-	1	-	1	-	1	-	4	1	5	-	-	-	-	1	5	1	7
Total	18	-	-	18	4	-	3	7	3	3	2	8	5	12	1	18	8	12	-	20	39	27	6	72
Eyes Missing for Reticulin	4	-	-	4	-	-	-	-	-	1	-	1	4	1	2	7	3	4	2	9	*12	7*	4	23*
Grand Total	22	-	-	22	4	-	3	7	3	4	2	9	9	13	3	25	11	16	2	29	51	34	10	95

Total.....95 Cases Investigated.

*Includes 3 cases that are not grouped under the cell classification, one in Group II-Living, one in Eyes Missing Living, one in Eyes Missing Dead.

**Deaths Metastasis - 27, Unknown Cause - 3, Other Causes - 4.

See details on page 60

IX - Sarcoma of the Uvea - Is there a time limit after which a cure can be assumed ?

The prognosis of the sarcoma of the uvea is always very uncertain. The greatest difficulty in arriving at some conclusion is the fact that there seems to be no time limit after which secondary growths do not occur. E. Von Hippel's* observation "There is no limit after which a cure can be assumed" has been proved time and again by him and other workers on the subject. The same author**, however, in recording 23 cases which he has followed for more than 10 years states that 22 are either alive or have died from some other disease, and only one has succumbed to metastases. In the same paper while describing a series of 189 cases, he records that 17% of the survivors died after 5 years, and 10 percent after 10 years. He follows up the same subject in subsequent papers*** where he shows that 65 of his cases lived for more than 5 years, 45 for more than 10 years, and 11 for more than 20 years, in the translation, however, which I possess, it is not mentioned how many of these died of secondary growths, and how many from other causes.

Considering the small number of metastases after 10 years he comes to the conclusion **** that

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*See Reference No. 17
**See Reference No. 17
***See Reference No. 18
****See Reference No. 19

"A 10 year limit must therefore be taken as a basis if a clinical cure is to be mentioned at all", in support of this contention he records that in his series 37 deaths from metastases occured within 5 years of enucleation, 13 from 5 to 9 years, and only 3 after 10 years*.

Teraskeli**, on the other hand, considers 4 years long enough to assume permanent cure. In his series 68.4% were alive after 4 years, 21.1% and 10% had had metastases and recurrences respectively. Incidentally in the same paper he goes on to say that "Histological differences seem to have no particular effect on prognosis", which statement is quite contrary to what I have recorded in the previous chapters.

Choun*** discussing his 61 cases, records 14 deaths, 3 of them lived for more than 5 years.

****Denecke in his report on 36 cases, records 14 deaths, 11 within 5 years, 2 in 6th and 7th year, and one 14½ years after enucleation.

Terry & Johns*****also came to the conclusion that 5 year rule is of no use, as they have also recorded 6 deaths in their series of 94 cases after

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*See Reference No. 19
**See Reference No. 33
***See Reference No. 5
****See Reference No. 10
*****See Reference No. 34

this period,4 out of these occured 9 to 12 years after enucleation.

From the figures qouted above it is clear that a ceratin number of metastases do occur after 5 years,but that number is relatively small,and therefore a patient who has passed the 5 year limit can to a certain extent assumed to be safe from secondary growths,although an absolute assurance to this effect cannot even be given after 10 years.

In the present series,as I have recorded elsewhere,27 cases died of Metastases,the time interval between the operation and death is as under :-

Within 1 year	4 cases
1 - 1½ Years	7 "
1½ - 2 Years	3 "
2 - 2½ Years	2 "
2½ - 3 Years	3 "
3 - 4 Years	3 "
4 - 5 Years	1 "
Over 5 Years	Nil
Interval Unknown	4 cases
Total	27

The earliest death in this series was 6 months after the operation.

It will be noticed from the above table that 11 out of 23 cases whose date of death is known died within 18 months of enucleation, one after 4 years, and none after 5 years, so perhaps it is resonable to assume that very few deaths occur after a patient has passed the 5 year limit, so I am inclined to agree with Teraskeli* in regarding the 4 year period as a basis for permanent cures.

In this series I am not able to give the time interval after which the metastases were first noticed, but it appears from the dates of deaths of various cases that the statement of Schovanic** "The majority of metastases appear in the first three months after enucleation" does not allow long enough time, E. von Hippel is nearer the mark when he states*** "Most metastases occur in the first year after enucleation", and that "Late metastases can be considered as relative cures".

I have recorded in the previous chapters that 51 cases out of the 95 cases operated upon at Moorfieds were alive at the time of the enquiry, the periods for which they have been living obviously free from the disease is as follows :-

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*See Reference No. 33
**See Reference No. 30
***See Reference No. 18

Year	Total No. Cases	No. Living	Alive for
1930	11	5	8 years
1931	18	7	7 Years
1932	20	11	6 Years
1933	13	6	5 Years
1934	13	11	4 Years
1935	20	11	3 Years
Total	95	51	

In the above table, in the total No. cases no account has been taken of the cases that have not been treated, or of one private case which was not traced, and in the cases living only those are included who were known to be alive. One patient although living was known to be suffering from metastases is counted under deaths. The percentage worked below is calculated accordingly.

So it will be noticed that 29 cases out of 62 are alive for more than 5 years, that is 48.4%, not taking into consideration the cases which have not been traced or have died from other disease. E. von Hippel* taking all these factors into consideration and after following up his series for a number of years some of them for over 20 has come to the conclusion that approximately 45% of all sarcoma cases die of secondary growths.

*See Reference No. 19

X - Early Diagnosis and Prognosis in Sarcoma of the Uvea

Most of the writers while discussing the prognosis in uveal sarcoma are agreed on the statement that "Earlier the operation the better the prognosis". (Teraskeli*, Renard**, Choun***, Scovanic****, Sir J. Parsons*****, and other authors of text-books on Ophthalmology). But a discordant note has been sounded by E. von Hippel****** who writes that "It is not yet possible to state that early enucleation gives a good prognosis, and late enucleation a bad one". He while analysing his cases shows that whereas among 609 cases with 162 metastases, the metastases are approximately equally distributed between the three stages at which the enucleation was performed, von Hippel in his own 84 cases finds that out of the 33 who had metastases, 14 occured in 41 cases of I stage (34%), 16 in 34 cases of II stage (47%), and 3 among 8 cases of III stage (37%), thus II stage with 47% comes out worst as regards the incidence of metastases is concerned. He also adds that among his own 58 cases observed for 5 to 23 years the great majority of those treated during the first stage are well, but on taking into consideration all

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*See Reference No. 33
**See Reference No. 27
***See Reference No. 5
****See Reference No. 30
*****See Reference No. 26
******See Reference No. 17

the 189 cases,most of the survivors are found in the second stage,but also the largest (absolute) number of metastases are found in the same stage. E von Hippel with many other workers has recorded very early metastases in cases in which diagnosis and treatment was carried out very early in the disease,and converse also holds good.

Jaensch* does not agree with von Hippel that metastases are more frequent after enucleation in II stagethan after enucleation in I stage,and also he confirms the fact that extension of the tumour to the sclera does not necessarily pave the way to metastases. In his series 21 cases were operated upon in the I stage,11 out of these have passed the 5th year,and 4 have passed the 10th year. 8 cases were operated upon during the II stage,4 out of these have passed the 5th year,and 2 the 10th year.

Schovanic** in his paper fully reports 2 cases of sarcoma of ciliary body,one of which resulted in death in spite of very early diagnosis and enucleation, and the other shows no sign of metastasis 6 years after operation although the tumour had already existed for 2 years before the operation was performed.

Teraskeli*** reports 2 cases of sarcoma of choroid,and neither of these were treated,and yet they did not die of metastases (after 7 years and $2\frac{1}{2}$ years

*See Reference No. 21
**See Reference No. 30
***See Reference No. 33

respectively).

There can hardly be a dissention to the fact that the moment sarcoma is diagnosed, it must be operated upon, whether the operation is enucleation, evisceration, or exenteration of the orbit followed or not followed by irradiation, depending upon the stage of the disease and the choice of the operator, but on the other hand it must be understood that a late diagnosis does not necessarily mean a bad prognosis, as is evidenced by the writings of the authors quoted above, and the following examples in this series :-

1. Female aged 76, eyeball excised in May 1931, at operation a very large gross extraocular extension of the growth was found, the orbit was exenterated, and later followed by radium treatment. This patient is still alive with no sign of metastases or local recurrence, she is now 84 years of age, and operation was performed over 7 years ago.

   Histological classification - mixed cell growth with Spindle Sub-type B in very large numbers.

   Reticulin +++-

   There are four other cases in this series of gross extraocular extension, and they have

all died of Metastases, they all belonged to either mixed-celled, or epitheloid types with low Reticulin content.

2. There were 22 patients with microscopic evidence of extra-ocular extension either along veins, ciliary nerves etc, and in one case along optic nerve, 14 of them are still alive, and 7 of the 14 have passed the 5th year.

3. Scleral involvement by itself does not seem to influence the prognosis either way, there were several cases in this series in which scleral infilteration was present in varying degree, I am unable to draw the deduction that the prognosis in these cases is any worse than the cases in which sclera was not involved.

It is perhaps as well to emphasise here the importance of sceral barrier against extension of the sarcoma. (Cozza F.*)

There is one subject which still requires mention, that is one often finds early or late metastases in the cases which have been diagnosed and treated in a very early stage, in cases in which the growth is small and limited, and there is no microscopic evidence of extension along any known channel, and in cases in which there is no scleral

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*See Reference No. 8

infilteration,it is obvious that transplantation of tumour cells in these cases must have occured before the eyeball was excised,then why such late metastases ? Since in these cases the tumour breaks through the blood-vessels at an early stage,the enucleation is done too late to prevent it,and these transported cells remain latent in other organs for a long time.E.von Hippel* and Jaesch** emphasise the importance of body resistence in these cases,and it appears that body can evidently "deal with" a few transported cells (von Hippel). This fact might explain the occurence of very late metastases,in some cases 10 Or 15 years after the original disease,that is the ability of the body to prevent the growth of transplanted cells for a very long time.

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*See Reference No.17 & 18

**See Reference No.21.

XI - Conclusions.

From the preceding pages, the facts and figures quoted therein, it seems resonable to infer that *Callander, and Callander & Wölder** have made a very important contribution towards the solution of this very vague problem the prognosis in sarcoma of the uvea. It also seems reasonable to conclude from the authors quoted in the previous chapter, that good results in many cases are not so much due to early diagnosis and treatment, as to other factors, such as Reticulin Content of the growth or the Histologic Type the growth is composed of. Early diagnosis does play a part, but a subsidiary part only, as there are many a case in which the diagnosis and enucleation was carried out in the first stage, yet the patient succumbed to secondary growths. From the series published by Callander*, Terry & Johns***, Mckee****, Histological Types have definitely established a place for themselves in the Pathology of the Uveal Sarcoma, I mean as regards the prognosis is concerned, the same, however cannot be said yet of the Reticulin Content basis. For the latter, further records and statistics carried over a large number of years are still necessary.

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*See Reference No. 2, 3. **See Reference No. 4.
***See Reference No. 34. ****See Reference No. 23.

To recapitulate, Three grade of malignancy can be distinguished from the Histological Types :-

Grade I. Spindle Type A, comparatively a benign type, in so far as if other circumstances such as early diagnosis and treatment are favourable, there is hardly any death recorded from metastases in this group.

Grade II. Spindle Type B, More malignant than type A, but less malignant than the other types.

Grade III. Fascicular, Epithelioid, and Mixed-Cell Types, very much more malignant than the other two types, showing a mortality of about 40%, the last more malignant than the other two.

Reticulin Content seems to influence the prognosis considerably, and it is possible by the examination of Argyrophile fibres to determine the prognosis very much more accurately, as to which patient is likely to survive from, and which likely to succumb to metastases in malignant types.

From the examination of both, that is combined study of Histological Types, and Reticulin, it should be possible to foretell the prognosis in a very large number of cases, further checking

and rechecking is required before a final verdict is delivered, as I have quoted several times in the text, that following these cases for a period of 3-8 years is not sufficient, as many observers have shown that metastases occur after this period.

The total mortality from secondary growths in this series works out at approximately 30%, E. von Hippel records that it is 45%, he has of course followed his cases over a large number of years, some of them for over 20.

XII - Sarcoma of the Iris - Prognosis.

Prognosis in sarcoma of the Iris is relatively better thatn the prognosis in sarcoma of the other parts of uvea. For instance E. von Hippel* records 4 cases of sarcoma of iris alive for 10, 21, 23, and 25 years respectively, Denecke** reports two cases of sarcoma of iris in his series of 36 cases, and both of them are alive for 12½ and 4½ years respectively.

In this series there are 4 cases of sarcoma of the iris, and none of them is known to have died of metastases, in the case of one the eye was not excised at Moorfieds. The results of follow-up in these cases are as under :-

Alive (for 8 years).....1.
Dead from other cause.....1.
Lost (Untraced).....1.
Eye not excised.....1.

Total.....4

In the three eyes excised, the type of cell found in all of them was Epitheloid, and only in case of one Reticulin content could be calculated, as the other two blocks were missing.

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*See Reference No. 18

**See Reference No. 10.

The Reticulin content, Histological Cell-Types, and the results of follow-up are as under :-

Year Diag.	No. Case	Cell Type	Reticulin	Result Follow-up
1930....	1.....	Epitheloid.....	++++	Alive
1933....	2.....	Epitheloid.....	Missing....	Dead other cause
1933....	3.....	Epitheloid.....	Missing....	Lost
1933....	4.....	Eye not excised, not attempted to trace.		

It is obvious from above that in view of the fact. that I found only one patient alive, and one dead from other causes, and one untraced patient, I am not in a position to give any views about prognosis in sarcoma of the iris.

Appendix I - Statistics - Indidence, Age, Sex, etc.

As explained in the previous chapter 100 patients suufering from sarcoma of the uvea were admitted to the Royal London Ophthalmic Hospital (Moorfields) during the years 1930 to 1935 both inclusive.

Incidence Table I - showing the number of cases by years

1930.....11

1931.....18

1932.....20

1933.....16

1934.....14

1935.....21

Total 100

Table II - showing the percentage incidence of sarcoma to the New Out-Patients during the period, that is percentage incidence to all diseases

Year	Sarcoma cases	New Out-Patients	Percentage of sarcoma to all eye diseases	or one case of sarcoma in every
1930	11	46,517	.024	4,229
1931	18	44,282	.0407	2,460
1932	20	47,078	.0425	2,354
1933	16	47,915	.0334	2.995
1934	14	51,672	.027	3,691
1935	21	53,712	.039	2,558
Total	100	291,176	.0343	2,912

Table III - showing percentage incidence of sarcoma to all Out-Patients New and Old. the latter with first attendance in the year.

Year	Sarcoma cases	New Out-Patients	Old Out-Patients	Total Out-Patients	% Sarcoma to all eye diseases	or one case of sarcoma in every
1930	11	46,517	5,855	52,372	.021	4,761
1931	18	44,282	5,792	50,074	.036	2,782
1932	20	47,078	6,658	53,736	.037	2,687
1933	16	47,915	7,177	55,092	.029	3,443
1934	14	51,672	6,831	58,503	.024	4,179
1935	21	53,712	8,288	62,000	.034	2,952
Total	100	291,176	40,601	331,777	.03	3,318

In this series the incidence works out as 1 in 3,000,it is higher than the ones previously recorded at Moorfields,but lower than most of those recorded by other observers such as *Stallard gives it as 1 in 4,000

**Fuch -- .066 of all eye diseases

***Davenport in his series of 35 cases says that incidence at Moorfields is 2 in 10,000,and he states that usual incidence is 3-6 per 10,000.

****Terry and Johns -- 5 in 10,000

The percentage in my series works out as .03 % of all eye diseases.

Table IV - showing percentage admissions for sarcoma in Moorfields to total admissions (In-Patients).

Year	Admissions for sarcoma	Total In-Patients	% Sarcoma In-Patients to Total In-Patients	or one sarcoma In-Patient to every
1930	11	2,547	.432	224
1931	18	3,133	.575	174
1932	20	3,276	.61	164
1933	16	3,279	.488	205
1934	14	3,263	.429	233
1935	21	3,739	.56	178
Total	100	19,237	.52	192

*In Berens Eye and its diseases Reference No.32.
Reference No.16A,*Reference No.9,****Reference No.34.

So approximately for every 200 In-Patients in the hospital (Moorfields) there is one admission for sarcoma of the uvea, to be exact a percentage of .525.

Age Incidence.

Table V - showing the incidence of sarcoma in different age-groups by decades.

Year	Sarcoma cases	Age 20-30	Age 31-40	Age 41-50	Age 51-60	Age 61-70	Age over 70	Age not known
1930	11	1	-	2	3	1	2	2
1931	18	3	3	2	4	1	3	2
1932	20	2	2	6	4	5	1	-
1933	16	-	3	1	5	4	2	1
1934	14	-	1	4	3	5	1	-
1935	21	-	2	6	5	6	2	-
Total	100	6	11	21	24	22	11	5

Youngest patient in the series was 26 years of age .
Oldest patient in the series was 77 years of age.

From the above table it will be noticed that the optimum as regards the incidence of sarcoma is concerned is in the decade 50-60 years with a total of 24 cases in this series, the decade before it (i.e. 41-50) accounts for 21 cases, and the decade after it (i.e. 61-70) for 22 cases, the years 41-70 account for 67 cases out of 100, that is

67%, while in the years preceding these and following these there is a sharp fall in the incidence.

Table VI - Showing Average Age.

Year	Year	Average Age
	1930.....	55.55
	1931.....	50.19
	1932.....	50.95
	1933.....	56.27
	1934.....	56.21
	1935.....	54.76

Average Age for the whole series..... 53.70

Average Age as given by other authors

Lawford & Collins 48.42

Marshall..... 54.63

Davenport..... 50.4

Fuchs..... 44.2

Sex Incidence.

Table VII - Showing the incidence in both sexes.

Year	No. Cases	Males	Females	Not known
1930	11	6	5	-
1931	18	10	8	-
1932	20	7	13	-
1933	16	7	8	1
1934	14	6	8	-
1935	21	8	13	-
Total	100	44	55	1

Davenport in his series of 35 cases records 12 Males and 23 Females, that is 34.3% and 65.7% respectively. But he adds that in 345 cases at Moorfieds up to that date there were 167 Males, and 175 Females, sex not recorded in three cases.

In the present series Males and Females are affected in the proportion of 44.4% and 55.6% respectively.

Various parts of Uvea Affected

Table VIII - Showing the incidence in various parrts of uvea.

Year	No. Cases	Choroid	Choroid & Ciliary Body	Iris
1930	11	8	2	1
1931	18	16	2	-
1932	20	17	3	-
1933	16	13	-	3
1934	14	11	3	-
1935	21	18	3	-
Total	100	83	13	4

So in this series the Choroid, Ciliary body, and Iris are affected in the following percentages respectively, 83%, 13%, and 4%. These figures more or less agree with those of Fuchs who records Choroid

affected in 85%, Ciliary body in 9%, and Iris in 6 %.* The figures given by others are :-

Iris	*Martin	1 in 43 cases
	*Collins	1 in 103 cases
	*Fuchs	16 in 259 cases (6%)
	**Teraskeli	No cases in 33
Ciliary Body		
	*Fuchs	22 in 259 cases (9%)
	**Teraskeli	2 in 33 cases. (6%)

Summary.

1. Incidence of Sarcoma to all eye diseases. or 1 in 3000 cases.		.03%
2. Incidence of Sarcoma to In-Patients or 1 case in every 200		.52%
3. Average age for sarcoma of the uvea		53.70
4. Incidence in sexes	Males	44.4%
	Females	55.6%
5. The various parts of uvea affected		
	Choriod	83%
	Iris	4%
	Ciliary body	13%

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*See Reference No. 26A.
**See Reference No. 33

Appendix II.- A list of all cases liming with their Histological Types and Reticulin Content

Summary. Alive.....51 Deaths.Metastases..27
Patients Lost....10 Dead other Cause...4
Eyes not excised.4 Dead Unknown Cause.3
Not attempted to trace.....1

Total.....100

List of Patients alive on 1.9.1938

Year Op.	Serial No.	Ref. No.	Histological Types	Reticulin
1930.	1	1	Spindle Type A....	+++-
	2	7	Spindle Type A....	++++
	3	12	Mixed Type A.....	++--
	4	92	Epitheloid.....	++++
	5	96	Mixed Type B.....	++++
1931.	6	14	Spindle Type A....	++++
	7	15	Mixed Type B.....	++++
	8	18	Spindle Type A....	++++
	9	20	Spindle Type A....	+---
	10	21	Mixed Type B.....	+++-
	11	22	Fascicular.....	+++-
	12	23	Spindle Type A....	+++-
1932.	13	29	Spindle Type B....	++++
	14	33	Missing.....	+++-
	15	36	Spindle Type A....	Missing
	16	38	Spindle Type A....	+++-
	17	39	Spindle Type A....	+++-
	18	40	Spindle Type A....	++++
	19	41	Spindle Type A....	++++
	20	42	Epitheloid.....	++--
	21	44	Mixed All.....	Missing
	22	45	Spindle Type A....	++++
	23	46	Spindle Type B....	++++
1933.	24	50	Epitheloid.....	Missing
	25	51	Spindle Type A....	Missing
	26	53	Spindle Type A....	Missing
	27	56	Spindle Type A....	Missing
	28	58	Epitheloid.....	++--
	29	59	Fascicualr.....	++++

Case No.12 had a very large extraocular extension.

List of Patients alive on 1.9.1938 (Continued)

Year Op.	Serial No.	Ref. No.	Histological Types	Reticulin
1934.	30	60	Spindle Type A	+++-
	31	61	Epitheloid	Missing
	32	63	Missing	Missing
	33	64	Spindle Type A	+++-
	34	66	Spindle Type B	++++
	35	67	Mixed Epitheloid	Missing
	36	68	Mixed Spindle A	+++-
	37	69	Epitheloid	Missing
	38	70	Spindle Type A	+---
	39	71	Mixed All	Missing
	40	98	Epitheloid	Missing
1935.	41	72	Fascicular	++++
	42	73	Mixed Epitheloid	++--
	43	75	Spindle Type A	++--
	44	78	Mixed Type A	++--
	45	80	Epitheloid	++++
	46	81	Epitheloid	++--
	47	82	Spindle Type A	++++
	48	83	Mixed All	+++-
	49	87	Spindle Type B	----
	50	90	Spindle Type A	++++
	51	91	Spindle Type A	++++

After Mixed variety the cell which is found in largest number is mentioned, in the slides in which the preponderating cell could not be made out, expression 'Mixed all ' is used.

Appendix III - A List of all Cases Dead with their Histological Types and Reticulin Content.

Summary

Dead Metastases	27
Dead Other Cause	4
Dead Unknown Cuase	3
Total	34

Deaths from Metastases

Year Op.	Serial No.	Ref. No.	Histological Type	Reticulin	Date Death
1930.	1	4	Mixed Spindle A...	+---	7/1933
	2	6	Mixed Spindle B...	++--	7/1931
1931.	3	8	Epitheloid.....	++--	3/1935
	4	9	Epitheloid.....	+---	------
	5	17	Epitheloid.....	----	6/1934
	6	25	Mixed Epitheloid..	+++-	------
	7	27	Mixed All.....	+---	------
	8	19	Mixed Spindle B...	+---	4/1933
1932.	9	28	Epitheloid.....	+---	12/1933
	10	30	Epitheloid.....	+++-	1/1935
	11	31	Mixed All.....	++--	6/1936
	12	34	Epitheloid.....	----	6/1933
	13	43	Mixed Spindle B...	+++-	after 2 years
	14	47	Epitheloid.....	+---	after 1¼ years
1933.	15	48	Mixed Epitheloid..	Missing	6/1937
	16	54	Mixed Spindle B...	+---	7/1935
	17	57	Fascicular.....	+---	11/1935
1934.	18	62	Missing.....	Missing	9/1935
1935.	19	74	Mixed Epitheloid..	+---	9/1936
	20	76	Mixed Spindle B...	+---	6/1938
	21	77	Fascicular.....	+---	2/1937
	22	79	Fascicular.....	----	--------
	23	84	Fascicular.....	Missing	4/1938
	*24	85	Epitheloid.....	+---	Still Alive
	25	86	Epitheloid.....	+---	2/1936
	26	88	Mixed All.....	Missing	2/1936
	27	89	Mixed All.....	+---	winter '35

*This patient although still alive is classed under death from secondary growths, as it is known that she is definitely suffering from metastases.

Deaths from Other Causes

Year Op.	Serial No.	Ref. No.	Histological Ty Types	Reticulin	Date Death
1930.	1.....	5.....	Epitheloid.....	----	9/1934
1932.	2.....	32.....	Epitheloid.....	----	after 5 yr
1933.	3.....	93.....	Epitheloid.....	Missing	6/1935
1934.	4.....	65.....	Mixed Spindle B....	+---	10/1937

Deaths from Unknown Cause

1931.	1.....	13.....	Epitheloid.....	++++	
1932.	2.....	37.....	Mixed Spindle B....	Missing	
1933.	3.....	52.....	Mixed All.....	Missing	10/1936

Appendix IV - List of Cases which are untraced with their Histological Types and Reticulin Content.

Cases Untraced.

Year Op.	Serial No.	Ref. No.	Histological Types	Reticulin
1930.	1.....	2.....	Fascicular.....	++++
	2.....	3.....	Fascicular.....	+---
1931.	3.....	10.....	Spindle Type B.....	+++-
	4.....	11.....	Spindle Type B.....	+---
	5.....	16.....	Epitheloid.....	Missing
	6.....	24.....	Mixed Spindle B....	Missing
	7.....	26.....	Mixed Spindle A....	Missing
1932.	8.....	35.....	Spindle Type B.....	+++-
1933.	9.....	55.....	Epitheloid.....	----
	10.....	94.....	Epitheloid.....	Missing