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"PROGNOSIS IN SARCOMA OF THE UVEA"*

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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 the 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.

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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.

I.—Introduction and Plan of This Work

DURING recent years a 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 occurrence of the disease and the time of 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^{17 18 19 20}, Callander^{2 3}, and Callander and Wilder^{4 35} merits 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, which he has been checking and re-checking time and again, Callander's, and Callander and 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.

The three methods are:—

(1)^{4 35} *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 *Amer. Jl. 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. and E. staining gives 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 Callander² 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 be discussed in a later chapter.

(2) *Prognosis as judged by histological cell-types.*—Callander^{2 3} describes how each sarcoma can be classified in one of the following four groups according to the type of cell found in it. They are: 1. Spindle cell (Sub-type A or B); 2. Fascicular type; 3. Epithelioid type; 4. Mixed-cell types, and he goes on to describe that

each particular type differs in malignancy: whereas spindle types 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 the above.

Other authors (Terry and Johns³⁴, McKee²³) have also published their cases supporting the above classification with some variations.

The details will be discussed in a later chapter.

(3) E. von Hippel²⁰ 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 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 died from metastases. The test should be repeated at intervals, and the patient should be kept under observation for at least ten years. Further research and co-operation 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 into the Royal London Ophthalmic Hospital (Moorfields). For the purposes of this investigation I chose the cases from the above six years 1930 to 1935 for the following reasons:—

1. In the hospital class of patients considerable difficulty is experienced in tracing the patients after the lapse of a 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 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 the other, four 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 on which to carry out my investigations.

Unfortunately, from the 95 eyes that were excised, 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 reticulin content, as well as in conjunction with histological types was judged, and the results are recorded in a later chapter.

Side by side the H. and E. section of each patient was examined and classified according to Callander's² classification, that is whether it was purely spindle cell sub-type A or B, fascicular, epithelioid, or mixed cell growth; if last which was the predominant type of cell. In a certain number of slides, some difficulty was experienced in grouping them in their respective classes, the reasons 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, three H. and 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 these sections, an attempt to get in touch with the patients was made. The following procedure was adopted.

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

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 patients were 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, as it was in many cases, calls were made at the new addresses received from these sources, thereby the 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 ten. 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 of	(i) Metastases	...	...	27	
	(ii) Other causes	...	...	4	
	(iii) Unknown cause	...	...	3	
	Total dead	...	...	...	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, to out-patients, to in-patients, incidence as regards age and sex are concerned, and the various parts of the 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 ten years, that von Hippel's¹⁷ 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 develop metastases after five 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 five years.
2. Those who are alive from three to five 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.

II.—Reticulin

In the intra-cellular elements of connective tissue, three kinds of fibres are found:—i. collagen fibres; ii. elastin fibres, and iii. reticulin fibres. It is with the study of the last named that we are concerned, that is with the quantity of reticulin found in a given section of the sarcoma of the eyeball, 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 argyrophile fibres. With silver stains its fibres appear as prominently black branching extensively against brownish stains of the tumour cells and their nuclei.

Several silver staining methods have been described such as Ranson-Ramon-Y-Cajal, Bielschowsky and other methods, Foot's method for general laboratory purposes as modified by Wilder is the one used by me for staining my sections^{11 12 13 14 15 35}. 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, that is the one described by H. C. Wilder in the *Amer. Jl. of Path.*, Sept., 1935. This method is a modification of 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 sensitised with uranium nitrate solution.

The exact technique is as follows:—

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

2. *Pre-treatment.* Place the section in 0·25 per cent. potassium permanganate solution for 30 minutes in the sun, or at a temperature of 39° for a few minutes. Ten per cent. phosphomolybdic acid for one minute may be used instead. Rinse in distilled water, and place the section in hydrobromic acid (Merck's concentrated 34 per cent. one part, and distilled water three parts) for one minute.

Hydrobromic acid may be omitted if phosphomolybdic acid is used.

3. *Sensitization.* Wash in tap water, then in distilled water, and dip the section in one per cent. uranium nitrate (sodium free) for five seconds or less.

4. *Silver impregnation.* Wash in distilled water for 10-20 seconds and place it in silver di-amino-hydroxide for one minute.

Silver di-amino-hydroxide is prepared as follows:—To 5 c.c. of 10·2 per cent. silver nitrate solution add ammonium hydroxide drop by drop until the precipitate which forms is just dissolved. To this add 5 c.c. of 3·1 per cent. sodium hydroxide and just dissolve the resulting precipitate with a few drops of ammonium hydroxide. Then add distilled water to make the solution up to 50 c.c.

5. *Reduction.* Dip quickly in 95 per cent. alcohol, and reduce for one minute in a solution consisting of distilled water 50 c.c., 40 per cent. neutral formalin (neutralised by magnesium carbonate) $\frac{1}{2}$ c.c., and uranium nitrate 1 per cent. 1·5 c.c.

6. *Toning.* Wash in distilled water, and place the section in 0·2 per cent. (1/500) gold chloride (Merck's) for one minute. Rinse in distilled water and place the section in 5 per cent. sodium thiosulphate for 1-2 minutes.

7. *Counterstaining.* Wash in tap water, and if required sections can be counterstained with haematoxylin, 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 per cent. 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 stoppered bottles indefinitely.

Summary. Bromuration as pretreatment is better than pyridine 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.

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 vary 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 into 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 lobulated masses of cells, but they did not penetrate between individual 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 from the following microphotographs.

MICROPHOTOGRAPH 1.

Showing dense reticulin network. Magnification 110.

MICROPHOTOGRAPH 2.

Same as 1, but under high power. Magnification 340.

In the photograph No. 2 it will be seen that the reticulin fibres are branching extensively, and they are penetrating between individual cells. In this section very large quantities of fibres were met with.

MICROPHOTOGRAPH 3

Showing dense reticulin fibre network, but not so dense as in photo No. 1. Low power, 110.

MICROPHOTOGRAPH 4.

Same as No. 3, but under high power. Note extensive branching and fibres penetrating between individual tumour cells. Magnification 340.

MICROPHOTOGRAPH 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 blood-vessels is noticed. Low power 110.

MICROPHOTOGRAPH 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 nuclei can be recognised as dots: these are nucleoli. High power 340.

MICROPHOTOGRAPH 7.

The reticulin network is not so dense as in preceding ones, the fibres are branching extensively, in some clumps of cells the fibres have penetrated between individual cells, in the others they have not. Note the origin of the fibres from blood-vessels. Magnification 340.

The above are some of the pictures to illustrate the type of growth in which large quantities of reticulin are 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 cells. In my series 20 sections showed this type; that is that they belonged to Group 1. From this statement it must not be assumed that large quantities of reticulin are only found in the spindle-cell variety, because they are found in other types of sections also. In this series of 20 cases belonging to this group (Group 1), 12 are from spindle-cell variety, three fascicular, three epithelioid, and two from 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 between 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.

MICROPHOTOGRAPH 8.

It will be noticed that reticulin is present round clumps of cells, although it is branching, but the branches are not abundant, and their extension between individual cells is not marked. To get an idea that this slide is from the mixed variety, *i.e.* Group II, see photos 9 and 10.

This group is further divided into three sub-groups:—

(a) In which reticulin is found in the 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 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 reticulin is only present in less than half the section looked at.

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

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 sub-group A, 10 to B, and 19 to C.

Again it is noticed that the spindle-cell variety shows greater tendency to fibre formation than other varieties, in 16 sub-group (a) cases, 8 are spindle-celled, 1 fascicular, 1 epithelioid, 5 mixed-celled cases, and 1 not classified. In sub-group (b), 1 spindle-celled, 4 epithelioid, and 5 mixed-celled, a total of 10. Sub-group (c), 3 spindle-celled, 3 fascicular, 5 epithelioid, and 8 mixed-celled type, a total of 19 cases.

MICROPHOTOGRAPH 9.

This is a silver stained section to show almost 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 110.

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

MICROPHOTOGRAPH 10.

Same as No. 9 but under high power to show total absence of reticulin fibres. Magnification 340.

In this series of 72 sections, only 7 belonged to this group, 1 spindle-celled, 1 fascicular, and 5 epithelioid, none from mixed-celled cases.

Summary

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

IV.—Reticulin Content and Prognosis in Sarcoma of the Uvea

Callander and Wilder in the *Amer. Jl. of Cancer*^{4 36} first published the prognostic significance of argyrophile fibres, and they came to the conclusion that the presence of reticulin was of very good prognostic significance. They recorded :—

No deaths in Group 1.	
22 per cent. in Group 2 A	} 68 per cent.
76 per cent. in Group 2 B	
87 per cent. in Group 2 C	
100 per cent. 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 the presence of areas containing no argyrophile fibres.

In the main during this investigation, my findings are more or less the same as theirs except that there is a difference from the percentages they have recorded, both as regards the incidence of various types and the number of deaths in each group. There is no doubt that in the cases which are full of reticulin, whether they 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 in the case of one private patient no attempt was made to trace him.

Alive	...	...	...	...	51
Patients untraced	...	...	...	...	10
Deaths: i. Due to metastases	...	...	...	...	27
ii. Other causes	...	...	...	...	4
iii. Unknown causes	...	...	...	...	3
				—	
			Total	...	95
Eyes not excised	...	...	...	...	4
Not attempted to trace	...	...	...	...	1
				—	
			Total	...	5
Total No. of cases	...	...	...	...	100

Cases Alive.—The cases which are alive are divided by me into two groups, one which are alive for more than five years, that is the ones which were operated upon during the years 1930 and 1933, and the second group which are alive from three to five 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:—

Reticulin Groups		Cases alive over 5 years		Cases alive 3 to 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 2A, 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 three years ago. It is also seen from above that the number of cases alive falls as we descend in the reticulin content scale.

Deaths and reticulin.—I have recorded above that out of the 85 cases traced, 27 died from metastases, 4 from other causes, and 3 from unknown cause. The reticulin analysis of these cases is as under :—

Reticulin Groups		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 in this group could not be ascertained. The majority of deaths from metastases are found in group 2C, *i.e.*, those in which the major portion of the growth did not contain reticulin, and as the amount of reticulin diminishes 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 to 1935, 23 were missing, and therefore I was able to prepare the sections of 72 eyes only, and these were stained with silver stains described above, and their reticulin content and the results of follow-up are as follows :—

Reticulin Groups	Total	Cases Alive				Cases Dead					Un-traced
		Over 5 years	3 to 5 years	Total alive	% alive	Metastases	Unknown cause	Other causes	Total deaths	% deaths due to metastases	
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 secondary growths.

‡Owing to deaths under 'Other causes' and one untraced patient, this percentage is lower than it 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 above that the patient alive in group 3 was operated upon as recently as in 1935, that is that he is alive just for three years, and this fact should be taken into account when judging the percentages 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 deaths from metastases are as follows:—

	Callander and Wilder		Present Series	
	Per cent.		Per cent.	
Group 1.	...	None	...	5*
Group 2A.	...	22	...	12
B.	...	76	...	30
C.	...	87	...	74
Group 3.	...	100	...	43‡

*See note below the table above.

‡See note below the table above.

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 those dead from 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 1, then a good prognosis can be given with reasonable certainty, on the other hand, if the slide belongs to group 3 or to group 2C, 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 will be discussed in greater detail after description of the 'cell type classification.'

Summary

		Alive		Dead		Untraced		Total
Group 1.	...	18	...	1	...	1	...	20
Group 2A.	...	11	...	3	...	2	...	16
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-cell growths show greater tendency to fibre formation than other type of growths, although this is not invariably the case, as there are cases in this series belonging to the spindle-celled group yet showing total absence of reticulin, and there are also cases of fascicular, epithelioid, and mixed-celled variety, which belong to group 1 of reticulin classification. In studying the relation of reticulin and the cell type found, the following figures were arrived at:—

Reticulin groups		Spindle A and B		Fascic- ular		Epith- elioid		Mixed Growths		Total
Group 1.										
(+ + + +)	...	12	...	3	...	3	...	2	...	20
Group 2A.										
A. (+ + + —)	...	8	...	1	...	1	...	5	...	16*
B. (+ + — —)	...	1	...	—	...	4	...	5	...	10
C. (+ — — —)	...	3	...	3	...	5	...	8	...	19
Group 3.										
(— — — —)	...	1	...	1	...	5	...	—	...	7
		—		—		—		—		—
Total	...	25	...	8	...	18	...	20+1*	...	72

*Includes one case not included in cell classification.

From the above table it is obvious that beyond the fact that spindle-cell type growths in most cases show a greater quantity of reticulin, and epithelioid growths usually show a small quantity of reticulin, no other relation can be established. But what is important is that malignant growths like epithelioid when they do show a large quantity of reticulin, become less malignant. This aspect will be discussed in the next chapter.

VI.—Classification of sarcoma of the uvea by histological types

Callander in describing the histological types in *Transactions of the American Academy of Ophthalmology*, 1931² 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. Epithelioid 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, and the ends appear to terminate in fibres, thereby resembling fibroblasts. Cells are closely packed, and they have a long oval nucleus.

According to the type of nucleus the purely spindle-cell growths are further divided in two sub-groups.

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 the centre of the nucleus in coarse nuclear network. These tumours are generally lightly pigmented, and many of them are white tumours or leucosarcomas. This type is often found in mixed-celled tumours, and ingrowths of choroid and ciliary body.

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 and fibre-like, there is an oval nucleus with a prominent nucleolus resembling that of spindle-cell Sub-Type B.

MICROPHOTOGRAPH 11.

Showing a pure spindle-cell growth, this particular section belongs to Sub-Type A. Magnification 110.

MICROPHOTOGRAPH 12.

Showing Sub-Type A cells, no distinct nucleolus can be recognised. Magnification 340.

MICROPHOTOGRAPH 13.

Showing spindle-cell Sub-Type B, this photograph is from a mixed-cell growth, but spindle cells with prominent nucleoli can be recognised. Magnification 340.

MICROPHOTOGRAPH 14.

Also showing spindle-cell Sub-Type B. Prominent nucleolus can be seen. Magnification 340.

MICROPHOTOGRAPH 15.

Showing a fascicular type of growth. Note the arrangement of the cells radiating out from blood vessels. Magnification 110.

MICROPHOTOGRAPH 16.

Same as No. 15 showing fascicular type of cells under high power. Magnification 340.

3. *Epithelioid 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 nucleoli. This type of cell is also commonly found in mixed-cell growths.

MICROPHOTOGRAPH 17.

Showing epithelioid type of growth under low power. Magnification 110.

MICROPHOTOGRAPH 18.

Showing epithelioid growth under high power. Magnification 340.

MICROPHOTOGRAPH 19.

Showing epithelioid growth under high power. The cells in this growth are very large ones. Compare this size with the size of the cells in photo No. 18. Magnification 340.

4. *Mixed-cell type*.—These are the commonest melanotic tumours of the eye, there is an irregular mixture of spindle and epithelioid cells, with an occasional area 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 the American Academy of Ophthalmology and Laryngology*³ gives the following figures from 237 cases.

Spindle-cell	Sub-Type A	...	31
	Sub-Type B	...	54
Epithelioid	...	...	17
Fascicular	...	...	12
Mixed	...	...	123
Total			237

Terry and Johns³⁴ from a series of 65 cases record almost similar incidence, their exact figures being :—

Spindle-cell	Sub-Type A	...	6
	Sub-Type B	...	12
Epithelioid	...	...	8
Fascicular	...	...	8
Mixed	...	...	31
Total			65

McKee's figures²³, on the other hand, vary very considerably from those of these authors. From a series of 27 cases he records:—

Spindle-cell	Sub-Type A	...	14
Epithelioid	...	...	7
Fascicular	...	...	4
Mixed	...	...	2
Total			27

He makes no mention of Sub-Type B. As my own figures also differ from those of Callander, and Terry and Johns, I am not going to attempt any explanation regarding the divergence in percentages 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 Callander². 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 to decide as to which type a slide belonged. 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 the 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 above were classified as:—

Spindle-cell	Sub-Type A	...	22
	Sub-Type B	...	7
Epithelioid	...	...	25
Fascicular	...	...	9
Mixed	...	...	29
Total			92

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 the sub-type being the commoner of the two, also in this series epithelioid percentage is higher at the expense of the mixed-cell type, the latter fact, however, is of no consequence as both varieties are almost equally malignant.

iii.—*Quantity of pigment in various types.*

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

	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
Epithelioid	1	1	10	13	25
Mixed	4	1	14	10	29
Total	14	10	41	27	92

Apart from the fact that spindle-cell growths show less pigment, and epithelioid and mixed-cell varieties have a tendency to contain larger quantity of pigment, I do not think any further comments are required.

VII.—*Histological types and prognosis*

Callander in his original paper² on the histological classification of sarcoma of the uvea states that in order of malignancy various types rank as follows :—

1. Epithelioid type—most malignant.
2. Fascicular—next.
3. Spindle type B—more malignant than Type A.
4. Spindle type A—least malignant.
5. Mixed type—malignancy varies with the type of cell preponderating, it is the presence of epithelioid cells which is responsible 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 paper³ gives the following figures :—

Type of Growth	No. Cases	No. Followed	Deaths Metastases	% Dead of Metastases
Spindle A	31	25	—	0·00
Spindle B	54	44	3	6·81
Epithelioid	17	14	3	21·42
Fascicular	12	12	3	25·00
Mixed	123	101	37	36·64
Total	237	196	46	23·47

From the point of view of malignancy this author⁴ divides the uveal sarcomas in two groups:—

1. More malignant group consisting of epithelioid, fascicular, and mixed cell types.
2. Comparatively benign group, spindle-cell type A & B.

Terry and Johns³⁴ discussing the same question from a study of 94 cases disagree with Callander as regards spindle-cell B, they state that spindle-cell sub-type B is just as malignant as epithelioid and fascicular types, they grade these tumours in three groups:—

Grade 1.—Comparatively benign spindle A.

Grade 2.—Next in order of malignancy, spindle B, epithelioid, and fascicular.

Grade 3.—Most malignant mixed-cell type.

They give the following percentages from 65 cases which they have followed for more than five years:—

Type of Growth	No. Cases	No. Deaths Metastases	% Dead of Metastases
Spindle A	6	—	0·00
Spindle B	12	5	41·5
Fascicular	8	5	41·5*
Epithelioid	8	3	37·5
Mixed	31	16	51·6
Total	65	29	41·5*

*These figures are not correct, but are copied from his tables.

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

Type of Growth	No. Cases	No. Followed	Deaths Metastases	% Dead of Metastases
Spindle A	22	22	—	0·00
Spindle B	7	4	—	As three cases are untraced, therefore no percentage can be given.
Fascicular	9	7	4	44·5
Epithelioid	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 and Johns.—

	Present Series	Terry and Johns	Callander
Spindle A ...	0·00	0·00	0·00
Spindle B ...	None given	41·5	6·81
Fascicular ...	44·5	41·5	25·00
Epithelioid ...	36·00	37·4	21·42
Mixed ...	45·00	51·6	36·64
Total ...	28·26	41·5	23·47

The percentages of Terry and 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 three to nine years ago.

Table showing details of 95 cases according to histological types

Cell type	Total No. Cases	Cases living				Cases dead					Cases untraced
		Over 5 years	3 to 5 years	Total living	% living	Metastases	Cause unknown	Other causes	Total dead	% Deaths due to Metastases only	
Spindle A ...	22	15	7	22	100	—	—	—	—	—	—
Spindle B ...	7	2	2	4	57	—	—	—	—	*	3
Fascicular ...	9	2	1	3	33	4	—	—	4	44·5	2
Epithelioid ...	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 in the preceding Table.

From the preceding table it can be reasonably deduced that:—

1. Spindle A growths have a very good prognosis, in my series, and from the series of the authors quoted above, no death from secondary growths has been recorded in this group.

2. Fascicular, epithelioid, and mixed-cell growths each show approximately a mortality of 40 per cent. from secondary growths, 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 have died of metastases, as they probably have, then spindle B growths can reasonably be classed mid-way between the other two groups from the point of view of malignancy.

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, and epithelioid groups from the point of view of malignancy. I also disagree with Callander when he states that this type of growth is only slightly more malignant than spindle A group. From the results of the follow-up I would suggest the following grades:—

Grade I.—Spindle sub-type A, with few or no metastases. The most benign group.

Grade II.—Spindle sub-type B, mid-way between the other two groups, definitely more malignant than sub-type A, but not so malignant as the grade III group, this is obvious from the number of survivors traced. I am unable to record the exact percentage of metastases owing to reasons given before.

Grade III.—Fascicular, epithelioid, and mixed-cell growths, with a mortality from secondary growths of about 40 per cent. The mixed-cell growths are slightly more malignant than the other two.

The total mortality from secondary growths in this series is in the neighbourhood of 30 per cent.

VIII.—Prognosis from combined study of reticulin content and histological types

Obviously the next question which arises is, can an accurate prognosis be given in spindle B, fascicular, epithelioid, 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 cases which have died from metastases, and of all the cases which are alive, is required.

Cases known to have died of metastases.—These tables are only prepared from those cases in which both reticulin sections and H. and E. sections were available.

Type cell	RETICULIN CONTENT					Total
	++++	+++	++--	+-	----	
Spindle A ...	-	-	-	-	-	-
Spindle B ...	-	-	-	-	-	-
Fascicular ...	-	-	-	2	1	3
Epithelioid ...	-	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.

Cases which are alive.—To compare the above with the cases which are alive, necessarily requires two sets of figures, that is the cases alive for more than five years, and the cases alive from three to five years.

These tables are only taken from those cases in which both reticulin and H. and E. results were available.

Type growth	Total	RETICULIN CONTENT									
		Alive more than 5 years					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	-	-	-	-
Epithelioid	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 is as follows :

Type growth	RETICULIN CONTENT					Total
	++++	+++	++--	+-	----	
Spindle A ...	9	6	1	2	-	18
Spindle B ...	3	-	-	-	1	4
Fascicular ...	2	1	-	-	-	3
Epithelioid ...	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

upon as recently as 1935, so one may be permitted to be dubious about his future. There are only two patients alive with reticulin content of less than half (+ — — —), both of these belong to spindle sub-type A, which I have shown above as a rule gives 100 per cent. good prognosis. All the other patients who are alive contain either half (++++), or more than half (++++), (++++). From the comparison of the tables of cases which are alive and dead, it seems reasonable to deduce that reticulin examination considerably aids the histological classification in arriving at a prognosis.

To Summarise :—

1. Spindle-cell sub-type A growths have always a very good prognosis.

2. Spindle-cell sub-type B growths when aided with reticulin content of half, or more than half give a good prognosis.

3. Fascicular, epithelioid, and mixed growths, good prognosis can only be given when the reticulin content is definitely more than half, that is that the slide must belong to group (++++), or (++++), the more the reticulin the better the prognosis. If the reticulin content is about half (that is +++—), the prognosis becomes doubtful, as some cases survive, and the others succumb to metastases. And when the reticulin content falls below half (that is + — — —), or is totally absent (— — — —), a definitely bad prognosis can be foretold.

To summarise, on the next page in a table I am giving the results of follow-up of all 95 cases with details of histological classification and reticulin content examination. The information that the 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 classifications were available, this table contains the results of all the cases in which an attempt was made to trace.

To complete the table the deaths recorded should be further divided into the deaths due to secondary growth, unknown causes, and those due to other causes. Their details are as under:—

Deaths due to other causes	...	...	...	...	4 cases
Type growth	Reticulin content			Remarks	
1. Epithelioid	...	— — — —	...	All these cases belong to malignant cell-types with low reticulin content.	
2. Epithelioid	...	— — — —	...		
3. Epithelioid	...	Missing	...		
4. Mixed	...	+ — — —	...		
Deaths due to unknown cause	...	...	...	...	3 cases
1. Mixed	...	...	...	Missing	
2. Epithelioid	...	...	...	++++	
3. Mixed	...	...	...	Missing	

Reticulin Groups	Spindle A				Spindle B				Fascicular				Epithelioid				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	—	—	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	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	8	9	13	3	25	11	16	2	29	51	34†	10	95

Total No. Investigated ... 95

*Includes 3 cases not grouped under cell classification, 1 in Group II A living, 1 in eyes missing dead, and 1 in eyes missing living.

†Causes of deaths—metastases 27, unknown causes 3, other causes 4. Details on page 271.

IX.—Sarcoma of the uvea—Is there a time limit after which a cure can be assumed

The prognosis of 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 may not occur. E. von Hippel's¹⁷ 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 author¹⁷, however, in recording 23 cases which he has followed for more than ten 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 per cent. of the survivors died after five years, and 10 per cent. after ten years. He follows up the same subject in subsequent papers¹⁸ where he shows that 65 of his cases lived for more than five years, 45 for more than ten years, and 11 for more than twenty 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 ten years he comes to the conclusion¹⁹ that "A ten 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 occurred within five years of enucleation, 13 from five to nine years after, and only three after ten years¹⁹.

Teraskeli³³, on the other hand, considers four years long enough to assume permanent cure. In his series 68 (4 per cent.) were alive after four years, 21 (1 per cent.) and 10 per cent. 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.

Choun⁵ discussing his 61 cases, records 14 deaths, three of them lived for more than five years.

Denecke¹⁰ in his report on 36 cases, records 14 deaths, 11 within five years, two in 6th and 7th year, and one 14½ years after enucleation.

Terry and Johns³⁴ also came to the conclusion that a five year rule is of no use, as they have also recorded six deaths in their series of 94 cases after this period, four out of these occurred 9 to 12 years after enucleation.

From the figures quoted above it is clear that a certain number of metastases do occur after five years, but that number is relatively small, and therefore a patient who has passed the five year limit can to a certain extent be assumed to be safe from secondary

growths, although an absolute assurance to this effect cannot be given after ten 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 cases
1½-2 years	...	3 cases
2-2½ years	...	2 cases
2½-3 years	...	3 cases
3-4 years	...	3 cases
4-5 years	...	1 case
Over 5 years	...	Nil.
Interval unknown	...	4 cases
Total	...	27 cases

The earliest death in this series was six 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 four years, and none after five years, so perhaps it is reasonable to assume that very few deaths occur after a patient has passed the five year limit, so I am inclined to agree with Teraskeli³³ in regarding the four 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 Schovanic³⁰, "The majority of metastases occur in the first three months after enucleation," does not allow a long enough time, E. von Hippel is nearer the mark when he states¹⁸ "most metastases occur in the first year after enucleation," and that very 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 Moorfields were alive at the time of this enquiry, the periods for which they have been living obviously free from the disease are as follows :—

Year	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	3 to 8 years

In the above table, in the total number of 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

which were known to be alive. One patient although living was known to be suffering from metastases and is counted under deaths. The percentage worked below is calculated accordingly.

So it will be noticed that 29 cases out of 62 (total for the years 1930 to 1933) were alive for more than five years, that is 48.4 per cent., not taking into consideration the cases which have not been traced or have died from other disease. E. von Hippel¹⁹ taking all these factors in 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 per cent. of all sarcoma cases die of secondary growths.

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 the "earlier the operation the better the prognosis," (Teraskeli³³, Renard²⁷, Choun⁵, Schovanic³⁰, Sir J. Parsons²⁶, and other authors of text-books on ophthalmology). But a discordant note has been sounded by E. von Hippel¹⁷ 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, E. von Hippel in his own 84 cases finds that out of the 33 which had metastases, 14 occurred in 41 cases of I stage (34 per cent.), 16 in 34 cases of II stage (47 per cent.), and 3 among 8 cases of III stage (37 per cent.) thus II stage with 47 per cent. comes out worst as far as 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 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 the converse also holds good.

Jaensch²¹ does not agree with von Hippel that metastases are more frequent after enucleation in II stage than 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 1st stage, 11 out of these have passed the 5th year, and 4 have passed the 10th year. Eight cases were operated upon during the 2nd stage, 4 out of these have passed the 5th year, and 2 the 10th year.

Schovanic³⁰ in his paper fully reports two cases of sarcoma of the ciliary body, one of which resulted in death in spite of very early diagnosis and enucleation, and the other showed no sign of metastases six years after operation although the tumour had already existed for two years before the operation was performed.

Teraskeli³³ reports two cases of sarcoma of the choroid, and neither of these was treated, and yet they did not die of metastases (after 7 years and 2½ years respectively).

There can hardly be a dissent 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 (resulting in a late operation) 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 years, eyeball excised in May 1931, at operation a very large extra-ocular extension of the growth was found, the orbit was exenterated, and later treated by radium. This patient is still alive with no sign of metastases or recurrence, she is now 84 years of age, and operation was performed seven years ago.

Histological classification.—Mixed-cell growth with spindle sub-type B very largely preponderating.

Reticulin content:—++— (Group 2 A).

There are four other cases in this series of gross extra-ocular extension, and they have all died of metastases, they all belonged to either epithelioid or mixed-cell groups with low reticulin content.

2. There were 22 patients with microscopic evidence of extra-ocular extension either along veins or ciliary nerves, and in one case along the optic nerve, 14 of them are still alive, and 7 of the 14 have passed the fifth 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 infiltration 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 the sclera was not involved.

It is perhaps as well to emphasise here the importance of scleral barrier against extension of the sarcoma. (Cozza F.⁸)

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 infiltration, it is obvious that transplantation of tumour cells in these cases must have occurred before the eyeball was excised, if that is the case then why such late metastases? Obviously 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^{17 18} and Jaensch²¹ emphasise the importance of body resistance in these cases, and it appears that evidently the body can "deal with" a few transported cells (von Hippel). This fact might explain the occurrence of very late metastases, in some cases 10 or 15 years after the original disease, the explanation lies in the ability of the body to prevent the growth of these transported cells for a very long time.

XI.—Conclusions

From the preceding pages and the facts and figures quoted therein it seems reasonable to infer that Callander,^{2 3} and Callander and Wilder⁴ 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 due, not so much to early diagnosis and treatment, as to other factors, such as reticulin content of the growth and its histological type. Early diagnosis does play a part, but a subsidiary part only, as there are many cases in which the diagnosis and enucleation were carried out in the first stage of the disease, yet the patient succumbed to secondary growths. From the series published by Callander,^{2 3} Terry and Johns,³⁴ and McKee,²³ histological cell-type classification has definitely established a place for itself in the pathology of the uveal sarcoma, I mean as regards the prognosis, the same, however, cannot yet be said of the reticulin content basis. For the latter further records and statistics over a large number of years are necessary.

To recapitulate, three grades 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 other types.

Grade III.—Fascicular, epithelioid, and mixed-cell types, very much more malignant than the other types, showing a mortality of about 40 per cent., the last named is 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 patient is 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 re-checking is required before a final verdict is delivered. As I have quoted several times in the text following these cases for a period of 3 to 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 per cent., E. von Hippel records that it is 45 per cent., 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 in

Prognosis in sarcoma of the iris is relatively better than the prognosis in sarcoma of the other parts of uvea. For instance, E. von Hippel¹⁸ records 4 cases of sarcoma of the iris alive for 10, 21, 23, and 25 years respectively, Denecke¹⁰ 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 four cases of sarcoma of the iris, and none of them is known to have died of metastases; in the case of one patient the eye was not excised at Moorfields. The results of follow-up in these cases are:—

Alive (for 8 years)	...	1
Dead from other causes	...	1
Lost (untraced)	...	1
Eyes not excised	...	1
		—
Total	...	4

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

The reticulin content, histological cell-types, the year of operation, and the results of follow-up are as under:—

Year Operation	No. Case	Histological Type	Reticulin Content	Result Follow-up
1930 ...	1 ...	Epithelioid ...	++++ ...	Alive
1933 ...	2 ...	Epithelioid ...	Missing ...	Dead (other cause)
1933 ...	3 ...	Epithelioid ...	Missing ...	Lost
1933 ...	4 ...	Eye not excised, and not traced		

It is obvious from the above that in view of the fact that I found only one patient alive, 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.

As already explained in the previous chapters 100 patients suffering from sarcoma of the uvea were admitted to the Royal London Ophthalmic Hospital during the years 1930 to 1935 both inclusive.

TABLE I—Showing the number of cases by years.

1930	...	...	11
1931	...	...	18
1932	...	...	20
1933	...	...	16
1934	...	...	14
1935	...	...	21
Total			100

1. TABLE II—Showing the percentage incidence of sarcoma to the New Out-patients during the period, that is the percentage incidence to all eye 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	0'024	4,229
1931	18	44,282	0'0407	2,460
1932	20	47,078	0'0425	2,354
1933	16	47,915	0'0334	2,995
1934	14	51,672	0'027	3,691
1935	21	53,712	0'039	2,558
Total	100	291,176	0'0343	2,913

TABLE III—Showing percentage incidence of sarcoma to all Out-patients, new and old, the latter with first attendance in the year. (Percentage to all eye diseases).

Year	Sarcoma Cases	New Out-Patients	Old Out-Patients	Total Out-Patients	Percentage of Sarcoma to all eye diseases	or one case of Sarcoma in every
1930	11	46,517	5,855	52,372	0'021	4,761
1931	18	44,282	5,792	50,074	0'036	2,782
1932	20	47,078	6,658	53,736	0'037	2,687
1933	16	47,915	7,177	55,092	0'029	3,443
1934	14	51,672	6,831	58,503	0'024	4,179
1935	21	53,712	8,288	62,000	0'034	2,952
Total	100	291,176	40,601	331,777	0'03	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 the ones recorded by several other observers. The percentage in this series works out as 0·03 per cent. of all eye diseases. The other figures are:—

Stallard³² gives it as 1 in 4,000 at Moorfields; Fuchs^{16a} 0·066 of all eye diseases; Davenport⁹ in his series of 35 cases says that the incidence at Moorfields is 2 in 10,000, but he says the usual incidence is 3 to 6 per 10,000; Terry and Johns,³⁴ 5 in 10,000.

2. TABLE IV—*Showing percentage In-patients for sarcoma to total In-patients at Moorfields.*

Year	Sarcoma In-Patients		Total In-Patients	% Sarcoma In-Patients to total In-Patients		or one Sarcoma Patient to every	
1930	...	11	...	2,547	...	0·432	...
1931	...	18	...	3,133	...	0·575	...
1932	...	20	...	3,276	...	0·61	...
1933	...	16	...	3,279	...	0·488	...
1934	...	14	...	3,263	...	0·429	...
1935	...	21	...	3,739	...	0·56	...
Total	...	100		19,237		0·52	

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 0·52.

3. AGE INCIDENCE—TABLE V—*Showing the incidence of sarcoma in different age-groups.*

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

The youngest patient in the series was 26 years of age; the 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 (61-70) for 22 cases, the years 41-70 show 67 cases out of 100, that is 67 per cent., while in the years preceding these and following these there is a sharp fall in the incidence.

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TABLE VI—*Showing average age in this series.*

Year					Average age
1930	...	...	...	...	55'33
1931	...	...	...	...	50'19
1932	...	...	...	...	50'95
1933	...	...	...	...	56'27
1934	...	...	...	...	56'21
1935	...	...	...	...	54'76
Average 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

4. SEX INCIDENCE—TABLE VII—*Showing the incidence in both sexes.*

Year	Sarcoma 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 per cent. and 65·7 per cent. respectively, but he adds that in 345 cases at Moorfields up to that date there were 167 males and 175 females, sex not known in three cases.

In the present series males and females are affected in the proportion of 44·4 per cent. and 55·6 respectively.

5. VARIOUS PARTS OF UVEA AFFECTED—TABLE VIII—*Showing the incidence in various parts of uvea.*

Year	Sarcoma Cases		Choroid		Choroid and 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 per cent., 13 per cent., and 4 per cent. These figures more or less agree with those of Fuchs who records choroid affected in 85 per cent., ciliary body in 9 per cent., and iris in 6 per cent. of his 259 cases.*

The figures given by other workers are:—

<i>Iris.</i>	Martin*	...	1 in 43 cases.
	Collins*	...	1 in 103 cases.
	Fuchs*	...	16 in 259 cases (6 per cent.)
	Teraskeli ³³	...	No cases in 33.
<i>Ciliary Body.</i>	Fuchs*	...	22 in 259 cases (9 per cent.)
	Teraskeli ³³	...	2 in 33 cases.

6. SUMMARY.

1. Incidence of sarcoma to all eye diseases, 0·3 per cent., or 1 in 3,000 cases.
2. Incidence of sarcoma in-patients to all in-patients, 0·52 per cent., or 1 in 200 cases.
3. Average age for sarcoma of the uvea, 53·70.
4. Incidence in sexes, males 44·4 per cent., females 55·6 per cent.
5. Various parts of uvea affected—choroid, 83 per cent.; iris, 4 per cent.; ciliary body, 13 per cent.

APPENDIX II—*A list of all cases living with their histological types and reticulin content.*

SUMMARY.

Alive	...	...	51	Deaths, metastases	...	27
Patients untraced	...	...	10	Dead, other causes	...	4
Eyes not excised...	...	...	4	Dead, unknown cause	...	3
Not attempted to trace	...	...	1			
Total			...	100		

List of patients alive on September 1, 1938.

Year	Op.	Serial No.	Ref. No.	Histological type	Reticulin content			
1930	...	1	...	1	...	Spindle type A	...	+++ -
		2	...	7	...	Spindle type A	...	++++
		3	...	12	...	Mixed spindle A	...	+ + - -
		4	...	92	...	Epithelioid	...	+ + + +
		5	...	96	...	Mixed spindle B	...	+ + + +

* Pathology of the Eye by Sir J. Parsons. Edition 1904.

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Year Op.	Serial No.	Ref. No.	Histological type	Reticulin content					
1931	...	6	...	14	...	Spindle type A	...	++++	
		7	...	15	...	Mixed spindle B	...	++++	
		8	...	18	...	Spindle type A	...	++++	
		9	...	20	...	Spindle type A	...	+---	
		10	...	21	...	Mixed spindle B	...	+++-	
		11	...	22	...	Fascicular	...	+++-	
1932	...	12	...	23	...	Spindle type A	...	+++-	
		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	...	Epithelioid	...	+--+	
		21	...	44	...	Mixed All	...	Missing	
		22	...	45	...	Spindle type A	...	++++	
		23	...	46	...	Spindle type B	...	++++	
	1933	...	24	...	50	...	Epithelioid	...	Missing
			25	...	51	...	Spindle type A	...	Missing
		26	...	53	...	Spindle type A	...	Missing	
		27	...	56	...	Spindle type A	...	Missing	
		28	...	58	...	Epithelioid	...	+--+	
		29	...	59	...	Fascicular	...	++++	
1934	...	30	...	60	...	Spindle type A	...	+++-	
		31	...	61	...	Epithelioid	...	Missing	
		32	...	63	...	Missing	...	Missing	
		33	...	64	...	Spindle type A	...	+++-	
		34	...	66	...	Spindle type B	...	++++	
		35	...	67	...	Mixed Epithelioid	...	Missing	
		36	...	68	...	Mixed Spindle B	...	+++-	
		37	...	69	...	Epithelioid	...	Missing	
		38	...	70	...	Spindle type A	...	+---	
		39	...	71	...	Mixed All	...	Missing	
1935	...	40	...	98	...	Epithelioid	...	Missing	
		41	...	72	...	Fascicular	...	++++	
		42	...	73	...	Mixed Epithelioid	...	+--+	
		43	...	75	...	Spindle type A	...	+--+	
		44	...	78	...	Mixed Spindle A	...	+--+	
		45	...	80	...	Epithelioid	...	++++	
		46	...	81	...	Epithelioid	...	+--+	
		47	...	82	...	Spindle type A	...	++++	
		48	...	83	...	Mixed All	...	+++-	
		49	...	87	...	Spindle type B	...	----	
		50	...	90	...	Spindle type A	...	++++	
		51	...	91	...	Spindle type A	...	++++	

Case No. 12 had a very large extra-ocular extension.

Note.—After the mixed-cell growths, the cell which is found in largest numbers (the preponderating cell) is mentioned. In the slides in which all varieties were almost equally distributed the 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 causes	...	4
	Dead, unknown cause	...	3
	Total Dead	...	34

List of cases which died of metastases.

Year Op.	Serial No.	Ref. No.	Histological type	Reticulin content	Date death
1930	1	4	Mixed spindle A	... + — — —	7/1933
	2	6	Mixed spindle B	... + + — —	7/1931
1931	3	8	Epithelioid	... + + — —	3/1935
	4	9	Epithelioid	... + — — —	—
	5	17	Epithelioid	... — — — —	6/1934
	6	25	Mixed Epithelioid	... + + + —	—
	7	27	Mixed all	... + — — —	—
	8	19	Mixed Spindle B	... + — — —	4/1933
1932	9	28	Epithelioid	... + — — —	12/1933
	10	30	Epithelioid	... + + + —	1/1935
	11	31	Mixed all	... + + — —	6/1936
	12	34	Epithelioid	... — — — —	6/1933
	13	43	Mixed spindle B	... + + + —	after 2 yrs.
	14	47	Epithelioid	... + — — —	after 1½ yrs.
1933	15	48	Mixed epithelioid	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 epithelioid	... + — — —	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	Epithelioid	... + — — —	Alive
	25	86	Epithelioid	... + — — —	2/1936
	26	88	Mixed all	Missing	2/1936
	27	89	Mixed all	... + — — —	Winter 1935

* This patient though still alive is definitely suffering from secondary growths, and hence she is classed under deaths from metastases.

List of cases dead from other causes.

Year Op.	Serial No.	Ref. No.	Histological type	Reticulin content	Date death
1930	1	5	Epithelioid	... — — — —	9/1934
1932	2	32	Epithelioid	... — — — —	after 5 yrs.
1933	3	93	Epithelioid	Missing	6/1935
1934	4	65	Mixed spindle B	... + — — —	10/1937

List of cases dead from unknown causes.

1931	...	1	...	13	...	Epithelioid	...	+	+	+	+	...	—
1932	...	2	...	37	...	Mixed spindle B	...	Missing	...	...	...	...	—
1933	...	3	...	52	...	Mixed all	...	Missing	...	...	...	10/1936	...

Note.—See note on the foot of page 283.

APPENDIX IV—*List of cases which could not be traced with their histological types and reticulin content.*

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

See note on the foot of p. 283.

LIST OF REFERENCES

1. ALEXANDER, B.—Pathology of melanosis of ciliary body. *Arch. Ophthalm.*, Vol. VII, pp. 521-527, April, 1932.
2. CALLANDER, G. R.—Malignant melanotic tumours, histological study of types in 111 cases. *Trans. Amer. Acad. of Ophthalm.*, Vol. XXXVI, pp. 131-142, 1931.
3. ——— From minutes, *Trans. Amer. Acad. of Ophthalm. and Otolaryn.*, p. 476, 1934.
4. CALLANDER, G. R. and WILDER, H. C.—Melanoma, prognostic significance of argyrophile fibres. *Amer. Jl. of Cancer*, Vol. XXV, pp. 251-258, October, 1935.
5. CHOUN, C. K.—Statistical data on prognosis of sarcoma. *Klin. Monatsbl. f. Augenheilk.*, Vol. XCV, pp. 444-457, October, 1935.
6. COLLINS and MAYOU.—Pathology and bacteriology of the eye, 1925 edition.
7. COSGRAVE, K. W.—Sarcoma. *Southern Med. Jl.*, Vol. XXX, pp. 379-382, April, 1937.
8. COZZA, F.—Routes of generalisation and propagation, histo-clinical studies, cases. *Boll. d'Ocul.*, Firenze, Vol. XIV, pp. 1647-1686, December, 1935.
9. DAVENPORT, R. C.—Sarcoma of the uveal tract. *Brit. Jl. of Ophthalm.*, Vol. XI, pp. 609-612, December, 1927.
10. DENNECKE, H.—Prognosis sarcoma. *Klin. Monatsbl. f. Augenheilk.*, Vol. XCVII, pp. 594-599, November, 1936.
11. FOOT, N. C.—A rapid method for silver impregnation of reticulin. *Arch. Path.*, Vol. IV, p. 211, 1927.
12. ——— Silver impregnation of melanotic tumours. *Amer. Jl. of Path.*, Vol. VII, p. 619, 1931.
13. ——— Technique silver impregnation for general laboratory purposes. *Amer. Jl. of Path.*, Vol. VIII, p. 245, 1932.
14. ——— Histology of melanoma. *Amer. Jl. of Path.*, Vol. VIII, p. 321, 1932.
15. ——— Concerning histology of melanoma. *Amer. Jl. of Path.*, Vol. VIII, p. 309, 1932.
16. FRIEDENWALD.—Pathology of the eye.
- 16A. FUCHS, A.—Diseases of the eye, translation by Brown.

17. HIPPEL, E. VON—Prognosis of uveal sarcoma. *Arch. f. Ophthal.*, Vol. CXXIV, pp. 206-220, 1930.
18. ——— Continuation of statistical report on sarcoma patients. *Arch. f. Ophthal.*, Vol. CXXIX, pp. 552-568, 1933.
19. ——— Continuation of statistical report on sarcoma patients. *Arch. f. Ophthal.*, Vol. CXXXV, pp. 76-78, 1936.
20. ——— A new way of evaluating prognosis of uveal sarcoma. *Arch. f. Ophthal.*, Vol. CXXXV, pp. 79-86, 1936.
21. JAENSCH, P.—Prognosis of enucleation of melanosarcoma. *Klin. Monatsbl. f. Augenheilk.*, Vol. LXXXIV, pp. 649-662, 1930.
22. KING, E. F.—Pathogenesis of melanoma. *Trans. Ophthal. Soc. U.K.*, Vol. LVII, Part I, pp. 97-106, 1937.
23. MCKEE, S. H.—Primary sarcoma uveal tract, analysis of 27 cases. *Canadian Med. Assoc.*, Vol. XXXVI, p. 361, 1936.
24. MORAX, V.—Diagnosis and prognosis of melanotic tumours. *Bull. et Mem. de la Soc. Franç. Ophthal.*, Vol. XLIV, p. 365, 1931.
25. MUIR, SIR ROBERT.—Text book of pathology.
26. PARSONS, SIR J.—Diseases of the eye, 1936 edition.
27. RENARD, G.—Intra-ocular malignant tumours. *Le Bulletin Médicale Librarie Arnette*, Vol. LI, p. 368, 1937.
28. SAMUELS, B.—Study of anatomic and clinical manifestations of necrosis in 84 cases of sarcoma. *Trans. Ophthal. Soc. U.K.*, Vol. LIII, pp. 520-570, 1933.
29. SCALES, J. L.—Melanosarcoma. *New Orleans Med. and Surg. J.*, Vol. LXXXIX, p. 567, 1937.
30. SCHOVANIC, B.—Intra-ocular sarcoma and its prognosis. *Casopis Lekarů Ceských Vladislavova Ulice*, Vol. LXXVI, p. 920, 1937.
31. SEIDEL E.—Biology of sarcoma. *Ber. uhr. die Versamm. d. deutsch., Ophthal.*, Vol. LI, p. 459, 1936.
32. STALLARD, H. B.—Chapter on choroid in "The eye and its diseases" by Berens.
33. TERASKELI, H.—Prognosis of malignant tumours. *Acta Ophthal.*, Vol. VI, p. 110, 1928.
34. TERRY, T. L. and JOHNS, J. P.—Sarcoma—malignant melanomas, statistical study of 94 cases. *Amer. J. of Ophthal.*, Vol. XVIII, p. 903, 1935.
35. WILDER, H. C.—An improved technique for silver impregnation of reticulin fibres. *Amer. J. of Path.*, Vol. XI, p. 817, 1935.
36. WILDER, H. C. and CALLANDER, G. R.—See No. 4 above.

VITAMIN "C" (ASCORBIC ACID)—ITS THERAPEUTIC VALUE IN INFLAMMATORY CONDITIONS OF THE CORNEA

BY

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ALTHOUGH during the past six years a certain amount of research work has been carried out upon the somewhat doubtful relationship of vitamin "C" to the development of cataract, little attention has been given to the therapeutic value of this vitamin in certain other ocular diseases, namely, inflammation and ulceration of the cornea.

It has been held that the administration of vitamin "C" to patients suffering from certain types of cataract has met with some slight improvement in the visual acuity.¹ Further, it has been