Section of Ophthalmology

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Uveitis

PRESIDENT'S ADDRESS

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IN spite of the amount that has been written and spoken about uveitis in recent years, the ætiology of endogenous uveitis is still an unsolved problem and many features of the disease are obscure. I shall comment briefly on some clinical changes in the pattern of uveal inflammation and discuss the findings, both clinical and pathological, on the first 200 cases in the recently established Uveitis Clinic at the Institute of Ophthalmology. It was of special interest for me that from the clinical point of view A. G. Cross read a paper to this Section last year on Uveitis in Children (*Proceedings*, 1954, **47**, 971) and in the September 1955 issue of the *British Journal of Ophthalmology*, Smith and Ashton reviewed the ætiological aspect basing their paper on the laboratory findings of 200 cases they examined at the Institute. In reporting these findings I should like to take the opportunity of saying how much the work of both clinicians and pathologists serving the Uveitis Clinic is valued. Much of it is detailed and routine, and readily becomes tedious. I should like to thank them, and the Department of Illustration which has made slides for projection, for the very large contribution to the make-up of this Address. I knew that Smith and Ashton were engaged on this investigation last year but heard nothing of their findings until a few days before the paper appeared and it is perhaps of value that the pathological findings in their series can be compared with those of a similar number of cases from another series investigated in the same department. The main difference between the two groups, and Smith and Ashton referred to this aspect, is that their 200 had a preponderance of long-established uveitis cases attending clinics over the years where hitherto investigation and treatment had produced little result. The 200 cases which I have reviewed were referred in most instances from the first clinic visit. Many were comparatively mild, rapidly responding to treatment. Though perhaps not an entirely random selection they present another aspect of the picture complementary to that presented by Smith and Ashton.

In the edition of Parsons' which I used as my first textbook the traditional pattern of classification of uveal inflammation, viz. iritis, iridocyclitis and choroiditis, was followed, although it was stressed in the first paragraph of the appropriate chapter that "uveitis" (perhaps reasonably referred to as an uncouth term) was the accurate description for each and every case of such inflammation. I think the anatomical divisions were based in part at least on the clinical picture in which inflammation did seem more sharply confined to the several parts of the uvea than it does to-day. From the ætiological point of view we then knew the cause of a considerable proportion of the cases for, as quoted by Parsons, 25–30% of iritis and most cases of disseminated choroiditis were of syphilitic origin. I think a fair although crude picture of uveitis thirty or forty years ago would have been:

Iritis—recurrent in middle-aged and older males=gonorrhœal.
—recurrent in older people of both sexes="gouty" or "rheumatic".

Iridocyclitis—acute uniocular (usually single attack) in younger people=septic focus (e.g. teeth or tonsils).
—acute or subacute and often bilateral=syphilitic.
—chronic plastic, in middle-aged people, especially women=unknown ætiology, in younger people=tuberculous.

Choroiditis—disseminated, at any age=syphilitic, congenital or acquired.
—solitary, in young people=tuberculous (with less certainty about this ætiology as time went on).

In many instances the inflammation was severe and often blinding, and treatment was of limited value but at least the ophthalmologist knew the cause and derived human and professional satisfaction from this knowledge. The picture to-day is, of course, very different. I am afraid I am not able to quote figures of the comparative incidence of uveitis as seen at Moorfields or elsewhere. Records over the years do not give enough accuracy, but although the venereal element has for all practical purposes disappeared there is still plenty of inflammation of the uveal tract in every eye clinic. I propose to review the above classification against the clinical picture to-day.

The sharply defined clinical entity of gonorrhœal iritis has virtually disappeared but attacks abrupt in onset, sharp in course with rapid decline, affecting one eye or the other and recurrent over the years are quite frequently seen in young people, particularly in my experience in young women. The clinical course, the gelatinous exudate in the anterior chamber and the almost complete dispersal of all traces on subsidence of the attack, makes this a strikingly similar clinical picture to the other. One girl in my clinic had had recurrences in either eye at least yearly from the age of 15 to 25 and I have twice seen a hypopyon present with an attack in the right eye. Investigation has so far failed to find a cause and even now her vision is 6/5 in each eye.

A proof that the cases of iritis attributed to gonorrhœa were either infective or allergic from the gonococcus was not normally obtainable. It was quite customary for these clinical types to be treated with gonococcal vaccine but, on the acceptance of the fact that the ocular lesions stemmed from damage in the posterior urethra and vesicles, some held that a pyogenic infection of already damaged tissue was the cause of the iritis. Accordingly they used mixed staphylococcal and streptococcal vaccine in treatment and by implication the lesion was considered to be caused by focal infection. Is the response of the uvea here similar for various stimuli or is the stimulating agent the same in both cases?

In my experience recurrent iritis of old people—"gouty" or "rheumatic"—is far less frequently seen to-day and diabetic iritis has always been a comparative rarity. One patient in this series was described as having clinical gout over the years—a woman aged 33 with attacks since the age of 17. The history given was that her mother had had similar attacks of gout from her young adult life. The blood uric acid level was quite normal in this case and no clinical evidence of gout has been seen while she had been under hospital attention. The woman showed a typical bilateral anterior uveitis and the clinical picture was unlike the "gouty iritis" of the past. The E.S.R. in her case was consistently high but the antistreptolysin titre was in the low normal range.

The association of articular disease and anterior uveitis has been carefully studied and reported. For this series a routine X-ray of the sacro-iliac joints and vertebral column was not carried out but wherever there was any suspicion in the history or clinical picture radiography was used and in 6 cases ankylosing spondylitis was confirmed or found (4 men, 2 women). Their ages ranged from 28 to 63 (in this latter case the spondylitis was known to have been present for thirty years). As I am sure will be the general experience I have seen the association of severe anterior or even generalized uveitis with active spondylitis and equally the incidence and recurrence of attacks of anterior uveitis in men and women whose ankylosing spondylitis had been present many years and had been pronounced inactive over a long period prior to the onset of uveitis. The reverse can hold, for a previous history of, and the sequelæ of, anterior uveitis have been reported at the first examination of a case of ankylosing spondylitis.

Two elderly women in the series were cases of marked rheumatoid arthritis.

I have the impression, but I have not the figures to substantiate the statement, that destructive chronic uveitis, especially the type seen in middle-aged women and sometimes labelled involuntary but as far as I know of unknown ætiology, is becoming less and less commonly seen.

The typical clinical picture of disseminated choroiditis of the past, so often of syphilitic origin, seems to me to be replaced by a diffuse type of inflammation perhaps more commonly confined to the posterior pole than the periphery in which there is not infrequently seen retinal hæmorrhage and a generalized turgidity of the retinal venous system. The association of uveal inflammation, usually anterior, with vasculitis of one form or another in the retina seems to me to be increasingly frequently seen, for since I spoke of this association at the O.S.U.K. Congress in Newcastle in 1954 I have seen a number of such cases in my own clinic and more through the courtesy of my colleagues. Of the 200 cases examined at the Uveitis Clinic 24 (14 female, 10 male) showed sufficient change in the retinal vascular system to bring comment in the clinic report. In two or three patients the note was merely

that the retinal veins were turgid and these and one or two other cases where turgid veins and œdema of the nerve head were noted may all be explained by the anatomical proximity of uvea and retina. A number of cases, however, showed in varying degree actual vasculitis, exudates and hæmorrhages, and in one case arteritis with optic atrophy in one eye. Of the 24 cases only 2 were aged 40 or over and 18 were in the young adult range. In the large majority of this group no findings as to cause of either retinal or uveal inflammation could be established just as has always been the case with so-called Eales' disease. One of the cases of quite definite retinal vasculitis was the one case of sarcoidosis proved by biopsy. Two other were Mantoux negative at 1 : 100, and of the 24 cases 5 had a positive toxoplasma reading in the serum. Toxoplasmosis has been put forward in the United States as a cause of retinal vasculitis and it is perhaps of further interest that the case of uveitis associated with brucellosis reported by K. D. Foggitt in the *British Journal of Ophthalmology* last year showed retinal periphlebitis in one eye, perhaps also arteritis, as some degree of optic atrophy was present.

I am sure that during the last few years I have seen far fewer cases than formerly of sharply defined patches of acute solitary choroiditis in young adults. These inflammations with the gross haze in the vitreous settled in due course whatever treatment was employed. A fair proportion became reactivated in later years commonly adjoining the atrophic area of the first attack. The causation of these seems to me to have gone through the sequence of tuberculosis, focal infection and, more recently, toxoplasmosis. A firm proof of any of these causes has usually been lacking, and I think the sharply defined picture is much less frequently seen, the more diffuse posterior uveal inflammation taking the place of both this and, as I have suggested, the original disseminated choroiditis picture.

In reporting the pathological findings (Table I) I propose to set them out in the same way as did Smith and Ashton.

TABLE I.—CLASSIFICATION BY AGE, SEX, AND CLINICAL CATEGORY

Clinical category	*Sex*	*Age group* 0–9	10–19	20–29	30–39	40–49	50–59	60+	*Total*
Anterior	M	0	1	19	23	19	4	3	69
	F	1	8	15	14	12	13	7	70
Posterior	M	0	2	8	5	1	0	0	16
	F	1	6	4	2	3	0	0	16
Pan-uveitis	M	0	1	2	1	0	1	0	5
	F	0	0	0	0	1	0	1	2
Others	M	0	2	2	2	2	2	5	15
	F	0	0	0	1	3	0	3	7
		2	20	50	48	41	20	19	200
			Under 40=120.				Over 40=80.		

It will be seen that in total the females numbered 95 and the males 105. This is the reverse of the figures in Smith and Ashton's paper, and rather to my surprise and again against the findings of Smith and Ashton the male and female numbers are essentially the same in the 139 cases of anterior uveitis. There is no particular feature of the posterior uveitis cases to which I would draw attention but only 7 cases have I classed as pan-uveitis. The particular case which comes under this heading is perhaps somewhat arbitrarily decided, but Smith and Ashton's figure of 48 cases in this group is probably explained largely by the different type of patient with which they were dealing—the longstanding case of plastic uveal inflammation. The cases I have listed as "other" are a mixed lot in which I have included some sent to the Clinic for investigation although the presence of uveitis was not definite, 1 sympathetic ophthalmitis and possibly 1 other such case, the diabetics (4) and the heterochromic cyclitis and zoster cases. In age the numbers under 40 and over 40 are similar in the two groups (120–80) and although I only have memory and impression on which to base the statement I feel pretty sure that this 3 : 2 ratio for patients under 40 against those over this age would not have been the finding of 40 years ago.

Wassermann and Kahn reactions.—None of the 200 cases had a definitely positive Wassermann or Kahn reaction when examination was made this year. There was one doubtful positive result in a West Indian patient who did not return for a repeat test. 4 cases, however, had a positive case history of syphilis and of these 3 were known to have had a positive Wassermann finding at a previous date.

Gonococcal complement-fixation test.—In no case was this test positive but 3 men gave a history of gonorrhœa many years previously.

Mantoux test.—The issue of tuberculosis as a factor in the production of uveitis gets no clarification from this series and Smith and Ashton state that their survey failed to provide any laboratory criteria for the diagnosis of tuberculosis.

Of these 200 cases 24 were negative to a concentration of 0·002 P.P.D. (1 : 100 dilution). In both series of cases therefore the incidence of Mantoux-negative cases was just about that of the general population (12%). One girl in the present series was proved by gland biopsy to be a case of sarcoidosis but it is the only case so proved up to date and this survey offers little help in the assessment of the extent to which sarcoidosis can be the cause of uveitis. The case reported in the *British Medical Journal* (1955, ii, 593) by Ross of Carlisle makes very interesting reading. The bilateral anterior uveitis with nodules in the iris occurred in 1934 and regressed to complete settlement in spite of persisting hilar masses shown by X-ray; then occurred the subsequent involvement of the brain with death in 1954, and the demonstration at autopsy of cerebral, thoracic and liver foci of sarcoidosis.

TABLE II.—POSITIVE TOXOPLASMA RESULTS BY CLINICAL CATEGORY

		Dye test		*Complement-fixation test*	
Clinical category	*No.*	*Positive*	*Per cent*	*Positive*	*Per cent*
Anterior	139	50	36	11	8
Posterior	32	14	44	6	19
Pan-uveitis	7	1	—	1	—
Others	22	2	—	—	—

Toxoplasmosis (Table II).—The results in my series, although they show some degree of higher positive rate in the cases of posterior uveitis as against anterior, have not the same wide difference as in the results of Smith and Ashton's group where the figures were 67% against 39% by the dye test. I have found it very difficult to sort out any clinical pattern in the positive cases, for example, of the 6 cases in which ankylosing spondylitis was present 4 showed a positive toxoplasma result, 2 of them being strongly positive. I feel that in all this uncertainty as to the cause in any one case of uveitis the presence of ankylosing spondylitis is so satisfying from a clinical point of view that it seems a little hard that in 4 out of 6 cases the issue has to be queered by the serological reports.

Table III, which gives the age grouping of the positive cases, has one definite feature. Nearly 60% of uveitis patients over the age of 60 present a positive serological finding. The numbers are probably too small to be of account but the finding is of some interest.

TABLE III.—AGE GROUPS OF POSITIVE TOXOPLASMA

Age	1–19	20–39	40–59	60+
No.	7=32%	28=29%	21=34%	11=58%

Brucellosis.—1 patient in the posterior uveitis group agglutinated *Brucella abortus* to a titre of 1 : 256. There was no history or evidence of clinical infection in this case.

Anti-streptolysin assays.—The numbers, especially in the posterior uveitis group, are too small to give reliable figures on breakdown. Of the first 208 cases examined from the Clinic 53 showed a titre of over 100. This corresponds very closely to the rate 1 : 4 with a similar titre in the cases of anterior uveitis analysed by Smith and Ashton and is, I understand, a much higher rate than in the population in general.

Stress.—One of the workers in the Clinic has been going into the "stress" factor in the cases he examines. I imagine he wants many more cases on which to base conclusions but this possible element has not been overlooked.

In the problem of uveal inflammation why is it that so often the only area attacked in an otherwise very fit person is the scrap of uveal tissue? And how can we get at the causes? I feel sure that anterior uveitis is being seen more frequently in the younger age groups. When I was a student the aphorism was current "K.P. in a child means syphilis," but in 1954 Cross pointed out that the manifestations of syphilis in children are becoming rarities. Equally the severity seems to me to have diminished, largely, I think, because of decreased

incidence of chronic plastic uveitis aided by early diagnosis and modern treatment. This should mean fewer and fewer cases certified blind as a result of uveal inflammation. Mr. C. A. G. Cook kindly brought a patient to see me at Moorfields and has said I may quote the findings. I do this to show one pattern of case increasingly frequently seen and I will follow with the brief details of one case in the series. The two seem to illustrate so well the difficulty of ætiology.

In 1951 the child at the age of 7 gave the history of being struck in the left eye by a tennis ball and subsequently complained of affected vision. On examination at hospital the right eye gave 6/12 vision only, with an appearance of the optic disc described as pseudo-papillœdema, macular changes and tortuous retinal veins. The left eye showed much grosser changes with retinal hæmorrhages and exudates and vision of 6/60 only. All investigations as to the cause of this bilateral retinal lesion were negative. The right eye became more normal in appearance but the condition in the left altered little for four years at which time each eye developed an acute, though mild, generalized uveitis. There was still œdema of the discs and retinæ and some optic atrophy in the left eye suggested arteritis as well as involvement of the retinal veins. Every test has again been negative and there is no evidence of Still's disease or any other associated lesions.

Case No. 113 of my series was a female from my clinic who 14 years ago at the age of 27 first suffered from bilateral sclero-kerato-uveitis in each eye. Although there was no history of syphilis or sign of congenital origin the blood Wassermann was reported positive. There was, however, some doubt about the finding at that time. At any rate she was given a course of arsenical treatment and a full follow-up of mercury and iodide. Her Wassermann has been negative twice since the course of treatment. Now her Mantoux is positive 1/10,000 and her serum is positive to toxoplasma to 1 in 40 by the dye test. She has had gross dental sepsis, much "rheumatism" including severe lumbago, and her blood pressure at the age of 41 is 190/120. In spite of recurrent anterior uveitis her left eye still has 6/5 vision, though the right by reason of early complicated cataract has much lower acuity.

What has caused the uveitis in these two cases? The one has no trace of cause, the other a wide choice, for the patient seems to show the possibility of infection of various sorts, allergy from various causes and even "stress" and hypertension.

I think when we cannot get in the younger people even a clue as to the cause in such a high proportion of cases, and until we have a means of sorting out between multiple possible causes in one patient it seems almost hopeless to speculate even as between infection, whether by bacteria or a virus on the one hand, or tissue sensitivity on the other.

The veterinary surgeons have the same problem in the recurrent iridocyclitis of horses and you will remember the discussion in 1953 on this subject in conjunction with the Section of Comparative Medicine (*Proceedings*, 1954, **47**, 233). The disease in horses was first described in the Fourth Century A.D. and has, as in humans, been ascribed to all sorts of causes although I do not know that a stress element has been invoked. The general opinion now seems to be that there is no one cause but that the condition is one of allergic sensitivity which may be induced by a number of remote conditions in the animal. The epidemiology and the distribution of the diseases would seem to bear this out and give some support to the sensitivity causation of an inflammation in a small specialized pigmented tissue of the body. The Professor of Veterinary Science at the University of Belgrade, however, told me recently that in 80% of their affected horses the aqueous had a high titre to leptospirosis but that as in so many of our serological assays the picture was spoilt by the fact that in unaffected horses 30–40% showed a positive aqueous.

The classification of endogenous uveitis as between granulomatous and non-granulomatous, upon which Alan Woods has done so much detailed work, does not seem to me to have a clear clinical meaning, in the pattern of uveitis seen in our clinics to-day. At first sight the large majority of this group would be classified as non-granulomatous but while admitting the absence of streptococcal skin sensitivity tests it is hard to get any firm evidence that focal infection is the cause, and I for one could not frame a clinical "cause and effect" until more certain means of eliciting organism and site have been evolved. I wonder whether in the future, while all the time watching the clinical picture, we may not get more help from the study, especially perhaps the physiological study, of the uveal tract, than from a continued approach to the problem from the direction of the ways in which the uvea may be attacked.

REFERENCES

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