STUDIES ON THE AETIOLOGICAL PROBLEM OF UVEITIS*

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DESPITE modern methods of investigation those cases of endogenous uveitis in which the aetiology is known with certainty are few, so that this group of diseases remains to-day one of the major problems of ophthalmology. For example, statistical studies show that, of all causes of blindness, uveitis is responsible for 7.95 per cent. in England and Wales (Sorsby, 1950), 8 per cent. in Norway (Holst, 1952), and 11.9 per cent. (Cowan and English, 1941) and 11.5 per cent. (Hurlin and others, 1947) in the United States.

The clinical classification of uveitis into anterior or posterior, acute or chronic, serous or plastic, gives little information as to the underlying pathological process and it has been suggested that endogenous uveitis may be more usefully grouped as "granulomatous" or "non-granulomatous" (Woods, 1947, 1949b). These terms relate the clinical picture to the histological changes and thus separate two types of inflammatory response, of which "granulomatous" is believed to signify a direct infection of the uvea and "non-granulomatous" a sterile allergic reaction.

That this classification has much to commend it is shown by the advances it has stimulated and by its wide acceptance in ophthalmology, but it is doubtful whether its basic assumptions are wholly tenable. The evidence that granulomatous lesions are necessarily infective and non-granulomatous reactions allergic in origin is certainly not generally true (Ashton, 1954a), and in ocular pathology the cause of these two histological reactions is frequently obscure.

It would seem that, if we are to advance our knowledge of the aetiology of uveitis, it would be well in laboratory studies to abandon any preconceived notions of classification, to carry out an unbiased investigation of each case irrespective of its particular clinical features, and subsequently to attempt a correlation of the findings. To this end we have carried out a number of investigations of a series of cases of uveitis irrespective of their clinical classification, and have later considered the findings in relation to the site of the lesion, *e.g.* anterior, posterior, or pan-uveitis.

The main methods used in these studies have been:

- (a) Comparing blood and serological findings in uveitis with the findings in control groups;
- (b) Observing the response of lesions to specific therapy;
- (c) Attempting to isolate infective agents from the eye.

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This paper containing the first report of our results is mainly concerned with the first of the above methods, namely the correlation of ocular lesions with blood and serological findings.

Material and Methods

Source of Patients.—To enable the survey to be undertaken, patients were referred to a central clinic at which a history was taken and a detailed inquiry made into past infectious illnesses and contacts with infectious conditions. In each case an *x* ray of the chest was taken before the patient attended for investigation, and, in certain cases, in which there was evidence of dental caries or of a sinus infection, further *x* rays were taken of teeth and sinuses respectively. Even if a probable diagnosis had been made, as for example in sarcoidosis showing typical bony changes, the case was nevertheless retained in the series and analysed according to the site of the lesion.

In the main the patients were drawn from the Moorfields and Westminster Ophthalmic Hospitals and to a lesser extent from the Swanley Eye Sanatorium, which, although theoretically an institution for cases of tuberculous ocular disease, actually treats many cases of chronic uveitis of unknown cause, so that in reality there is no tendency for the series to contain a disproportionate number of tuberculous cases from this source.

One point, however, which tends to produce a bias in our series is the fact that many mildly affected patients were not willing to make a special visit to the clinic, particularly if they were still working; it is therefore probable that the whole series contains more severe and chronic cases than would be seen in a random sample in the out-patients department. This bias was accentuated by the fact that many patients were referred only when routine treatment had failed, and it must be assumed that if such treatment had been successful the patient would not have been seen.

At the first attendance the patients were venesected and a Mantoux test and complete blood count were carried out; on subsequent visits other investigations, such as aqueous puncture, were made in selected cases. Further investigations of the blood were Wassermann and Kahn reactions, gonococcal complement-fixation test, and complement fixation and cytoplasm modifying dye tests for toxoplasmosis. On the first one hundred cases Middlebrook-Dubos tests for tuberculosis were carried out, but these were later discontinued and replaced by *Brucella* agglutinations and anti-streptolysin "O" assays. In general the technique employed for the anti-streptolysin assays was that of Ipsen (1944) and all assays were controlled against standard sera supplied by the State Serum Institute, Copenhagen.

After the investigations were complete, the cases were categorized according to the clinical findings as anterior, posterior, or pan-uveitis. Seventeen cases which could not be satisfactorily classified under these headings were grouped as "Others".

Results and Discussion

(1) General Considerations.—The total number of patients referred was 200 (106 females and 94 males); these have been classified by age, sex, and clinical category in Table I (opposite).

From the analysis of the series in Table I two interesting points emerge: first, a significantly greater incidence of anterior uveitis in females (female/male ratio $59/43=1.35$), and secondly, an apparently earlier onset of posterior uveitis in males than in females (of seventeen male cases, six were under 20 years and a further six were between 20 and 29; of sixteen female cases, only three were under 30 years and none was under 20).

TABLE I
CLASSIFICATION BY AGE, SEX, AND CLINICAL CATEGORY

Clinical Category	Sex	Age Group							Totals
		0/9	10/19	20/29	30/39	40/49	50/59	60+	
Anterior ...	M	0	1	5	12	13	9	3	43
	F	1	6	15	14	13	7	3	59
Posterior ...	M	1	5	6	2	3	0	0	17
	F	0	0	3	8	4	1	0	16
Pan-uveitis ...	M	0	3	5	7	5	2	2	24
	F	0	1	3	9	6	4	1	24
Others ...	M	0	2	3	3	1	1	0	10
	F	0	2	4	0	0	1	0	7

It is, of course, possible that both these points are merely artefacts due to the small number of patients in each group and to the fact that the series as a whole does not represent, for reasons previously discussed, a true random sample of uveitis cases. It would, therefore, be unwise to reach any firm conclusions upon questions of age, onset, and sex ratio from our figures. It is interesting to note, however, that a higher incidence of anterior uveitis in females has also been reported by other investigators. Sorsby (1950), in a statistical survey of causes of blindness in England and Wales, reported a female/male ratio of $4.2/2.7=1.55$ for iritis and iridocyclitis. Müller (1950) found a predominance of anterior uveitis in females, and also noted that posterior uveitis was more common in the male, with no sex differentiation in pan-uveitis.

In the whole of our series ten cases (5 per cent.) were under 16 years of age, a similar incidence to that of Kimura and others (1954), who found 5.8 per cent. under 16 years in 810 cases, but higher than that of Blegvad (1941), who found 2.2 per cent. under 15 years of age in 896 cases.

2(a) Wassermann and Kahn Reactions.—None of the 200 cases had a positive Wassermann or Kahn reaction.

2(b) Gonococcal Complement-Fixation Test.—In only two cases in our series was the test positive and in neither instance was a history of venereal disease obtained. The first case was an acute uniocular iritis in which gonorrhoea was thought to be a possible cause. The second was a slowly progressive uveitis commencing in the left eye and affecting the right eye 3 months later. Vision was slowly lost, but at no stage was there an acute infection and clinical opinion was against a diagnosis of gonococcal uveitis. There is considerable doubt as to the value of this test and frequently repeated

results may show a change from positive to negative without any treatment. For this reason it would probably be unwise to regard the Gonococcal Complement-fixation Test as diagnostic in the absence of other evidence of the disease.

Thus in none of our cases could the uveitis be ascribed with certainty to either syphilis or gonorrhoea; it would appear that during recent years there has been a yet further decline in the importance of venereal infection in the causation of uveitis in Great Britain.

3(a) Middlebrook-Dubos Test.—This was carried out on the first hundred patients and was positive in thirteen cases. Active extra-ocular tuberculosis was present in only one of these patients, whereas in two with old treated pulmonary tuberculosis (one with tuberculous adenitis and one with lupus vulgaris) the test was negative. The results bore no relation to a clinical diagnosis of tuberculous uveitis, and, furthermore, a control group of one hundred cases showed a similar incidence of positive results. The Middlebrook-Dubos test has, therefore, proved to be of no value in our hands and we have not confirmed the suggestion of Brodhage (1951) and Fine and

Flocks (1953) that the test assists in the diagnosis of uveitis. Nor is this surprising, for other serologists have found the test unreliable in the diagnosis of systemic tuberculous infection (Kirby and others, 1951).

3(b) Mantoux Test.—The results are shown in Table II by age group and in Table III by clinical category.

TABLE II
RESULTS OF MANTOUX TESTS BY
AGE GROUP

Age Group	Positive	Negative
0-9	2	0
10-19	11 (58 per cent.)	8
20-29	32 (84 per cent.)	6
30-39	45 (90 per cent.)	5
40-49	40 (92·5 per cent.)	3
50-59	21 (84 per cent.)	4
60+	6 (75 per cent.)	2

In general, these figures, both as regards the percentage positive in the whole group and in the various groups, follow closely those to be expected in the population at large (McDougall, 1949). Table III shows, however, that high cutaneous sensitivity appears to be more frequent in those patients with anterior than in those with posterior uveitis.

TABLE III
RESULTS OF MANTOUX TESTS BY CLINICAL CATEGORY

Clinical Category	Percentage Positive at each Concentration of P.P.D.			Total Percentage Positive	Total Percentage Negative
	0·00002 mg.	0·0002 mg.	0·002 mg.		
Anterior	60	19	9·5	88·5	11·5
Posterior	42	17	24	83	17
Pan-uveitis	51	13·5	19	83·5	16·5
Others	50	25	18·75	93·75	6·25

No other factors were found which would relate either the Mantoux or the Middlebrook-Dubos test to ocular pathology, and our survey failed to provide any laboratory criteria for the diagnosis of tuberculosis. The chief, if not the only, value of the Mantoux test in our cases was in excluding tuberculosis, particularly in the younger age groups, and in demonstrating anergy to tuberculo-protein in sarcoidosis.

(4) Blood Counts.—A normal blood count was the rule and the occasional abnormalities are discussed under each type of estimation.

(a) *Haemoglobin Level.*—In twelve cases this was below 80 per cent. (Haldane) and was considered abnormal; in three it was below 60 per cent. and was causing symptoms. Nine of the twelve cases and all three cases below 60 per cent. were in women. In every case the anaemia was of a simple iron deficiency type and over the whole series the average female haemoglobin was 10 per cent. lower than that of the male. No relationship could be found between the uveitis and the haemoglobin level; although six of the twelve anaemias were found in cases of anterior uveitis there was no apparent correlation between the two conditions, nor was the general haemoglobin level in the whole group of anterior uveitis cases lower than in any other group.

(b) *Total White Count.*—Twelve counts showed more than 12,000 white cells per cu. mm.; these were spread equally in males and females, five being in anterior uveitis, one in posterior uveitis and six in total uveitis.

(c) *Polymorphonuclear Leucocytosis.*—This was considered to be present if there were more than 7,000 per cu. mm. There were thirteen such cases and in ten of these infections could be found as follows:

- (i) Two with a positive gonococcal complement-fixation test.
- (ii) Three with staphylococcal infections.
- (iii) One with active pulmonary tuberculosis.
- (iv) One with Behçet's disease with an acute hypopyon at the time of the count.
- (v) One with laryngitis.
- (vi) One with septic teeth.
- (vii) One with active toxoplasmosis.

(d) *Eosinophils.*—An eosinophilia was considered to be present if there were more than 350 eosinophils per cu. mm. This was found in seven cases, three with anterior uveitis, three with posterior uveitis, and one with pan-uveitis. Of these seven cases, that with pan-uveitis had received para-aminosalicylic acid therapy and this probably accounted for an eosinophilia of 880 per cu. mm. One of the patients with anterior uveitis was a small boy who had had one eye removed previously for the same disease; no aetiological diagnosis could be made on either clinical or histological grounds. The remaining five patients all possessed toxoplasma antibodies in their serum and two also had a monocytosis. The toxoplasma antibodies may well be significant in view of the recently described eosinophilia that may be found in certain cases of glandular fever syndrome from which toxoplasma have been isolated.

(e) *Monocytes.*—In twenty cases the monocyte count rose above an absolute value of 550 per cu. mm., which is usually taken as the upper limit of normality, but no relationship could be found between monocytosis and any other factor.

(f) *Lymphocytosis*.—No cases were found in which there was an absolute lymphocytosis unless there was a concomitant rise in neutrophils and no importance could be attached to these findings.

(5) *Brucella Agglutinations*.—Serum agglutinations were set up against standard suspensions of *Brucella abortus* and *B. melitensis*. Living organisms were not used. The test was performed at 56°C. and read after standing at 4°C. overnight; 103 cases were tested in this way with two positive results.

One patient with anterior uveitis agglutinated *B. abortus* to a titre of 1/40 but a positive titre at this level is of doubtful value. Examination of Wassermann sera in Great Britain showed that about 1.5 per cent. agglutinated *B. abortus* to a titre of 1/40 or over, so that neither the titre level nor the incidence of this positive case differs from that to be expected in the population at large.

In the second case a *melitensis* suspension was agglutinated to the same titre; as this patient was a Cypriot with proven Behçet's syndrome, there seems no reason to doubt that this was an incidental finding related to an old infection.

The findings do not therefore suggest that brucella infection plays an important role in uveitis in Great Britain. On the other hand, its significance may be less negligible than it at first appears, for our series of cases is small, skin testing with brucellin or brucellergen was not carried out, and the agglutination test is known to be not infrequently negative in proved cases of brucellosis. Thus Barrett and Rickards (1953) found negative results in seven of 25 cases.

In future we propose to carry out intradermal tests as a routine in addition to agglutination tests before and after the skin test, in order to assess the frequency of chronic brucellosis more completely, but it is not expected to be as important an aetiological factor as was suggested by Foggitt (1954) or as has been found in America (Guyton and Woods, 1941).

(6) *Toxoplasmosis*.—The tests used were the cytoplasm modifying test and the complement-fixation test; no routine skin testing was performed. Toxoplasma tests were performed in 198 of our two hundred cases, serological evidence of infection was found in 87 (43.9 per cent.) of these. The positive results, irrespective of titre levels, are analysed by site of uveitis in Table IV (opposite).

In the dye test, toxoplasma antibodies in titres of 1/4 or more are accepted as evidence of infection and in Great Britain one can expect positive results in 25 per cent. of the "normal" population (Beverley and others, 1954). Table IV shows that in all groups of uveitis the incidence was above this figure, being most significantly raised in the posterior uveitis group (67.7 per cent.).

In the complement-fixation test there is some doubt as to the significance of low titres, but several workers have studied the "normal" incidence of positive results. In Great Britain, using normal adult serum, Cathie and

TABLE IV
POSITIVE TOXOPLASMA RESULTS BY CLINICAL CATEGORY

Clinical Category	No.	Dye Test		Complement-Fixation Test	
		Positive	Per cent.	Positive	Per cent.
Anterior	102	40	39.2	8	7.84
Posterior	31	21	67.7	9	28.2
Pan-uveitis	48	19	39.6	7	14.6
Others	17	7	41.1	4	22.2

Dudgeon (1949) found 1.5 per cent. positive between 1/4 and 1/6, MacDonald (1950) found 5 per cent. positive at titres of 1/10 or more, and Beverley and others (1954) found 1.3 per cent. positive at titres between 1/5 and 1/10. Thus it would appear that, for titres of 1/10 and under, the "normal" incidence of positive results is unlikely to exceed 5 per cent. and is probably even lower. In none of our two-hundred patients was the titre positive above 1/16, and in only two did it rise above 1/8, so that the titres fell within the "normal" range, but our figures in Table IV show a high incidence of positive results in all groups as compared with these figures, and once again this is particularly evident in the posterior uveitis group (28.2 per cent.).

It has been suggested that a positive complement-fixation test is an index of activity (Cathie, 1954), so that, in considering localized ocular lesions, it may be that the combination of a positive dye test and complement-fixation test, even although within "normal limits", is of greater significance in assessing activity than a dye test alone. Whether this is true or not, it is interesting to note that, if the cases with positive results in both tests are removed from Table IV, then the remaining percentages of cases with a positive dye test alone (Table IVA) are found to approximate to the "normal" figure of 25 per cent.

In Table IV the incidence of positive complement-fixation tests is shown to be lowest in anterior uveitis and relatively high in all other groups. On referring back to the clinical histories, however, it was found that three cases of pan-uveitis were posterior in origin, and that two began with localized choroidal foci. If these three cases are reclassified as posterior uveitis then the relevant part of Table IV may be revised as in Table IVB, thus showing that pan-uveitis had in fact an incidence closely comparable to that of the anterior group (7.84 per cent.) and revealing an even more significantly

TABLE IVA
POSITIVE DYE TEST AND
NEGATIVE COMPLEMENT-
FIXATION TEST

Category	Dye-test Percentage Positive
Anterior ...	32.3
Posterior ...	38.0
Pan-uveitis	25.0
Others ...	17.6

TABLE IV_b
MODIFIED SECTION OF TABLE IV

Category	Complement-Fixation Test Percentage Positive
Posterior	34.3
Pan-uveitis	9

high figure in cases of posterior uveitis.

The figures for the group composed of "other conditions" occupy an intermediate position in Table IV, but since this group contains only small numbers of any one disease it is difficult to interpret the find-

ings. It is of interest, however, that three of the positives were cases of Eales's disease and that in each of these both the dye test and the complement-fixation test were positive. We would suggest, therefore, that it might be of value to investigate further the possible role of toxoplasma as one of the aetiological agents in this obscure disorder.

The recognition of the importance of toxoplasmosis in ocular disease is a recent development; its role in congenital chorioretinitis is already fully appreciated, but in acquired uveitis, although recent papers have shown that it is known to be of importance (Wilder, 1952; Hogan and others, 1952; Duke-Elder and others, 1953; Woods and others, 1954; Jacobs and others, 1954a), its exact role is much more difficult to assess. In some previous surveys, for instance, it has been the custom to accept positive serology as evidence of infection only when the titres were above those found in the "normal" community. Thus Feldman (1952) and Woods and others (1954) based their analyses on such figures, but it has since been shown conclusively that viable toxoplasma may exist in the eye without stimulating the production of high levels of antibody (Jacobs and others, 1954b), or that if high titres are produced they may fall rapidly to "insignificant" levels (Ashton, 1954b), so that we can no longer insist upon titres of either the dye test or the complement-fixation test being above or below an arbitrary level to confirm or exclude the disease. The high percentage of positive results (67.7 per cent. dye test) obtained in our posterior uveitis group accords with the findings of Hogan and others (1952); furthermore, in our study, when the number of positive cases over and above the number to be expected in a control group was estimated, it was found to be as high as 25 per cent. of the whole group of cases of posterior uveitis. We feel, therefore, that, although the titre levels are not diagnostic in individual cases, they do show a striking association between toxoplasma infection and posterior uveitis, thus confirming the report of Woods and others (1954).

It is difficult to believe that this association is not aetiologicaly significant. In the future, when toxoplasma can be isolated more readily from cases of uveitis, and when specific therapy becomes available, the true explanation of this relationship should become apparent. At the present time it can only be said that toxoplasmosis appears to be a major aetiological factor in acquired posterior uveitis; the low serum antibody levels, even in the

presence of active lesions, warn us that the problem of toxoplasmosis in ocular disease may be a very different one from that in systemic infection.

There is already evidence to show that the eye may behave as a separate unit, both in such allergic reactions as tuberculosis (wherein the degree of ocular sensitivity may not necessarily parallel that of cutaneous sensitivity; Woods, 1947), and in such immunological reactions as leptospiral uveitis (in which specific antibody may be locally produced and give rise to aqueous levels exceeding those in the serum; Goldmann and Witmer, 1954).

It is conceivable, therefore, that small localized lesions within the scleral envelope may react quite differently from extra-ocular foci and cannot always be assessed by the same serological criteria. Hence, although certain serological criteria, such as a high titre, a rising titre, or a negative result, are essential to establish or exclude the diagnosis of toxoplasmosis in a given case of uveitis, low titres by no means exclude toxoplasmosis as the cause of the uveitis.

(7) **Anti-streptolysin Assays.**—Since the original observations of Schöne and Steen (1951) that acute iritis may be associated with a significant increase in the antihæmolyisin titres of the patient's serum, a similar report has been made by Leopold and Dickinson (1954). Analysis of our own cases also shows that in the anterior uveitis and "other" groups there were more positive results than in the groups of posterior uveitis and pan-uveitis, but the numbers in each group are too small to be of much significance. To overcome this difficulty, sera from 89 cases of anterior uveitis sent in for Wassermann reactions were compared with a similar group of sera from 106 ophthalmic patients without anterior uveitis, thus providing sufficiently large numbers for statistical analysis. The results are shown in Table V.

TABLE V
ANTI-STREPTOLYSIN TITRES AND ANTERIOR UVEITIS

Anterior Uveitis	Anti-streptolysin Titres (Units)					
	12	50	100	166	250+	Total Cases
Present	16	30	22	15	6	89
Absent	36	35	26	7	2	106
Total Cases ...	52	65	48	22	8	195

In Table V some of the groups are too small for statistical analysis and to overcome this the total number of cases with titres above 100, which is usually taken as the approximate upper limit of normality, may be compared with the number of cases with titres of 50 and below. Such an analysis shows that in the anterior uveitis group there are significantly more cases with a titre of over 100 (21 as compared with 9) and less with a titre of 50

and under than in the control group (46 as compared with 71). Such a finding might occur by chance once in a hundred similar groups, *i.e.* $P=0.01$.

This statistically significant relationship between anti-streptolysin titres and uveitis is in harmony with the findings in similar studies by Schöne and Steen (1951) and Leopold and Dickinson (1954), and closely corresponds to the titres associated with rheumatic carditis (Coburn and Pauli, 1932, 1935) in which the role of the streptococcus is more surely established. We are in agreement with the observation of Björk (1947) that no single titre can at present be considered of diagnostic value in any individual case of uveitis.

Our own study, however, shows in addition that the incidence of raised antistreptolysin titres is almost exclusively confined to the anterior uveitis group. As is well known, the presence of antistreptolysins in the sera indicates no more than a previous streptococcal infection, and gives no information of the degree of streptococcal hypersensitivity; nevertheless, the higher titres obtained in the group of anterior uveitis support the contention of Woods (1949a) that "non-granulomatous" uveitis—which is predominantly anterior—may not infrequently be due to an underlying streptococcal hypersensitivity. It will be recalled that Woods (1954) found a specific hypersensitivity to various strains of streptococci in 89 per cent. of patients with an allergic type of uveitis, whereas such sensitivity had a "normal" incidence of 20 per cent. in patients with infective uveitis.

There is, therefore, good reason to suppose that a certain proportion of these cases is associated with streptococcal infection. Unfortunately here again the diagnosis of an individual case is a matter of great difficulty and at the present time the multiple skin-testing method advocated by Woods appears to offer the most promising line of investigation. It is well to remember, however, that, even with the 42 separate strains he recommends, we are dealing with only a fraction of the possible variants of the streptococcus and that, moreover, we are completely ignoring the possible role of organisms other than the streptococcus.

In conclusion, it is clear that the laboratory investigations carried out on our series of two hundred cases of uveitis gave little assistance in establishing the cause of the condition in individual cases. In not more than 10 per cent. was a certain pathological diagnosis established and in a large percentage—probably of about 40-50 per cent.—we obtained no indication of the possible nature of the disease. On the other hand, when the findings were grouped and considered in relation to the site of the lesion, a striking association between anterior uveitis and streptococcal infection, and between posterior uveitis and toxoplasma infection was revealed. In the future much valuable information may be acquired by investigating these two apparently important causative agents, particularly with regard to the treatment of toxoplasmosis; when a completely effective protozoacide is discovered, an important advance in uveitis therapy may possibly ensue.

Summary

(1) The laboratory findings in a series of two hundred cases of uveitis have been studied and an attempt has been made to relate the results to the anatomical site of the lesion, *e.g.* anterior, posterior, or pan-uveitis.

(2) The main positive findings were these:

(a) There was a higher incidence of anterior uveitis in females and an earlier onset of posterior uveitis in males.

(b) High cutaneous sensitivity to tuberculo-protein appeared to be more frequent in patients with anterior uveitis than in those with posterior uveitis.

(c) Comparison of the serological findings in uveitis with the findings in control groups showed a striking association between toxoplasma infection and posterior uveitis, and between raised antistreptolysin titres and anterior uveitis.

(3) The chief negative findings were these:

(a) Apart from eosinophilia, as a possible indication of toxoplasmosis, the blood counts gave little information of value.

(b) In our hands the Middlebrook-Dubos tests proved of no diagnostic assistance, and the Mantoux tests, apart from excluding tuberculosis in the younger age groups and in demonstrating anergy to tuberculo-protein in cases of sarcoidosis, were of little use.

(c) No case in the whole series could be attributed to syphilis, gonorrhoea, or brucellosis.

(4) The findings are discussed and it is pointed out that, while the laboratory investigations employed were of very limited value in establishing a pathological diagnosis in individual cases, the possible roles of causative agents, such as toxoplasma and streptococci, became evident when the findings were considered as a whole and compared with control groups of cases without uveitis.

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