OBSERVATIONS ON UVEITIS ASSOCIATED WITH VIRAL DISEASE*

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Viruses have long been regarded as causes of uveitis, and the association of uveitis with such known viral diseases as herpes zoster and herpes simplex is a familiar one. In 1954 the subject of viral uveitis was reviewed exhaustively for the International Congress of Ophthalmology in New York by the late Professor Cavara (1). This review has been immensely helpful in the prosecution of the present study and has obviated the necessity of an independent search of the entire literature.

Investigative efforts to relate viral agents to uveitis have encountered almost insuperable obstacles, referable chiefly to the inaccessibility of the affected tissues. It is true that aqueous can be obtained with relative impunity in uveitis, but this fluid, which has to pass the blood aqueous barrier, probably only rarely contains the infecting agent. It is also not known with certainty whether in every case of viral uveitis there is an actual localization of the virus in the eye; there is still the possibility that certain cases represent allergic or toxic reactions.

In view of these difficulties, an attempt should be made to establish criteria for the implication of a virus as the etiologic agent of a uveitis. Such criteria might be set up under the following headings:

1. *The development of uveitis in the course of a known viral infection.* When this occurs it is necessary of course to eliminate the possibility that the association is accidental, or that a latent herpes simplex infection has been activated by the febrile disease.

2. *Isolation of a virus from the uveal tract.* It has been well established in virology that the isolation of a virus from a disease does not constitute proof of its etiologic relationship, and that viruses apparently unassociated with clinical disease may be recovered, particularly from

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the intestinal tract. Nevertheless, "orphan" viruses are apparently very rare in the eye so that the isolation of a virus from uveitis must be regarded as having considerable diagnostic significance.

3. *Serologic evidence.* Viral infections can often be diagnosed serologically on the basis of a rising titer of neutralizing or other antibodies during their course. Unfortunately endogenous uveitis is a secondary manifestation and neutralizing antibodies should ordinarily be well established at the time of onset.

4. *Therapeutic evidence.* Only in uveitis secondary to lymphogranuloma venereum, or to other members of the psittacosis-lymphogranuloma group of virus diseases, can therapeutic response be diagnostically significant, since no other viruses are susceptible to chemotherapy. In a patient known to have latent or active lymphogranuloma venereum, a chronic uveitis which responds rapidly to sulfonamide or medium- or broad-spectrum antibiotic therapy is in all probability due to lymphogranuloma venereum virus.

The following report on uveitis occurring in the course of known and suspected viral disease is the first in a series dealing with the relationship of viruses to uveitis. It is based on the analysis of more than a thousand cases seen in the Uveitis Clinic of the University of California Medical Center, and in the course of private practice, during the past five years. It will be followed by reports on the laboratory aspects of viral uveitis and on experimental viral uveitis in animals.

UVEITIS ASSOCIATED WITH KNOWN VIRAL INFECTIONS

HERPES SIMPLEX

A transient irritation of the iris is a common feature of dendritic keratitis and is characterized by a faint aqueous flare and a few cells. If the keratitis remains superficial, the uveitis remains uncomplicated. In our previously reported study of herpetic keratitis, such a transient iritis was noted in all cases of dendritic keratitis.

In herpetic keratitis with deep involvement, on the other hand, a severe uveitis, sometimes hemorrhagic in character and running a course of from two weeks to two months, has been a frequent complication. Medium-sized keratic precipitates have regularly been found, but in no case have there been mutton-fat deposits or nodules on either the cornea or the iris. Synechias have often developed in spite of the use of cycloplegics, since the corneal involvement has made it extremely difficult to achieve and maintain full dilation of the pupil. The iridocyclitis has often been hemorrhagic in character, uveitis with hyphema

complicating 11 of 92 cases of deep keratitis in our series. Hemorrhage has not occurred regularly enough, however, to be regarded as a characteristic feature of herpetic keratouveitis, as suggested by Cavara. Secondary glaucoma has developed more often than in other types of uveitis, and secondary cataract has been common in cases in which the uveitis has remained active for a protracted period. Vitiligo iridis has never been observed as a sequela.

The extent and severity of the uveitis have usually been indicated by the degree of pain. Herpetic keratitis alone is usually not painful, since there is in most instances a deep corneal anesthesia; but, with the onset of iridocyclitis, the patient complains bitterly of pain, and narcotics are sometimes required for its control. This severe pain has been a striking feature of chronic herpetic uveitis, even in cases unassociated with a rise in intraocular tension. In two instances in our series the pain was so severe that the patients demanded the removal of their affected eyes.

In general the uveitis has paralleled the keratitis in severity, but in a number of cases a severe uveitis has followed a rather mild keratitis, and in a small proportion the uveitis has persisted after apparent healing of the cornea. This persistence of the uveitis after corneal healing would seem to indicate that the uveitis was not strictly secondary in these cases but represented an actual viral invasion of the uveal tissue. During the course of the disease it was usually not possible to examine the posterior segment, but in follow-up studies after healing no evidence of posterior uveal involvement was discovered.

Aqueous punctates were taken in a small number of cases for cytologic study and for the inoculation of tissue cultures and experimental animals. The cytologic findings had no diagnostic value, for although mononuclear cells tended to predominate, they are known to be the most prominent cell in the aqueous of uveitis in general. In no instance was herpes simplex virus recovered, nor did experimental animals develop disease as a result of intraocular inoculations.

The possibility that herpetic uveitis can develop in the absence of keratitis was suggested by the relapse pattern in cases of recurrent dendritic keratitis. In four patients with a history of recurrent dendritic keratitis in whom fever appeared to be the trigger mechanism, a uveitis without keratitis developed after an upper respiratory infection, not influenzal in character; in each case the uveitis appeared in the same eye that on previous occasions, after similar upper respiratory infections, had developed typical dendritic keratitis. In one of the four cases there was an alternation of uveitis and keratitis in a series of attacks.

In all four cases the uveitis was nongranulomatous, accompanied by medium-sized keratic precipitates and synechias, and self-limited in from two to four weeks.

Cavara claimed that herpes virus may cause acute anterior uveitis not associated with herpetic keratitis or herpetic eruptions. In his report to the International Congress he described the isolation of herpes simplex virus from the aqueous humors of 7 of 13 patients suffering from acute anterior uveitis. Partial confirmation of these claims has come from Hewson (2), who reported to us by letter that he had demonstrated the presence of herpes simplex virus in the aqueous of a patient with iritis by inoculating the aqueous into the cornea of a rabbit. Other confirmation has not yet been forthcoming, but Cavara's interesting work should stimulate extensive laboratory study to determine whether or not herpes simplex virus is concerned in endogenous nongranulomatous uveitis in the absence of herpetic lesions of the skin and mucous membranes.

In our cases of uveitis secondary to herpetic keratitis, topical cortisone and other steroids were used freely at first, but later only exceptionally, because of their manifestly unfavorable effect on the keratitis. This has been discussed in an earlier report on herpetic keratitis. When the steroid preparations were used in this type of case, their anti-inflammatory effect seemed to be less striking than it was in typical endogenous nongranulomatous iridocyclitis. The associated keratitis may have interfered with the absorption of the drugs.

HERPES ZOSTER

We have seen 11 cases of herpes zoster ophthalmicus with uveitis. In all but one of these a keratitis preceded the onset of the uveitis, which differed markedly from the anterior uveitis of herpes simplex infection; the herpes zoster uveitis was milder and of longer duration, some of the cases showing mild activity for as long as six months.

Although the hemorrhagic iritis described by Cavara as a typical herpes zoster manifestation was not a feature of any of our cases, we have seen patches of iris atrophy and depigmentation (vitiligo iridis) in patients recovered from herpes zoster ophthalmicus which probably included a hemorrhagic iridocyclitis as one of its manifestations. Nor did the herpes zoster iridocyclitis with hypopyon reported by Donohue and others occur in our series. There was, in fact, nothing specific about any of our 11 cases; in the absence of zoster lesions of the skin there would have been nothing to relate the iridocyclitis to this disease. Lincoff, Wise, and Romaine (3) have reported a case of herpes zoster

ophthalmicus with choroiditis and retinal detachment, but no similar case occurred in our series.

In the one case of zoster uveitis without gross evidence of keratitis, there was typical skin involvement over the distribution of the nasociliary nerve. Corneal sensation was reduced, but no corneal opacification ever developed. The uveitis was chronic, accompanied by some neuralgic pain around the eyes, and characterized by minimal aqueous cells and flare. No synechias developed, but there was a transient secondary glaucoma.

Cortisone and other steroids were used freely in zoster uveitis without complications, but their suppressive effect on the inflammation was only moderate.

CHICKENPOX (VARICELLA)

There were no cases of varicella uveitis in this series, but a number of years ago the senior author had an opportunity to observe a case of uveitis in a child which developed during the convalescent phase of a typical attack of varicella. This case was reported by Hallett. It was acute in nature and self-limited. There were no corneal lesions, and no damage was sustained by the eye. While in military service he also saw a disciform keratitis secondary to varicella in which there was a severe, unresponsive iridocyclitis. It was of short duration but was followed by secondary glaucoma.

VACCINIA

During the course of this study, three cases of accidentally induced vaccinia of the lids occurred. In one of these the infection extended to the conjunctiva and cornea. A typical disciform keratitis developed, and there was an associated subacute anterior uveitis of short duration. The keratitis cleared with minimal scarring, and the uveitis subsided without synechias. No involvement of the posterior segment was noted. Uveitis secondary to smallpox of the conjunctiva is known to have occurred, but no such case was observed in this study. Nor have we seen any uveitis following smallpox vaccination or vaccination of any other type.

INFLUENZA

There is a vast literature describing the ocular lesions that are encountered in the course of influenza or during convalescence from it. With respect to influenza as a cause of uveitis, there seems to be some divergence of opinion. As reported in Cavara's review, Groenow stated

that uveitis comprised 8 percent of the ocular complications in influenza, and Gilbert stated that influenza was responsible for 1.6 percent of a series of uveitis cases of all types. In comparable series, Baum attributed 6.5 percent to influenza, and Esberg 4 percent.

In our study we have observed 18 cases of subacute iridocyclitis, all with a rapid course and favorable prognosis, in the convalescent phase of influenza. The uveitis was in each instance nongranulomatous in type, subacute in character, and without specific characteristics. In no instance did atrophy of the iris or synechias result. In all but 3 of the 18 cases the uveitis was bilateral. No involvement of the choroid or retina could be seen. It should be emphasized that all cases occurred during the convalescent phase of the disease. In none of them was there an associated herpes of the face or cornea, or any other feature which would suggest the possibility that a herpetic infection had been activated by the influenza.

EPIDEMIC PAROTITIS (MUMPS)

During the period of this study an effort was made to find a uveitis which might have been caused by epidemic parotitis virus. We found one case with dacryoadenitis and two cases with mild interstitial keratitis, but none with uveitis. The literature (8, 10, 13) contains many reports of iritis and iridocyclitis secondary to epidemic parotitis, however, and a larger series would probably have yielded some positive findings. There is the possibility, moreover, that mild cases of uveitis may develop in the course of the disease without being detected by the pediatrician or referred to the ophthalmologist for slit-lamp examination.

LYMPHOGRANULOMA VENEREUM

This interesting and relatively recently defined disease is caused by a virus of the psittacosis-lymphogranuloma group of viruses which are of large particle size and susceptible to chemotherapy. The virus has an affinity for mesodermal tissue and should therefore be expected to localize in the uveal tract. It is of special interest that there is available a specific skin reaction (the Frei test) which is of the utmost importance in diagnosis; since the disease is extremely rare in the general population, a positive Frei test is highly significant. There is also a valuable complement-fixation reaction, and there is a good therapeutic test by virtue of the response of the virus to the sulfonamides and broad- and medium-spectrum antibiotics. While the disease is primarily genitourinary, it takes on a systemic character, and there is sometimes widespread

systemic involvement, particularly of the joints. The number of cases reported in the literature would indicate that uveal involvement is by no means rare. These cases have been fully summarized by Cavara. Of special interest is Zonck's report of 23 cases with ocular manifestations, including 4 cases of recurrent iritis.

In our study we encountered only one patient in whom a clinical diagnosis of lymphogranuloma venereum had been made. This forty-seven-year-old Negro had been incompletely treated, but his genitourinary symptoms had been relieved and the disease was believed to be quiescent. He developed a chronic granulomatous lesion at the limbus of the left eye, accompanied by an iridocyclitis of torpid nature which had been active for six weeks at the time he was first observed by Dr. Thygeson. The Frei test and complement-fixation test were both positive. Serologic tests for syphilis (for which he never had been treated) and for tuberculosis were also positive. Both the limbal granuloma and the iridocyclitis responded rapidly to oral sulfonamide therapy. Since syphilis and tuberculosis are not affected by this treatment, the result supported the view that lymphogranuloma was the cause of the uveitis.

In our Uveitis Clinic the Frei test was used as a screening procedure in 397 cases of chorioretinitis and 626 cases of iridocyclitis, all in patients without obvious systemic disease. The test was positive in 24 of the 397 chorioretinitis cases. Complement-fixation tests were run on 14 of these 24, with positive results in 8. The Frei test was positive in 44 of the 626 iridocyclitis cases, and 15 of the 44 were subjected to the complement-fixation test; it was positive in 5. There were 61 cases of panuveitis; in 3 of these the Frei test was positive, and in one of the 3 the complement-fixation test was positive.

It is extremely difficult to evaluate the results of serologic and skin tests in patients without physical signs of systemic lymphogranuloma venereum. We believe, however, that in view of the rarity of lymphogranuloma venereum in the general population and the harmlessness of antibiotics and sulfonamide therapy, any chronic uveitis giving a positive Frei test or complement-fixation test should have the benefit of a therapeutic trial. If rapid response to therapy results, a causal relationship to lymphogranuloma venereum can be presumed. This aspect of uveitis will be the subject of a separate report.

PSITTACOSIS

Two patients with psittacosis were examined. Although uveitis never has been reported in connection with psittacosis, it seemed possible

that evidence of an iritis might have escaped detection. No ocular complications were found in these two patients, however. We interviewed Dr. Karl Meyer of this University, whose special interest has been psittacosis. He told us he knew of no instance of uveitis in any of the cases of psittacosis that he had had under his personal observation.

MEASLES (RUBEOLA)

The literature is full of reports of ocular complications in measles. The commonest of these is measles conjunctivitis. This is in reality a keratoconjunctivitis, since slit-lamp examination of the cornea almost invariably reveals an epithelial keratitis. Other complications are bacterial corneal ulcers and inflammation of the optic nerve. Only a few instances of uveitis have been reported. In connection with our study of viral keratoconjunctivitis we have examined numerous cases of measles with the slit lamp and the corneal microscope and have in no instance found any evidence of uveitis.

INFECTIOUS MONONUCLEOSIS

A conjunctivitis (12) frequently accompanies this important viral disease, which has a high attack rate among young people. Less commonly there is an episcleritis, and still less commonly retinal hemorrhages occur. Edema of the optic nerve has frequently been reported, but uveal lesions are apparently rare. Tanner (9) recently reported a case of bilateral acute nongranulomatous uveitis in a seventeen-year-old girl with infectious mononucleosis. The uveitis was characterized by keratic precipitates and marked circumcorneal flush, and there was an associated edema of the discs. The uveitis healed within a two-months period without sequelae.

We have seen three cases of mild bilateral iridocyclitis in the convalescent phase of this disease, all in young male adults. Mild, transient edema of the disc was seen in one case but no frank optic neuritis. The course of the uveitis was benign in every case, healing taking place spontaneously within a few weeks. The condition closely resembled the iridocyclitis accompanying influenza. It seems probable that this type of uveitis is much more common than generally believed, since many cases could easily be overlooked by the general practitioner caring for the illness.

EPIDEMIC KERATOCONJUNCTIVITIS

This virus infection, which was apparently introduced into the United States from Hawaii in 1941, has appeared in both sporadic

and epidemic forms. The writers have had the opportunity to examine numerous cases of the disease in its various stages with the slit lamp and the corneal microscope. In no case has a true uveitis ever been seen. In the more severe cases with extensive corneal infiltrates, a few cells in the aqueous and a transient beam have occasionally been noted, indicative of an iris irritation such as may occur in connection with any keratitis. In our opinion this has not represented a true localization of the infection in the uveal tract. In the literature, however, a number of instances of iritis secondary to epidemic keratoconjunctivitis have been reported. In his monograph Cavara mentions a single case of epidemic keratoconjunctivitis with which a relapsing hemorrhagic iritis was associated. He also mentions the occurrence of acute iritis in epidemic keratoconjunctivitis, with some tendency to form posterior synechias. Danielson, in a personal communication, reported an iridocyclitis that developed late in a case of epidemic keratoconjunctivitis that had been treated by cortisone.

GERMAN MEASLES (RUBELLA)

If one excludes the congenital anomalies induced by infection of the mother with the virus of rubella during the first trimester of pregnancy, it may be said that the ocular complications of German measles have been minimal. During the period of this study no instance of uveitis due to German measles was uncovered, although a number of cases were studied during their entire course as part of the viral keratoconjunctivitis project. No reference to uveitis associated with this viral infection was found in the literature.

INFECTIOUS HEPATITIS

A single instance of bilateral uveitis following infectious hepatitis was reported by Foural in 1950. With this report in mind we have made an effort to survey all possible cases of infectious hepatitis occurring in this area. A number of internists and practitioners who were seeing hepatitis as part of a minor epidemic in the Santa Clara Valley agreed to refer any cases with visual disturbance or ocular inflammatory signs. No referrals have been made.

VERUCCA VULGARIS

Although 3 instances of keratitis secondary to verucca on the lid margins and 2 instances of infectious papillomata of the conjunctiva were encountered during the period of this study, no signs of uveal irritation were seen in any case. With the exception of the case de-

scribed by Guignot and DeCasaban (cited in Cavara's monograph), no reports of uveitis secondary to warts of the eye or adnexa have been found in the literature. The exception was an acute iridocyclitis following a confluent eruption of flat juvenile warts on the forehead.

MOLLUSCUM CONTAGIOSUM

The literature contains many references to follicular conjunctivitis secondary to molluscum nodules of the lid margin, and there have been a few reports of actual localization of the disease on the cornea. During the period of this study we have observed 6 cases of molluscum contagiosum conjunctivitis. Three of them had an associated epithelial keratitis, but in none was there any sign of uveitis. Nor could we find any reference in the literature to uveitis secondary to molluscum contagiosum keratoconjunctivitis.

NEWCASTLE DISEASE CONJUNCTIVITIS

Newcastle disease is a viral infection of fowl appearing as a severe and often fatal pneumoencephalitis. The disease is frequently transmitted to poultry workers and veterinarians, but conjunctivitis is the only human lesion that has been noted. During the period of our study we were able to examine 5 cases, 4 in poultry workers and 1 in a veterinarian. In none of these was a uveitis uncovered. No reference to the occurrence of uveitis in connection with this disease in the human was found in the literature.

GENERALIZED CYTOMEGALIC INCLUSION DISEASE

Cytomegalic inclusion disease (4, 5) is a viral intrauterine infection that affects the infant at or soon after birth. The causative agent is a salivary gland virus that probably infects a large proportion of the population subclinically at an early age. When the infection becomes generalized, visceral lesions involving the spleen and liver may occur. It is of interest that congenital brain damage with calcification, similar to that caused by toxoplasmosis, has been described, and it is believed that some of the affected infants survive. The retina appears to be involved primarily in this disease, but secondary uveal manifestations may occur. Recently Weller, Macauley, Craig, and Wirth (6) isolated a virus from the urine of an infant with hepatospleenomegaly, cerebral calcification, and chorioretinitis.

This important subject will be considered in a subsequent report. Studies like that of Weller and associates will almost undoubtedly uncover more examples of ocular involvement. Christensen of the Uni-

versity of Oregon recently published an interesting report (18) dealing with this infection.

VIRAL ENCEPHALITIS

Although viral encephalitis has been common in California of late, no instance of uveitis secondary to it has come to our attention. In this connection it is interesting that Rift Valley fever, a viral infection occurring in Africa and affecting sheep and cattle, produces encephalitis in humans, and that in a number of cases retinitis and chorioretinitis have been associated with the human disease (7).

UVEITIS ASSOCIATED WITH DISEASES FOR WHICH A VIRAL ETIOLOGY HAS BEEN SUGGESTED OR CLAIMED

MUCOCUTANEOUS SYNDROMES

Reiter's disease.—The typical manifestations of Reiter's disease are chronic urethritis, polyarthritis, and conjunctivitis. It affects young men predominantly and tends to recur. Cavara in his monograph states that inflammation of the uveal tract in Reiter's disease has been regarded as very rare, but that recent slit-lamp examinations have shown it to be much more frequent than previously supposed. He states that the uveitis usually involves both eyes, and that it often appears during the course of the conjunctivitis but may also occur as a primary symptom independent of other ocular lesions. He states that it develops typically in the convalescent stages of the disease and may recur when the other manifestations of the disease recur. There are a number of other claims in the literature that uveitis occurs in Reiter's disease, and some authors have considered it to be as characteristic as the conjunctivitis in the triad of symptoms. Cavara describes his personal observations of the syndrome and notes that in 3 cases observed by him, 2 had a scleroconjunctivitis and 1 an iritis.

During the period of our study we have had the opportunity to observe 6 typical cases, all with urethritis, conjunctivitis, and arthritis. Uveitis was not observed in any of them.

The etiology of Reiter's disease is still unknown. We were able to make extensive virus studies of 3 of our cases, but the results were negative.

Behçet's syndrome.—In this mucocutaneous disease (15) there is a symptom complex that consists typically in a uveitis with hypopyon, aphthous ulcerations of the mouth and genital mucosae, and skin changes of various types. All the symptoms tend to recur, and the

uveitis, which is the major lesion of the disease, may recur at regular intervals. Iritis with hypopyon is a fundamental characteristic of the syndrome and is occasionally the first or only manifestation. Normally, however, the ocular symptoms develop late, after the appearance of aphthae in the mouth and genitals. Recently Sezer (16) described the isolation of a virus from a number of cases and claimed a serologic relationship between the virus and the disease. At the time of writing no corroboration of Sezer's findings has been forthcoming.

We have been able to examine a limited number of patients with this disease, but only one was available for thorough laboratory study. This case, although believed to be an example of the disease, was atypical in that at the time of study aphthae of the skin and mucous membranes had not appeared. The patient had typical recurrent uveitis with hypopyon, however, and was sufficiently interesting, we believe, to warrant a full report of his case:

J.P.D., a sixty-year-old white male, was first seen by us in February, 1956, at the request of Dr. Robert Shaffer, to whom we are indebted for permission to publish the findings. Four years prior to the onset of the ocular disease, the patient developed fever with chills and night sweats, followed by attacks of syncopy. He was hospitalized and subjected to intensive study, but no cause for his difficulty came to light. The febrile spells recurred at ten- to fourteen-day intervals for the next three years and then ceased. One year prior to our observation he developed an iridocyclitis of the right eye which became recurrent, and later in the same year he developed a similar inflammation of the left eye. In early 1956 the attacks were accompanied by hypopyon, the most severe attack occurring in March. At the same time the febrile episodes recurred.

At the time of our first examination there was a marked bilateral iridocyclitis with cells and flare and with hypopyon. There was no secondary glaucoma. Scattered posterior synechias were observed, and vision was reduced to 20/200 in each eye. General physical examination showed no abnormalities. Anterior chamber fluid was aspirated repeatedly from both eyes for culture study. The hypopyon gradually disappeared but the iridocyclitis persisted. Glaucoma with iris bombe developed, and an iridectomy was performed. This was accompanied by severe bleeding and was followed eventually by hypotony and atrophy of the eye. The excised iris tissue and the aspirated vitreous were available for culture study.

Aqueous humor, vitreous, and iris tissue were inoculated into mice, guinea pigs, and HeLa cell tissue cultures, and onto the chorioallantois of fertile eggs. No evidence of viral growth developed in any of these media. Spinal fluid and blood were used for similar inoculations, with the same negative results.

A more typical example of the disease was referred to us for consultation by Dr. A. E. Maumenee, then of Stanford University Medical School. Detailed studies of ocular fluids and blood were made from this

case at the State Virus Laboratory in Berkeley by Dr. Edwin H. Lennette. He reported inability to isolate a virus.

Erythema multiforme.—This disease is a classic example of a mucocutaneous syndrome. Typically it is characterized by bullous lesions of the skin, by severe stomatitis, and by conjunctivitis varying in severity from a catarrhal conjunctivitis to a severe pseudomembranous or membranous conjunctivitis with ulceration of the cornea that may be followed by perforation and panophthalmitis. A number of reports in the literature indicate that a uveitis occasionally occurs in conjunction with the conjunctivitis, as is apparently the case in Reiter's syndrome. The isolation of a causal virus has been claimed for erythema multiforme but has not been confirmed.

During the period of our study, 6 typical cases of this disease were studied. The conjunctivitis was severe in all of them, but keratitis did not develop and in no instance was there any evidence of uveitis.

UVEOMENINGITIC SYNDROMES

Harada's disease, the Vogt-Koyanagi syndrome, and sympathetic ophthalmia.—The syndromes of Harada and Vogt-Koyanagi are both characterized by bilateral uveitis and by extraocular symptoms consisting in meningeal irritation, disturbances of hearing, and disturbances of the hair and skin. The eye lesions may appear alone or with one or more of these associated lesions, and the two syndromes differ from each other only with respect to the characteristic localization of their uveal tract manifestations: the Vogt-Koyanagi syndrome is typically an anterior uveitis while Harada's disease is typically a posterior uveitis with retinal detachment. Both syndromes are found much more frequently in Asiatics and other heavily pigmented individuals, so that much of our information about them comes from Japan and other oriental countries. The viral theory of their origin is based on animal experiments with rabbits in which vitreous extracted from affected patients has apparently produced optic neuritis and uveitis. No virus has as yet been isolated, however.

Sympathetic ophthalmia appears to bear a certain relationship to these syndromes by virtue of the poliosis, depigmentation of the skin, auditory disturbances, and meningitis and meningoencephalitic symptoms that have been noted in severe cases. A viral etiology has also been claimed for it but not confirmed.

During the course of our uveitis studies we have examined 8 cases considered to be typical of Harada's syndrome and 6 considered to be typical of the Vogt-Koyanagi syndrome. One of the cases of Harada's

disease was reported in detail by Cordes (14). It was possible to make virus studies in only two of the Harada's disease cases and in only one of the Vogt-Koyanagi cases. The results were consistently negative.

There were no cases of sympathetic ophthalmia available for study during this period, therefore no attempts could be made to test the theory of a virus etiology originated by Schreck (17) in Heidelberg. Helenor Foerster, however, has been reviewing the pathological material from cases in our pathology collection for histologic evidence of viral infection and will be reporting her findings in a separate communication.

DISCUSSION

The precise role of viruses in the production of uveitis is still to be determined. Clinical observations indicate, however, that uveitis is an important feature of certain viral infections, as for example, herpes simplex and herpes zoster, and an infrequent complication of many other viral infections, as for example, influenza and infectious mononucleosis. The role of viruses in causing endogenous uveitis, not associated with manifest systemic disease, is still a matter of conjecture.

There has been an unfortunate lag in the application of new virological techniques to uveitis research which at best is fraught with difficulty, principally by virtue of the fact that it is impossible to obtain tissue specimens during the early phases of uveal disease. In spite of this handicap, however, the future holds considerable promise that important advances can be made.

In the preliminary study here reported, the clinical data indicating or suggesting that a given uveitis is due to a virus have been analyzed. It has been noted that most cases of uveitis associated with viral disease develop during its convalescent phase. This has been particularly characteristic of the uveitis that has developed in influenza and infectious mononucleosis. Before a uveitis can be specifically related to the viral disease in question, however, the possibility that the association is coincidental, or that the uveitis may be due to herpes simplex virus, activated by the febrile disease, must be ruled out. Coincidental association must be given special consideration when the uveitis is a rare complication, as in varicella. Iridocyclitis is such a great rarity in children, however, that when it appears in association with varicella the possibility of an etiologic relationship must be seriously entertained.

Uveitis associated with viral disease varies widely in clinical type. For example, the unilateral uveitis, often severe and painful, that is associated with herpes simplex virus keratitis, differs greatly from the

low-grade, painless iridocyclitis seen so characteristically in the convalescent phase of influenza and infectious mononucleosis. It is of interest that in none of these virus-associated cases of uveitis have the mutton-fat K.P. characteristic of granulomatous disease been seen. Even in the one case of uveitis definitely believed to be etiologically associated with lymphogranuloma venereum, this typical granulomatous reaction was lacking. It is also of interest that vitiligo iridis, described in the literature as a "stigma of viral action," has been found in our cases only in connection with the uveitis associated with herpes zoster.

There is a distinct possibility that mild forms of viral uveitis are frequently overlooked. It became apparent in the course of this study, for example, that mild uveitis occurred more frequently in connection with influenza and infectious mononucleosis than was commonly believed. The fact that many patients have given a history of transient blurring of vision during early convalescence from these two diseases indicates that slit-lamp study of a statistically valid number of cases will have to be made before the figures on the incidence of viral uveitis can be accepted as meaningful.

Only in lymphogranuloma venereum was there any evidence to indicate that uveitis could occur during the latent phase of a viral infection in the absence of signs of systemic disease. In this viral infection there seems to be a distinct possibility that uveitis can develop without manifest signs of the venereal disease.

Except in lymphogranuloma venereum, attempts to use therapy to test viral etiology were unrewarding. In view of the insensitivity of typical viral infections to antibiotic or sulfonamide therapy, failure to respond to chemotherapy might theoretically be considered suggestive of a viral etiology. Most nongranulomatous endogenous uveitis, no matter what its cause, is insensitive to chemotherapy, however. Conversely, a positive response to sulfonamide or antibiotic therapy could be construed as favoring the diagnosis of lymphogranuloma venereum, since this disease is susceptible to chemotherapy. It might be argued that cortisone and other steroids could be used diagnostically since many experimental virus infections are made worse by steroids. In clinical practice, however, this cortisone effect seems to apply only to herpes simplex virus infection, and then inconsistently. In this study the response of uveitis patients to topically applied steroids yielded no diagnostic information whatever.

It is apparent that the value of the clinical study of uveitis associated with viral disease is definite but limited. Advances in the future can be expected to come from the laboratory. Unfortunately, laboratory studies

in uveitis are severely handicapped by the difficulty of obtaining specimens during the early, acute phases of the disease when conditions would be most favorable for virus isolation. Serologic studies, moreover, are enormously complicated, and their diagnostic value is limited by the fact that uveitis is not a primary entity but a secondary manifestation of a systemic disease, so that a specific rise in antibody titer cannot be expected. Nevertheless, there are a number of new virus study techniques of tissue culture, concerned particularly with the unmasking of latent viruses, that are being employed successfully in the study of other diseases and need to be applied to uveitis research. Certainly this phase of uveitis investigation warrants extensive combined clinical and laboratory study. There is always the exciting possibility that hitherto unknown agents will be found to be active in the uveal tract, as the new adenoviruses, for example, have been found to affect the conjunctiva and cornea.

SUMMARY AND CONCLUSIONS

1. In a study of more than a thousand cases of uveitis observed in the Uveitis Clinic of the University of California Medical Center and in private practice during the past five years, an effort has been made to define the characteristics of uveitis occurring in association with known viral infections.

2. Uveitis as part of known viral disease has been recognized clinically in herpes simplex, herpes zoster, varicella, vaccinia, influenza, lymphogranuloma venereum, and infectious mononucleosis. It has been observed most frequently as a feature of herpes zoster and herpes simplex. The clinical characteristics of uveitis associated with viral disease are described.

3. A special study of the characteristics of herpes simplex uveitis, secondary to deep herpetic involvement of the cornea, is reported. Illustrative cases suggesting that herpetic uveitis may occur without keratitis are offered for consideration.

4. The uveomeningitic syndromes of Vogt-Koyanagi, Harada, and sympathetic ophthalmia are discussed and illustrative cases presented. Although these entities have long been regarded as probably viral in origin, efforts to isolate viral agents from them in the course of this study failed.

5. The significance of serologic tests, skin tests, and cytologic studies of the aqueous and of excised uveal tissues, in efforts to determine the role of viruses in uveitis, is discussed.

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DISCUSSION

DR. ALSON E. BRALEY. This paper just delivered should be read in its entirety in order to understand some of its unusual features.

Before discussing it I should like to point out a number of interesting facts, particularly in relation to herpes simplex virus. While I have always held that this is primarily an epitheliotropic parasite and affects the cornea, the

authors have called our attention to the fact that a uveitis occurs in association with the keratitis, and they have ably made the clinical diagnosis of recurrent uveitis probably due to the direct invasion of the herpes simplex virus into the uveal tissue.

Although they have been unsuccessful in their isolation of the virus from the fluids of the eye, the virus might be present in the uveal tract. Herpes simplex represents a latent virus where the balance exists between the intranuclear virus and the extracellular fluids containing probably antiviral substances. When a tissue is obtained from any source for inoculation and investigation there must be enough free virus present to infect the growth media. This media must be some form of a tissue culture. Probably epithelial cells are used most widely. But I would suggest, since Dr. Thygeson feels that the invasion goes directly into the connective tissue cells, that it might be wise to use fibroblasts as the culture media instead of HeLa cells, which most of us use. These cells must of necessity be susceptible to the virus at this time.

With any study of uveitis we should investigate the possibility of hypersensitivity. Between 60 and 90 percent of the population of any country has herpes simplex. This is a most interesting latent virus infection. In the blood of the people who have the infection there is a high amount of neutralizing antibodies. Besides this, in recent years complement-fixing antibodies, which may or may not be the same as the so-called neutralizing antibodies, have been demonstrated. The presence of these neutralizing antibodies has no relationship whatsoever to the immunity to the disease of herpes simplex.

With this complex structure of a latent virus associated with a high degree of neutralizing antibodies, one would certainly suspect that hypersensitivity should occur. I should like to point out that these hypersensitivity findings must be considered when any discussion of uveitis is presented. There are, however, reports in the literature and in Cavara's and Beatti's monograph about herpes simplex, the primary type of herpes simplex causing a uveitis.

I should like to mention infectious mononucleosis as a cause of uveitis, so that we may keep in mind epidemic keratoconjunctivitis and the APC infections and, of course, the unknown group, the so-called mucocutaneous group. None of us working in the United States have been able to substantiate the work of Sezer and others in this field.

DR. HAROLD F. FALLS. I wish to make two points:

1. A pregnant woman may be exposed to a viral disease which may deleteriously affect the fetus and yet exhibit no evidence of its presence in the exposed female. An example of this was recently encountered. A pregnant school teacher, exposed to several (10) cases of measles during her first trimester, gave birth to a child who exhibited microphthalmia, chorioretinitis, and congenital zonular cataracts. The teacher herself had experienced no illness, however, and furthermore she had had the disease in her early childhood. She perhaps had sufficient immunity to protect herself, but apparently not enough to shield the fetus. There is available a fair amount of literature which further substantiates this observation.

2. This point concerns the so-called critical periods in organogenesis at which a noxious agent apparently is capable of more easily exerting a deleterious effect on the fetus or organs. Is it not possible to conceive of the

fact that the placenta may be *more permeable* to noxious agents during such very active periods of organogenesis and that the tissue or organ undergoing such active chemical and enzymatic alteration may also be most susceptible (at that specific moment) to the effect of the noxious agent?

DR. CONRAD BERENS. About fifteen years ago we reported before this Society eight years of study in which we had been unsuccessful in correlating uveitis clinically with any virus.

A question has been raised concerning infectious mononucleosis, and Dr. Thygeson said he has not seen a case of mononucleosis with bilateral detachment. We saw a patient with bilateral detachment of the retina two months after she developed uveitis. Laboratory tests and medical consultation clinched the diagnosis of mononucleosis, which is considered of possible viral etiology.

It is good to know that Thygeson and his associates are continuing their studies, because if any group can give us the answer to the possible viral etiology of uveitis, they will do it.

DR. RALPH O. RYCHENER. Have our authors had any experience with cataract surgery on eyes which have suffered attacks of herpes simplex? I am faced with such a problem in the near future, and aware of the possibility of lighting up another session of herpes, as well as that of producing some degeneration of the cornea. If they have any information on that I would be very glad to have it.

DR. PHILLIPS THYGESON. May I thank the discussers for their valuable comments.

It is important to stress the difference between the sequential uveitis of herpes simplex virus infection, in which the cornea is first involved, and the usual type of endogenous uveitis, in which the uveitis develops in the absence of gross systemic disease. There is no difficulty in diagnosing herpetic uveitis when it is preceded by a typical corneal lesion.

Dr. Berens has mentioned the great difficulties encountered in uveitis research in the past, and we are encountering the same difficulties in our present studies. Several new techniques applicable to virus study are now available, however, and these offer some hope for the future. Chief among them is the unmasking technique developed by Huebner and his associates in connection with their studies on the adenoviruses. By means of this technique the masking effect of antibody might be eliminated by cultivating uveal tissue in series.

Dr. Berens mentioned the occurrence of bilateral retinal detachment in infectious mononucleosis. It should be recalled that bilateral retinal detachment after herpes zoster has also been reported in the literature. Incidentally, most uveitis secondary to or associated with known viral diseases has been anterior, but in herpes zoster uveitis I am sure the anterior choroid participates in the inflammation and I think this accounts for the detachment which may result from choroidal exudation.

I cannot recall a cataract extraction after herpes simplex uveitis.

DR. ROBERT N. SHAFFER. We did have a patient who had such extensive herpes keratitis that eventually corneal transplantation was needed. This transplant

was done successfully by Dr. Hogan. Subsequently a cataract extraction was done without lighting up any herpetic infection. Unfortunately, a little later the graft again had herpetic involvement, which resulted in a great deal of scarring. Nevertheless, the trauma of the cataract extraction caused no trouble.

ADDENDUM

Since this article was written, two interesting reports have appeared. In the first of these Hewson has described the isolation of herpes simplex virus from the aqueous of a patient with recurrent acute iritis. (G. E. Hewson, Iritis due to herpes virus, *Irish J. M. Sci.,* 6:372, 1957.) In the second report Evans and his collaborators have described the isolation of a virus (on the chorioallantoic membrane of the developing chick embryo) from the aqueous of one of three cases of Behçet's syndrome. (A. D. Evans, C. A. Pallis, and J. D. Spillane, Involvement of the nervous system in Behçet's syndrome: report of 3 cases and isolation of a virus, *Lancet,* 2:349, 1957.)